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Introduction

Despite the proliferation of national and international guidelines since 2003, many questions about hypertension and its optimal treatment remain unanswered. This "expert essay" considers some of the more controversial issues surrounding hypertension treatment, including the following:

1- There is no longer any need to waste time, money, and effort on researching blood pressure (BP), which is, after all, only a minor determinant of cardiovascular risk.

2- Prehypertension is an artifact resulting from the desire of American guideline writers to increase public anxiety about relatively low levels of BP that have never been shown to benefit from treatment.

3- Traditional drug treatment of hypertension (with diuretics or beta-blockers) causes new-onset diabetes, which is why, in early comparisons of these drugs with placebo, stroke was reduced as expected, but coronary heart disease (CHD) was reduced by only half of what was expected.

4- Atenolol, or perhaps any beta-blocker, is a time-tested, excellent choice, first-line drug therapy, because it lowers BP as well as any other initial class of antihypertensive agent.

5- Some drugs or drug classes (especially angiotensin-converting enzyme (ACE) inhibitors, and perhaps angiotensin II receptor blockers have "benefits beyond BP control".

6- Blood pressure should never be lowered too far; or the risk of cardiac events will inevitably be increased.

7- Hydrochlorothiazide, the most popular and widely dispensed thiazide-type diuretic in the USA, is a better choice than chlorothalidone, because it is just as efficacious in lowering BP, has good outcomes data in several clinical trials and is available in many more combination pills.

5- Some antihypertensive agents provide "benefits beyond blood pressure control:

Marketing teams for several antihypertensive drugs claim that their agents provide 'benefits beyond BP control' in clinical trials. Perhaps the best example was the Morbidity and Mortality after Stroke: Eprosartan vs. Nitrendipine in Secondary Prevention (MOSES) trial. In this randomized comparison of an ARB with a dihydropyridine calcium antagonist with proven benefits in primary stroke prevention [37,38], BP during 2.5 years of follow-up was about 1.5/0.8 mmHg higher among the 681 patients given eprosartan than in the 671 patients given nitrendipine. Nonetheless, there was a significant (21%) reduction in the incidence of the primary end-point (mortality + total cardiovascular events) in the eprosartan-treated group [39].

In the Irbesartan Diabetic Nephropathy Trial, BP among the 579 patients randomized to receive irbesartan was very similar to BP in the 567 subjects given amlodipine, both at randomization (160/87 vs. 159/87 mmHg), and at the end of the study (140/77 vs. 141/77 mmHg). Despite this, the incidence of the primary end-point (doubling of serum creatinine, end-stage renal disease, or death) was 23% lower (p=0.006) in the irbesartan-treated group. In the Losartan Intervention For Endpoint reduction (LIFE) trial, BP values were only slightly lower during follow-up in the losartan-treated group (by 1.3/0.1 mmHg); however, a significant 13% reduction in the primary end-point (stroke,
MI, or cardiovascular death) was found in the losartan-treated group compared with the atenolol treated group [40].

During the 4.5-year follow-up in the Heart Outcomes Prevention Evaluation (HOPE), the 4645 patients randomized to ramipril treatment had BP values that were, on average, about 3/2 mmHg lower than those of the 1652 patients given placebo, but enjoyed a significant 22% reduction in first MI, stroke, or cardiovascular death. The authors asserted that this small BP difference might have accounted for perhaps 40% or 25% of the observed reductions in stroke and MI, respectively, but that the majority of the beneficial effect must have been unrelated to BP differences, and should be attributed to the drug itself. Meta-regression analyses of trials involving ACE inhibitors or calcium antagonists suggest BP-independent benefits of the former on coronary heart disease, and of the latter on stroke.

Even those who argue for a BP-independent effect of specific anti hypertensive drugs or drug classes concede that the majority of the effects on most cardiovascular end-points should be attributed to the reduction in BP caused by these drugs [43]. In the vast majority of the outcome trials, the group achieving the lowest BP after randomization exhibits the lowest risk of events [44]. In the analyses of Verdecchia et al, which included only trials of ACE inhibitors or calcium antagonists [41], a 10 mmHg reduction in systolic BP resulted in a 25% (highly significant) reduction in both stroke and CHF, whereas the effect of the individual drug classes was only about half that, and barely significant (p=0.042 and 0.028, respectively). The preponderance of the evidence, based on meta-regression analyses that include data from all clinical trials (Fig. 3) [44,45], suggests that for most end-points and most patients it is likely to be more important to achieve the target BP than to pick a specific agent to start the process.

**Figure 3:** Meta-regression plot of the average achieved difference in systolic BP between randomized treatment arms and the odds ratio for stroke in 16 clinical trials involving calcium antagonists. The curved dashed lines are the 95% confidence intervals for a similar meta-regression plot based on stroke outcomes involving 136124 patients enrolled in 27 studies (including NORDIL) completed before 2001 [45]. Note that very few trials with many strokes have results that fall outside the expected range.

The placebo-controlled studies are shown as open squares; the actively-controlled trials are shaded. Each trial is represented by a square in proportion to the number of strokes observed in the study. ALLHAT-D corresponds to the diuretic arm of the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT); ALLHAT-A corresponds to the ACEi arm of the same trial. STOP-2-C corresponds to the diuretic/beta-blocker therapy arm of the Swedish Trial in Old Patients with Hypertension #2; STOP-2-A corresponds to the ACEi arm of the same trial. IDNT-Pbo corresponds to the Placebo arm of the Irbesartan Diabetic Nephropathy Trial; IDNT-Irbe corresponds to the Irbesartan arm of the same trial. For acronyms of other trials, see text. Updated from Elliott et al [44].

**6- Lowering blood pressure "too far" increases risk for myocardial infarction:**

Because coronary arteries fill during diastole, there has been concern since at least 1987 that lowering diastolic BP below a particular threshold in patients with coronary disease will decrease coronary perfusion and increase the risk of MI [46].

Many epidemiological datasets have shown a significantly increased risk of coronary events, including death, among individuals with very low
diastolic BPs, in addition to the well-known risk with higher diastolic BPs [47]. This phenomenon, known as the "J-curve", suggests that it would be unwise to actively lower diastolic BP below a given threshold. Several post hoc analyses of data from clinical trials have also noted the existence of the "J-curve" the most recent of these comes from the International Verapamil SR/trandolapril Study (INVEST) [48]. In this analysis, data from both arms of the trial were pooled, since there were no significant differences in either BP or outcomes across the 22576 hypertensive patients with coronary disease who were randomized to either verapamil or atenolol. The relationship between average on-treatment BP and risk for the primary end-point (death, non-fatal stroke, or non-fatal MI), death, MI or total stroke was examined with a quadratic proportional hazards model, including adjustment for baseline differences. A J-shaped curve was seen for the primary end-point, death, and MI (but not stroke), with significantly higher risk below about 119184 mmHg. Although the ratio of MIs to strokes was relatively constant over a wide range of diastolic BP values >80 mmHg, at diastolic BP values <70 mmHg there were substantially more MIs than strokes. Individuals without prior coronary revascularization had a significantly higher risk of the primary end-point with low diastolic BPs than did those who had undergone prior revascularization. The authors concluded that `excessive reduction in diastolic pressure should therefore be avoided in patients with coronary disease who are being treated for hypertension.

To determine whether lowering BP "too far" is detrimental in hypertensive patients without coronary disease was the primary objective of the prospective, randomized Hypertension Optimal Treatment (HOT) study [49]. Investigators in this trial randomized 18790 hypertensive patients with a baseline BP of 170/105 mmHg to diastolic BP values of <80, <85, or <90 mmHg. After 3.4 years, there was no significant difference across the randomized groups in major cardiovascular events or MIs (Fig. 4), suggesting that the strategy of achieving a diastolic BP target <90 mmHg is neither harmful nor helpful. The extra effort and medications required to achieve the lower BP targets did not result in a significantly improved (or worsened) prognosis. Other analyses of these data, based on observed BPs (rather than the intent-to-treat paradigm), corroborate these conclusions [50].

Several other studies have also suggested that BP-lowering medications have few detrimental effects in patients with coronary disease, although none of the studies was designed to determine if low BP is harmful. The HOPE, and EUROPA trials found a significant benefit among high-risk patients who were given an ACEi (compared with the placebo-treated group, which exhibited only a slight reduction in BP, perhaps due to the relatively low BP at randomization) [51,52]. Calcium antagonists were also found to have significant long-term outcome benefits in patients with coronary disease in A Coronary disease Trial Investigating Outcome with Nifedipine (ACTION) [53], even in the subgroup with coexisting hypertension [54] and in the Comparison of AMLodipine vs. Enalapril to Limit Occurrences of 'thrombosis (CAMELOT) trial 155. In the latter, those given amlodipine had the fewest CHD events (primarily hospitalization for angina) and their average on-treatment BP was only 124.7/75.2 mmHg, which is lower than the nadir seen in the INVEST analysis.

According to the principles of "Evidence-Based Medicine"; data from the randomized clinical trial
with the primary objective of comparing cardiovascular outcomes across hypertensive individuals randomized to three different diastolic BP targets should be ranked higher than post hoc analyses of cohort studies or clinical trials. The HOT trial indicates that, for hypertensive patients, there is little to recommend diastolic BP lowering to ≤85 mmHg, but not because of evidence of harm.

Whether patients with coronary disease do better or worse with lower-than-usual diastolic BPs has not yet been as rigorously tested as was this hypothesis in hypertensive patients in HOT. Few would argue against the existence of a BP level beyond which further BP lowering should be harmful. In hypertensive patients that level seems to be ≤80 mmHg, but in patients with coronary disease it is not yet as clearly defined by prospective studies.

7- Hydrochlorothiazide is an acceptable alternative to chlorthalidone for hypertensive patients:

Hydrochlorothiazide (HCTZ) is the most popular thiazide diuretic in the USA (in terms of both prescription numbers and pills dispensed) and is marketed with at least 27 other antihypertensive drugs in combination pills [56]. A brief report of a network meta-analysis comparing cardiovascular outcomes in trials using either chlorthalidone or a (different) thiazide-type diuretic claimed no significant difference in efficacy for the two drug types (each vs. placebo) [57]. Nonetheless, some prefer chlorthalidone, for several reasons.

Although no clinical trials have directly compared HCTZ and chlorthalidone for cardiovascular risk reduction, there are several reports of better BP control with low-dose chlorthalidone than with similar doses of HCTZ. Comparative clinical trials in the 1970s used much larger doses of diuretics than are common today, but even these tended to show slightly better BP reductions with low-dose chlorthalidone. The most recent head-to-head comparison of 12.5 mg/day chlorthalidone force-titrated to 25 mg/day vs. 25 mg/day HCTZ, force-titrated to 50 mg/day in 30 hypertensive patients showed a near-significant difference in ambulatory systolic BP after 8 weeks (the primary end point), a significant (p=0.009) difference in night-time systolic BP, and a highly significant difference in office systolic BP at 2 weeks (p<0.0001). All end points favoured chlorthalidone at half the daily dose of HCTZ [58]. Switching 19 uncontrolled hypertensive patients from hydrochlorothiazide (in addition to 3.2 other medications) to the same once-daily dose of chlorthalidone resulted in a significant fall in systolic BP (from 152±5 to 144±2 mmHg, p=0.035) and no significant change in serum potassium, perhaps because the vast majority were concomitantly taking either an ACE inhibitor or an ARB [59]. The records of the two diuretics in outcomes-based clinical trials in hypertensive patients are shown in Table (5.1). If one tallies the results of these trials in a way similar to sports scores (e.g. in the last row of Table 5.1), chlorthalidone's record would be 6-0-1, whereas HCTZ would have only a 4-3-5 record. Based on these results, odds-makers would generally prefer chlorthalidone.

Perhaps more pertinent to the relative merits of these two drugs in preventing cardiovascular outcomes was the decision taken in 1989 by the MRFIT Steering Committee to mandate the use of only chlorthalidone for all patients randomized to "Stepped Care". In MRFIT, the choice of diuretic was not randomized, but the principal investigator at each participating centre chose either chlorthalidone or HCTZ as the first-line therapy for individuals randomized to "Stepped Care" at that centre. After an average follow-up of 5 years, outcomes were compared between the participants randomized to "Stepped Care" and those referred back to the community for their treatment "Referred Care". In those centres that primarily used HCTZ, the prevalence of coronary heart disease end-points was 44% higher, and the mortality rate 16% higher, among "Stepped Care" participants than among "Referred Care" participants. In the centres that primarily used chlorthalidone, the prevalence of CHD events was 58% lower, and the mortality rate 42% lower, among the "Stepped Care" participants than among their "Referred Care" participants. When the centres that had originally used HCTZ switched their "Stepped Care" participants to chlorthalidone, they experienced a 28% lower rate of coronary heart disease events and a 26% lower risk of death (p=0.04, 0.06, respectively) than their "Referred Care" participants. Over the long term, most "Referred Care" participants received HCTZ as their initial diuretic, whereas most of the "Stepped Care" participants received chlorthalidone, particularly after the mandated switchover. It is perhaps not surprising, therefore, that the "Stepped Care" participants had a lower risk of CHD and death in the long term [62].
A further indirect comparison favoring chlorthalidone over HCTZ involves the more recent large hypertension studies done in the USA and Australia: ALLHA T and ANBP-2. In ALLHA T, chlorthalidone was more effective in reducing BP and preventing stroke, combined cardiovascular events, and heart failure than the ACEi lisinopril [2]. Lisinopril differs chemically from enalapril only by the addition of an epsilon-amino group at the second carbon, but otherwise has a similar pharmacological and BP-lowering profile.

In ANBP-2, the authors claimed superiority of enalapril over HCTZ in reducing BP and incident myocardial infarction in men [74]. If one accepts the similarity of lisinopril and enalapril, and the conclusions of the studies’ authors, chlorthalidone is better than the ACEi lisinopril, which is similar to the ACEi enalapril, which was superior to HCTZ. By the associative property of mathematics (if \(A > B\) and \(B > C\), then \(A > C\)), the inescapable conclusion is that chlorthalidone is superior to HCTZ.

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Controversies in Hypertension


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Left Ventricle Geometry in Normotensive Type-II Diabetic Patients

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Objective: The study based on assessment of changes in left ventricular dimensions and mass in Type-II diabetic patients and to correlate the effect of plasma insulin and serum glucose levels on changes might affect the Lv in absence of increased systemic blood-pressure.

Background: Hyperglycemia, insulin resistance, cytokines, and vasoactive hormones are the most important factors that lead to advance and progression of abnormal cell growth. Like hypertension, diabetes can cause fibrosis of the myocardium and increased collagen deposition in absence of systemic hypertension or other causes of Lv hypertrophy.

Patients and Methods: The study includes 44 patients previously diagnosed as normotensives type-II diabetis and after applying exclusion criteria, they are divided into Four-groups based on the treatment protocol (oral or insulin) and the state of glycemic control (controlled or un-controlled). Group-I (controlled diabetics on oral therapy), included 10 patients with their age of mean $\pm$ SD (44.0±5.2), Group-II, (uncontrolled orally treated diabetics), included 12 patients with age of mean $\pm$ SD (46±4.2), Group-III (controlled diabetic on insulin therapy), included 9 patients with their age of mean $\pm$ SD (45±4.1) and Group-IV (uncontrolled insulin treated diabetics), included 13 patients with age of mean $\pm$ SD (45±3.8). All patients in all groups were subjected to (full clinical evaluation and routine examination, laboratory assessment of basal glucose and insulin serum levels after 8-hours of no calorie intake, estimation of insulin-resistance indices by Glucose/Insulin ratio and HOMA test was meticulously analyzed, then M-mode Echocardiographic assessment of Lv-diastolic dimensions to estimate Lv-mass and mass index in relation to their body surface area).

Results: After collection of both laboratory and Echocardiographic data, analyses of the results revealed that, in demographic features there’s no significant variation of age in between all groups, however, body weight was significantly increased in group III than other groups with (p=0.001) and no significant variation of body height and BSA among all groups.

Comparing the laboratory data between group I to group III-(controlled diabetics) revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA$_1$C and HOMA with significant lower G/I in group III versus group I with p=0.001 for all apart from p=0.05 for HBA1C only. Moreover, comparing laboratory data between uncontrolled-diabetic groups (group II & IV) revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA$_1$C and HOMA with significant lower G/I in group IV versus group II with p=0.001 for all results.

Comparing Echocardiographic data revealed that, there’s no significant variation in all Echocardiographic data between both groups in the form of; higher LVEDD, LVESD, LVPWT, IVS, posterior wall thickness (0.97±0.21 in group I Vs 0.86±0.01 in group III), L.V mass (168.8±21.17 in group I Vs 179.12±32.4 in group III) and L.V mass Index (91.2±10.8 in group I Vs 85.4±17.5 in group III). However, comparison between uncontrolled groups (group II & IV) revealed that, in spite of there’s no significant variation in relation to LVEDD and PWT, there’s a significant (p=0.03) increased septal thickness in group IV than group II (0.9±0.17 in group II Vs 1.15±0.11 in group IV) and a significant (p=0.03) increased LV mass and mass index in group IV (LV mass 196.5±25.4 in group II Vs 232.4±27.8 in group IV L.V mass index was 101.3±15.0 in group II Vs 120.4±13.5 in group IV).

Correlation of laboratory data to Echocardiographic findings between controlled and un-controlled groups revealed that, there’s a positive correlation of increased L.V-mass and mass index with higher basal glucose (p 0.018 and r 0.355) and insulin levels (p 0.001 and r 0.48). Also, positive correlation with elevated HBA$_1$C (p 0.001 and r 0.71), elevated HOMA level (p 0.001 and r 0.477). However, negative correlation with G/I Ratio (p 0.02 and r~0.34).
Conclusion: Laboratory data revealed a significant variation in all parameters between controlled and uncontrolled diabetics in relation to basal levels of glucose and insulin and more evidenced insulin resistance in uncontrolled groups, which means that, in uncontrolled glycemic state there’s more increase in glucose and insulin levels with resultant more insulin resistance whatever the mode of treatment (oral or insulin). Echocardiographic data revealed that, no differences in between controlled diabetics but, a significant increased septal wall thickness is observed in uncontrolled groups with resultant increased in their LV mass and mass index and this conclude that, in uncontrolled glycemic state, their a tendency to increased LV mass in spite of the mode of treatment (either oral or insulin). Elevated fasting blood glucose, basal insulin, HBA₁C, HOMA and reduced glucose/insulin ratio are highly correlated to increased LV mass and mass index and this is not related to either controlling blood glucose or the mode of treatment oral or insulin.

Key Words: Left ventricle mass – Hyperglycemia – Insulin resistance – Type II diabetes.

Introduction

Under some circumstances, of which we today only know a handful, the mass of the left ventricle of the heart increases. A too large left ventricular mass is known as left ventricular hypertrophy (LVH). LVH is a very common condition. The prevalence of echocardiographic LVH in the general population ranges from 10-20% in young and 1-3% in middle-aged subjects to 30-50% in elderly subjects and LVH is also more common in the settings of obesity, hypertension, valvular disease or previous myocardial [1,2] infarction. Irrespective of the underlying cause of LVH and diagnostic method, LVH imposes a great risk for cardiovascular and all-cause mortality and morbidity [3].

The only way of accurately determining the weight of the left ventricle is by autopsy, but several diagnostic methods give reasonable assessments of left ventricular mass in living subjects. Electrocardiography (ECG) was one of the first methods, and is still the most extensively used because of its low cost, widespread accessibility and proven prognostic value [4]. In the last decades, the introduction of cardiac ultrasound (echocardiography) has made direct assessment of cardiac geometry and calculation of left ventricular mass possible. Measuring left ventricular mass by nuclear magnetic resonance tomography has been found to have a high precision, but is yet expensive and time-consuming [5].

LV hypertrophy: Cardiac hypertrophy involves increase in the size and sometimes in the number of cardiac muscle cells with either increase in the number of connective tissue cells and/or deposition of connective tissue proteins in the interstitial space [6].

Functionally Meerson and Breger described three different stages in the evolution of LVH where Phase-1, is characterized by increased protein synthesis and energy production, Phase-2, shows stable hyper function or compensated hypertrophy and Phase-3, is caused by failure of mitochondria renovation with myofibrillar damage and cellular atrophy leading to contractility depression [7].

Left ventricular hypertrophy (LVH) is defined as an increase in the mass of the left ventricle (LV) and is caused by the response of myocytes to various stimuli. Mechanical and neurohormonal stimuli can lead to activation of myocardial cell growth, gene expression that leads to growth of interstitium and cell matrix components Thus, the development of LVH is characterized by myocyte hypertrophy and by an imbalance between the myocytes and the interstitium of the myocardial skeletal structure [8].

Echocardiography is a well established method of evaluating LV mass and LVH and remain a relatively inexpensive, accurate and diagnostic tool [9].

Diabetes and LV mass: Like hypertension, diabetes can cause fibrosis of the myocardium and increased collagen deposition. These effects are even more pronounced in patients with coexisting hypertension and diabetes. The most important factors that leads to advance and progression of abnormal cell growth are hyperglycemia, insulin resistance, cytokines and vasoactive hormones. The contributions of these factors to the development of such diabetic complications depend not only on the particular vascular tissue being affected but also on the specific phase of the disease process. Moreover, both the environmental and hereditary factors can adjust the risk and advancement of these complications [10].
Inappropriate cell growth and death are major pathologic processes in diabetic patients. The pathologic effects of elevated glucose levels on vascular function can include decreased proliferation of endothelial cells, the impairment of some parameters of vascular responsiveness and increased endothelial programmed cell death [11].

As similar as, glomerular mesangial cell growth and extra cellular matrix production have significant roles in the pathogenesis of diabetic nephropathy, the most common cause of end-stage renal disease (ESRD) in the United States, Hyperinsulinaemia (i.e., type 2 diabetes mellitus or exogenous insulin therapy) provides a mitogenic stimulus that accentuates Angiotensin II-mediated growth of vascular smooth muscle cell (VSMC) and mesangial cells [12].

On a cellular level, both hyperglycemia and insulin resistance have direct negative effects on myocardial metabolism through inhibiting glucose entry and glycolysis into the heart. As a result, intracellular metabolism shifts from glycolysis to free fatty acid oxidation. The production of oxygen free radicals may also be enhanced in this situation, further depressing myocardial contractile function [13].

Collectively, these various abnormalities potentiate the characteristic left ventricular remodeling of diabetes, clinically manifested as serial wall motion changes, reduced regional ejection fraction and increases in end-diastolic end systolic volumes [14].

Mechanisms where by increased levels of blood glucose produce myocardial disease include non-enzymatic glycosylation of proteins, an increase in oxidative stress, alteration in protein kinase C isoforms and cardioneuropathy. Cardiomyocyte hypertrophy occurs when protein synthesis exceeds protein breakdown, resulting in a net accumulation of protein and expansion in cell size. On the other hand, the molecular mechanisms that cause LVH are extremely complex and redundant and despite significant progress over the last 20 years, the precise signaling pathways remain only partially understood [15]. Insulin stimulates protein synthesis and inhibits protein breakdown in the heart [16,17]. Clinical studies have found that elevated plasma insulin is associated with LVH. Two basic molecular mechanisms are involved in pathogenesis of LVH (Akt-activation and PPAR-signaling pathways) [18,19].

1- Insulin-Akt-mTOR signaling in LVH:

Insulin receptor stimulation activates phosphoinositol-3 kinase (PI3K) and subsequently phosphorylates and activates of Akt. Common to these hypertrophic pathways is the phosphorylation and activation of the downstream mammalian target of rapamycin (mTOR) recent studies suggest that mTOR controls the translational machinery via activation of ribosomal p70 s6 kinase (p70s6k), which is critical for protein synthesis and hypertrophy. In addition to promoting protein synthesis, Akt activation can suppress protein degradation by N-activation of forkhead dependent transcription factors (FOXO), which promote proteolysis. Thus, insulin stimulation of Akt and downstream targets (mTOR, FOXO) link insulin receptor stimulation and downstream growth responses [20,21].

Insulin-like growth factor (IGF) receptor signaling can contribute to progressive cardiac dysfunction in aging as recently shown in fruit flies. Age-related heart dysfunction and heart failure were minimized with a reduction of systemic levels of insulin-like peptides, inactivating mutations in the insulin receptor, or over-expression of FOXO. There are three isoforms of Akt in mammals: Akt1, Akt2 and Akt3. Akt1 and Akt2 are expressed in the heart, while Akt3 is expressed primarily in brain as it regulates growth [22].

2- Lipid activation of PPAR signaling:

Cardiac gene expression and myocyte growth can also be activated by ligand binding to PPARs, specifically PPARα and PPARβ/δ. These transcription factors control gene expression by forming a heterodimer with the retinoid X receptors (RXR) and then binding to specific PPAR response elements (PPRE) located within promoter regions of many genes encoding metabolic enzymes [23].

Cardiac-specific over-expression of PPARα in transgenic mice results in LVH and LV dysfunction, particularly with high fat feeding. On the other hand, treatment of Fischer 344 rats with the PPARα agonists resulted in a 23% increase in cardiomyocyte diameter and a greater heart mass/body mass ratio. Activation of PPARα with fenofibrate for 12 weeks in rats with infarct-induced heart failure increased mRNA levels for PPARα-regulated genes and LV mass [24].

Insulin resistance: The term insulin resistance usually indicates resistance to the effects of insulin on glucose uptake and metabolism in adipocytes and skeletal muscle and impaired suppression of
hepatic glucose output. Insulin resistance is a significant risk factor for development of all cardiovascular complications [25].

Even in the absence of diabetes, insulin resistance is a major risk factor for CAD because impaired insulin action coupled with compensatory hyperinsulinaemia leads to a number of proatherogenic abnormalities referred to as the insulin resistance (Metabolic syndrome) [26].

Cardiac contractile function, gene expression, LV chamber volume and LV mass are affected by circulating hormones and substrates, including the concentrations of fatty acids and insulin in the plasma. Plasma fatty acid concentration is largely a function of net fatty acid output from adipocytes, which is inhibited by plasma insulin and increased by adrenergic stimulation. Plasma insulin levels reflect the rate of insulin secretion from pancreatic beta cells, which secrete insulin in response to the plasma glucose concentration. Impaired insulin signaling in adipose tissue and skeletal muscle is the hallmark of the whole body insulin resistance observed with metabolic syndrome or type-II diabetes and is largely responsible for the increase in plasma insulin and free fatty acids found in these patients [27].

**Insulin resistance and left ventricular hypertrophy as parallel phenomena:**

LVH and the insulin resistance syndrome may be parallel consequences of one or more common etiologic factors, such as an increased activity in the sympathetic nervous system, vascular alterations or aging. Left ventricular wall thickness and the prevalence of left ventricular concentric remodeling increase with age [28]. This is mainly due to cardiac myocyte hypertrophy, for which an increased stroke work resulting from increased arterial stiffness has been proposed to be an etiological factor. Because insulin sensitivity also decreases with age, the described association between components of the insulin resistance syndrome and the growth of left ventricular walls could in part be a consequence of aging, a process proceeding faster in some subjects prone to both insulin resistance and cardiac remodeling [29].

The risk for cardiovascular disease, particularly congestive heart failure, is significantly higher in patients with type-II diabetes mellitus than in individuals without diabetes. The presence of hyperglycemia has been associated with changes in the myocardium that are characteristic of diabetic cardiomyopathy and heart failure. Furthermore, insulin resistance may be associated with cardiomyopathy, even in the absence of hyperglycemia and has been linked with cardiovascular remodeling [30].

**Patients and Methods**

**Patients:**
A forty-four patients were studied, all of them were normotensives and diagnosed well as being diabetics. All patients underwent meticulous history taking, body weight and height assessment (in Kg and Cm respectively). A routine clinical examination was done with the following selection criteria (no history of hypertension in themselves or their parents – None of them was on sympathomimetic or sodium containing medications for at least previous six months – None of them having endocrine, metabolic disease or blood diseases or any other cause of LVH ). Echocardiographic exclusion criteria were (valvular heart diseases, presence of any wall motion abnormalities, Lv shape distortion by aneurysm or Right sided dilatation, paradoxical septal motion, pericardial diseases and any congenital malformations).

All were diagnosed based on laboratory blood glucose and basal insulin level and defined using criteria published in American Diabetes Association 2003.

**Patients were divided according to the mode of treatment into two groups:**
- Group-I: 22 patients of oral hypoglycemic drugs
- Group-II: 22 patients on Insulin therapy after secondary failure of oral hypoglycemic agents.

**Patients are then classified according to Glycaemic control into:**
- A- Controlled diabetes (with HBA1C 6-7gm%).
- B- Un-controlled diabetes (with HBA1C more than 7gm%).

**Therefore, four groups were resulted-according to the previous classification parameters:**
- Group I: Patients on oral treatment were in controlled state (they are 10 patients).
- Group II: Patients on oral treatment were in uncontrolled state (12 patients).
- Group III: Patients on insulin therapy were in controlled state (9 patients).
• Group IV: Patients on insulin therapy were in un-controlled state (13 patients).

Methods:

Estimation of glucose level and insulin-resistance: [31]

Fasting blood glucose & basal insulin level:

Fasting blood glucose level (FBG) is obtained by withdrawing the blood sample in the morning after 8 hours of no calorie intake and expressed as (mg/dL). Fasting basal insulin level (I0) is obtained at the same time of fasting blood glucose estimation and expressed as (µU/mL). Fasting hyperglycaemia is considered when FBG is more than 126mg/dL and basal hyperinsulinaemia is considered borderline if >20 µU/mL and highly positive if greater than 30µU/mL.

Insulin sensitivity index (ISI):

Insulin sensitivity is the ability of the hormone to reduce serum glucose. If fasting glucose is high-for example, in a patient with impaired glucose tolerance-that may indicate a diminished effect from circulating insulin (or in severe cases of insulin resistance, diminished quantity of the hormone).

a- Fasting serum insulin (I0) is an inexpensive assay and does not require any mathematical calculations. A fasting insulin >30µU/mL indicates insulin resistance.

b- Glucose/insulin ratio (G/I ratio) has become very popular since its first description in 1998 as an accurate index of insulin sensitivity. A G/I ratio of less than 4.5 has been shown to be sensitive (95%) and specific (84%) for insulin resistance.

c- Homeostatic model assessment (HOMA) has been widely employed in clinical research to assess insulin sensitivity. Rather than using fasting insulin or a G/I ratio, the product of the fasting values of glucose (expressed as mg/dL) and insulin (expressed as µU/mL) is divided by a constant: (I0 x G0)/405. Insulin resistance is considered if the resultant figure is >2.7.

Estimation of left ventricular mass: [32]

All cases underwent a standard echocardiography using a commercially available GE vivid 3 echo machine equipped with 2.5-3.5MHz transducer to examine for LV dimensions including (end-diastolic EDD, diastolic septal wall thickness and LV-posterior wall thickness). Left ventricular mass is generally calculated as the difference between the epicardium delimited volume and the left ventricular chamber volume multiplied by an estimate of myocardium density. Following this principle, several methodologies have been used to calculate left ventricular mass. M-mode echocardiography is widely used in epidemiologic studies to measure LV wall thickness and chamber dimensions for quantitative measures of LVM. Framingham Heart Study data indicate that abnormal LVM Index (LVMI) limits are 134g/m² for men and 110g/m² for women. Penn convention method is the most commonly used and popular method for assessment of LV mass.

Penn convention measurement:

This method is a highly accurate and the left ventricular mass is measured from the following formula:

$$LVMgm = 1.04 \times [(LVIDd+SWTd+PWTd)3 – (LVIDd)3] – 13.6$$

Where,

LVMgm = Left Ventricular Mass in grams.

LVIDd = Left Ventricular Internal Dimensions in diastole.

SWTd = Septal Wall Thickness in diastole.

PWTd = Posterior Wall Thickness in diastole.

Lv-mass Index and Body surface area measurement: [33]

After obtaining the weight and Height of every patient enrolled in the study and Echocardiographic determination of LVM in grams. LVM is then correlated to the body surface area, for each patient, using a net-derived automated model which utilizes the formula of DuBois and DuBois: BSA = (W 0.425 x H 0.725) x 0.007184 where the weight is in kilograms and the height is in centimeters and hence LVM index is obtained and expressed as (g/m²).

Statistical methods:

Data were collected and analyzed by Statistical Package for Social Sciences (SPSS) version 10. Data are given as mean (SD) for all results and comparison of the given data in four groups using Chi-square and the Student t test. Pearson’s correlation was made for the effect of elevated fasting blood glucose, basal insulin level and insulin sensitivity indices on the changes found in LV mass and mass index. A probability level of p-value ≤0.05 was considered as statistically significant in all tests.
Left Ventricle Geometry in Normotensive Type-II Diabetic Patients

**Results**

After collection of cases and applying exclusion criteria only 44 cases were enrolled on the study and grouping is defined as (group-I, orally-controlled patients, group-II, orally uncontrolled patients, group-III, insulin-controlled patients and group-IV, insulin treated uncontrolled patients). Their results are obtained and analyzed as follows:

**Table 1:** Demographic features of all groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I n=(10)</th>
<th>Group II n=(12)</th>
<th>Group III n=(9)</th>
<th>Group IV n=(13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44 ± 5.2</td>
<td>46 ± 4.2</td>
<td>45 ± 4.1</td>
<td>45 ± 3.8</td>
</tr>
<tr>
<td>Weight</td>
<td>83.0 ± 12.5</td>
<td>91.5 ± 8.1</td>
<td>108.1 ± 15.3</td>
<td>92.7 ± 7.1</td>
</tr>
<tr>
<td>Height</td>
<td>165 ± 8.4</td>
<td>166.9 ± 8.8</td>
<td>166.8 ± 4.6</td>
<td>162.0 ± 7.1</td>
</tr>
<tr>
<td>BSA</td>
<td>1.8 ± 0.18</td>
<td>1.9 ± 0.15</td>
<td>2.1 ± 0.15</td>
<td>1.9 ± 0.02</td>
</tr>
</tbody>
</table>

**Demographic data of all groups:**

The demographic features revealed there’s no significant variation of age in between all groups, however, body weight was significantly increased in group III than other groups with \((p=0.001)\) and no significant variation of body height and BSA among all groups.

**Comparison of echocardiographic results:**

Comparing Echocardiographic results between controlled diabetics (group-I & group-III) and uncontrolled diabetics (group II & IV) is best shown in Tables (2,3).

Comparing group I to group III-(controlled diabetics)-revealed that, there’s no significant variation in all Echocardiographic data between both groups with septal thickness, \((0.9±0.22\) in group I Vs \(0.93±0.11\) in group III), LVEDD \((45.4±6.6\) in group I Vs \(48.5±1.5\) in group III), posterior wall thickness \((0.97±0.21\) in group I Vs \(0.86±0.01\) in group III), LVEDD \((168.8±21.17\) in group I Vs \(179.1±32.4\) in group III) and LV mass Index \((91.2±10.8\) in group I Vs \(85.4±17.5\) in group III), as shown in Table (2).

**Table 2:** Echocardiographic data between Group I and Group III.

<table>
<thead>
<tr>
<th></th>
<th>Group I n=(10)</th>
<th>Group III n=(9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS</td>
<td>0.9 ± 0.22</td>
<td>0.93 ± 0.11</td>
</tr>
<tr>
<td>LVEDD</td>
<td>45.4 ± 6.6</td>
<td>48.5 ± 1.5</td>
</tr>
<tr>
<td>PWT</td>
<td>0.97 ± 0.21</td>
<td>0.86 ± 0.01</td>
</tr>
<tr>
<td>LVmass</td>
<td>168.8 ± 21.17</td>
<td>179.1 ± 32.4</td>
</tr>
<tr>
<td>LVmass-index</td>
<td>91.2 ± 10.8</td>
<td>85.4 ± 17.5</td>
</tr>
</tbody>
</table>

Comparing group II to group IV-(uncontrolled diabetics)-revealed that, there’s no significant variation in relation to LVEDD and PWT, inspite a significant \((p=0.03)\) increased septal thickness in group IV than group II \((0.9±0.17\) in group II Vs \(1.15±0.11\) in group IV) and a significant \((p=0.03)\) increased LV mass and mass index in group IV \((Lv mass\ = 196.5±25.4\) in group II Vs \(232.4±27.8\) in group IV Lv mass index was 101.3±15.0 in group II Vs 120.4±13.5 in group IV), as shown in Table (3).

**Table 3:** Echocardiographic data between Group II and Group IV.

<table>
<thead>
<tr>
<th></th>
<th>Group II n=(12)</th>
<th>Group IV n=(13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS</td>
<td>0.9 ± 0.17</td>
<td>1.15 ± 0.11</td>
</tr>
<tr>
<td>LVEDD</td>
<td>47.9 ± 3.7</td>
<td>46.3 ± 2.7</td>
</tr>
<tr>
<td>PWT</td>
<td>0.99 ± 0.15</td>
<td>1.15 ± 0.22</td>
</tr>
<tr>
<td>LVmass</td>
<td>196.5 ± 25.4</td>
<td>232.4 ± 27.8</td>
</tr>
<tr>
<td>LVmass-index</td>
<td>101.3 ± 15.0</td>
<td>120.4 ± 13.5</td>
</tr>
</tbody>
</table>

Figure 1: M-Mode shows Lv-mass within the normal range.

Figure 2: M-Mode measure the Lv-mass in patient with LVH.
It was clear that in controlled state either by oral therapy in group (I) or by insulin in group (III) there’s no significant variation of Lv geometry. But, it’s found that, Lv-mass index is significantly higher in group IV (uncontrolled insulin-treated patients, that’s best shown in Fig. (3).

Comparing group II to group IV-(Un-controlled diabetics)-data revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA\textsubscript{1}C, and HOMA with significant lower G/I in group IV versus group II with \(p=0.001\) for all results. The results obtained were (FBG 124.5±7.0 in group II Vs 137.1±5.3 in group IV), (basal insulin 29.5±1.7 in group II Vs 39.0±3.6 in group IV), (HBA\textsubscript{1}C 7.18±0.5 in group II Vs 8.4±0.3 in group IV), (G/I 4.2±0.19 in group II Vs 3.5±0.3 in group IV) and (HOMA was 9.1±0.95 in group II Vs 13.2±1.2 in group IV). This also revealed an important conclusion, in spite both groups were in an uncontrolled glycemic state, insulin treated patients exhibit a more increased basal insulin and glucose levels with more evidenced insulin resistance in the form of higher HOMA and Lower G/I indices.

Comparing group I to group III-(controlled diabetics)-revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA\textsubscript{1}C, and HOMA with significant lower G/I in group III versus group I with \(p=0.001\) for all apart from \(p=0.05\) for HBA\textsubscript{1}C only. The results obtained were (FBG 91.5±7.19 in group I Vs 133.1±6.8 in group III), (basal insulin 11.6±1.26 in group I Vs 31.5±1.6 in group III), (HBA\textsubscript{1}C 6.2±0.19 in group I Vs 6.5±0.34 in group III), (G/I 8.0±1.35 in group I Vs 4.2.1±0.15 in group III) and (HOMA was 2.6±0.19 in group I Vs 10.3±0.98 in group III). This revealed an important conclusion, in spite both groups were in controlled glycemic state, insulin treated patients exhibit a more increased basal insulin and glucose levels with more evidenced insulin resistance in the form of higher HOMA and Lower G/I indices.

Comparing group II to group IV-(Un-controlled diabetics)-data revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA\textsubscript{1}C, and HOMA with significant lower G/I in group IV versus group II with \(p=0.001\) for all results. The results obtained were (FBG 124.5±7.0 in group II Vs 137.1±5.3 in group IV), (basal insulin 29.5±1.7 in group II Vs 39.0±3.6 in group IV), (HBA\textsubscript{1}C 7.18±0.5 in group II Vs 8.4±0.3 in group IV), (G/I 4.2±0.19 in group II Vs 3.5±0.3 in group IV) and (HOMA was 9.1±0.95 in group II Vs 13.2±1.2 in group IV). This also revealed an important conclusion, in spite both groups were in an uncontrolled glycemic state, insulin treated patients exhibit a more increased basal insulin and glucose levels with more evidenced insulin resistance in the form of higher HOMA and Lower G/I indices.

**Comparison of laboratory results:**

Comparing Laboratory results between controlled diabetics (group I & group III) and uncontrolled diabetics (group II & IV) is best shown in Tables (4,5).

Comparing group I to group III-(controlled diabetics)-revealed that, there's a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA\textsubscript{1}C, and HOMA with significant lower G/I in group III versus group I with \(p=0.001\) for all apart from \(p=0.05\) for HBA\textsubscript{1}C only. The results obtained were (FBG 91.5±7.19 in group I Vs 133.1±6.8 in group III), (basal insulin 11.6±1.26 in group I Vs 31.5±1.6 in group III), (HBA\textsubscript{1}C 6.2±0.19 in group I Vs 6.5±0.34 in group III), (G/I 8.0±1.35 in group I Vs 4.2.1±0.15 in group III) and (HOMA was 2.6±0.19 in group I Vs 10.3±0.98 in group III). This revealed an important conclusion, in spite both groups were in controlled glycemic state, insulin treated patients exhibit a more increased basal insulin and glucose levels with more evidenced insulin resistance in the form of higher HOMA and Lower G/I indices.

**Table 4: Laboratory data between Group I and Group III.**

<table>
<thead>
<tr>
<th></th>
<th>Group I n=(10)</th>
<th>Group III n=(9)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>Mean 91.5 SD 7.19</td>
<td>Mean 133.1 SD 6.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Mean 11.6 SD 1.26</td>
<td>Mean 31.5 SD 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>HBA\textsubscript{1}C</td>
<td>Mean 6.2 SD 0.19</td>
<td>Mean 6.5 SD 0.34</td>
<td>0.05</td>
</tr>
<tr>
<td>G/I</td>
<td>Mean 8.0 SD 1.35</td>
<td>Mean 4.2 SD 0.35</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA</td>
<td>Mean 2.6 SD 0.19</td>
<td>Mean 10.3 SD 0.98</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparing group II to group IV-(Un-controlled diabetics)-data revealed that, there’s a significant variation in all laboratory data between both groups in the form of; higher FBG, basal insulin, HBA\textsubscript{1}C, and HOMA with significant lower G/I in group IV versus group II with \(p=0.001\) for all results. The results obtained were (FBG 124.5±7.0 in group II Vs 137.1±5.3 in group IV), (basal insulin 29.5±1.7 in group II Vs 39.0±3.6 in group IV), (HBA\textsubscript{1}C 7.18±0.5 in group II Vs 8.4±0.3 in group IV), (G/I 4.2±0.19 in group II Vs 3.5±0.3 in group IV) and (HOMA was 9.1±0.95 in group II Vs 13.2±1.2 in group IV). This also revealed an important conclusion, in spite both groups were in an uncontrolled glycemic state, insulin treated patients exhibit a more increased basal insulin and glucose levels with more evidenced insulin resistance in the form of higher HOMA and Lower G/I indices.

**Table 5: Laboratory data between Group II and Group IV.**

<table>
<thead>
<tr>
<th></th>
<th>Group II n=(12)</th>
<th>Group III n=(13)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>Mean 124.5 SD 7.0</td>
<td>Mean 137.1 SD 5.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Mean 29.5 SD 1.7</td>
<td>Mean 39.0 SD 3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>HBA\textsubscript{1}C</td>
<td>Mean 7.18 SD 0.5</td>
<td>Mean 8.4 SD 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>G/I</td>
<td>Mean 4.2 SD 0.19</td>
<td>Mean 3.5 SD 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA</td>
<td>Mean 9.1 SD 0.95</td>
<td>Mean 13.2 SD 1.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

It was clear now that insulin-treated groups (group III & group IV) exhibit a higher basal glucose and insulin levels with increase in insulin-resistance indices in the form of higher HOMA and lower G/I ratio, that’s best shown in Fig. (4).
It was found that there’s a positive correlation of increased LV-mass and mass index with higher basal glucose ($p=0.018$ and $r=-0.355$) and insulin levels ($p=0.001$ and $r=0.48$). Also, positive correlation with elevated HBA$_1$C ($p=0.001$ and $r=0.71$), elevated HOMA level ($p=0.001$ and $r=0.477$). However, negative correlation with G/I Ratio ($p=0.02$ and $r=-0.34$). As best showed in Figs. (5,6) and Scatter graphs (Figs. 7-10).

**Correlations between data (echocardiography & laboratory):**

Figure 4: Descriptive feature of Laboratory findings in all groups.

Figure 5: Basal glucose level and LVM-Index in all groups.

Figure 6: Basal insulin level (I0) and LVM-index index in all groups.

Figure 7: Graph shows a positive correlation between FBG & LVM, Correlation coefficient 0.355 and Slope, $p=0.01$.

Figure 8: Graph shows a positive correlation between basal insulin & LVM, Correlation coefficient 0.48 $p<0.001$.

Figure 9: Graph shows a positive correlation between FBG & LVM, Correlation coefficient 0.355 and Slope, $p=0.01$.

Figure 10: Graph shows a positive correlation between basal insulin & LVM, Correlation coefficient 0.48 $p<0.001$. 
Increased LV mass carry a high risk for cardiac mortality. A report from the Framingham heart study examined the relationship between left ventricular mass and hypertrophy and sudden death in 3661 subjects over the age of 40 who were followed for 14 years. The prevalence of left ventricular hypertrophy was 22 percent and the risk factor adjusted hazard ratio for sudden death was 2.16 ($p=0.008$) for each 50g/m increment in left ventricular mass, the risk-factor adjusted hazard ratio for sudden death was 1.45 ($p=0.008$) [34].

There is a positive relationship between LVH and plasma insulin concentration, suggesting that elevated insulin contributes to cardiac growth [35]. There have been few measurements of the effects of hyperinsulinemia on the human heart; however, it appears that insulin resistance in the myocardium in type-II diabetic patients is relatively minor, particularly if plasma fatty acid concentrations are matched [36]. This is in stark contrast to the high levels of resistance observed in adipose tissue and skeletal muscle. Thus, if there is insulin resistance in adipose and skeletal muscle, the plasma insulin and fatty acid levels will increase, which may activate insulin signaling and the PPAR pathway in the heart [37].

Our study conclude that, elevated fasting blood glucose level is associated with increased LV mass and mass index and this dictates that glucose uptake may in itself have an effect on LVH. Type-II diabetic This finding is observed in a study of American Indians that discover an increased RWT and LVMI in relation to changes in blood glucose levels in type-II diabetics during one year of follow-up and this have been shown to correlate to changes in LVMI [38]. Another study revealed that, the main glucose transporters (GLUT) in the heart are GLUT-1 and GLUT-4, of which GLUT-1 is the most important for basal glucose uptake and this is specifically leads to cardiac hypertrophy [39]. Conventionaly used therapeutic doses of the thiazolidinedione and troglitazone lead to a 3-4-fold increase in cardiac GLUT-1 and a <2-fold increase in GLUT-4 [40] and much higher doses lead to LVH [41]. Selective knock-out of the cardiac GLUT-4-receptor in mice leads to increased GLUT-1 levels and a 3-fold increase in cardiac basal glucose uptake and LVH [42]. Hyperglycemia induces activation of protein kinase C (PKC)-in the heart [43], which is capable of enhancing angiotensin effects and macrovascular contractility, among other things [44]. Transgenic mice which overexpress PKC-2 in the heart develop LVH and myocardial fibrosis [45].

We conclude also that, elevated serum basal insulin level is further linked to abnormal myocardial growth and LVH unrelated to either the patient is in controlled state or even the mode of treatment by oral or insulin therapy. Many authors support this idea of which insulin at high concentrations is capable of inducing hypertrophic effects via the insulin-like growth factor (IGF)-I receptor (which are abundant in the heart), but also at low concentrations via the insulin receptor. Stimulation of the IGF-I receptor by IGF-I causes myocyte hypertrophy in vitro and the effect on cardiac hypertrophy in vivo is probably mainly due to local rather than circulating IGF-I [46,47,48]. Cardiomyocytes produce
IGF-I during development of hypertrophy, a process suggested to be independent of the systemic renin-angiotensin system [48]. Administration of growth hormone to humans (which mainly exerts its cardiac effect via cardiac IGF-I) leads to left ventricular wall thickening and an increased utilization of carbohydrates and lower oxygen consumption. Long-term exposition to increased cardiac IGF-I levels result in myocardial fibrosis [49].

Several investigators explain the evidences indicate that hyperinsulinemia may be causal factors in the development of thick left ventricular walls and LVH. DeFronzo et al, in 1975 suggested that, Hyperinsulinemia leads to renal sodium and water retention, an increased blood volume and a higher preload, which is a known trigger of LVH [50]. Piatti et al, in 1996 discover that hyperinsulinemia has been shown to be a potent inducer of endothelin (ET)-1 release, more so in subjects with the insulin resistance syndrome than in normal subjects or subjects with insulinoma [51]. Another investigator found that hyperinsulinemia inhibits myocardial protein degradation in insulin resistant subjects. Myocardial protein undergoes continual turnover with a half-life of approximately 10 days and acute insulin administration has been shown to decrease myocardial protein degradation by 80%, which might lead to LVH [52].

The development from physiologic to pathologic LVH with increased myocardial fibrosis may also be accelerated by insulin. This is explained in literature, as hyperinsulinemia may increase serum aldosterone levels in obese, insulin resistant individuals and elevated aldosterone levels play an important role in the development of myocardial fibrosis [53]. Further support for the hypothesis that insulin resistance or hyperinsulinemia may play a causal role in the development of LVH comes from an elegant study in which induced chronic moderate hyperinsulinemia in rats, with control of hormones with effects opposing insulin, was followed by pronounced cardiac hypertrophy, without elevated blood pressure [54].

Our study revealed that, increased Lv mass is highly correlated to insulin resistance indices being positive with HOMA test and negative with G/I ratio.

This fact is previously explained by many authors who proved that insulin resistance and hyperinsulinemia have been shown to cause systemic and cardiac sympathetic activation, which has been related to cardiac hypertrophy in experimental studies [55]. Insulin resistance is related to an increased pressor response to angiotensin II [56].

Finally, Insulin resistance to glucose uptake is often related to a decreased vasodilatory response to insulin. Insulin resistance has been associated with a deranged microcirculation as well as a defect in the ability of insulin to increase aortic compliance. Increased vascular stiffness and peripheral resistance induce an increased afterload, which is of pathogenetic importance for left ventricular concentric remodeling and LVH [57,58].


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Left Ventricle Geometry in Normotensive Type-II Diabetic Patients


Aortic Elastic-Properties in Offspring of Hypertensive Patients

TAREK M ABDELRAHMAN, MD; MOHAMED SAAD, MD

**Objective:** The main objective of this study is to detect the changes that might affect the elastic properties of large central arteries in normotensive offspring of known hypertensive parents and to compare these changes to normal age-matched offspring of normal individuals. Also, to correlate age and gender effects on the results obtained.

**Background:** Arterial stiffening is associated with a number of known cardiovascular disease risk factors, raising the possibility that increased arterial stiffness may be a marker for advanced atherosclerotic vascular disease. The vascular dynamics of children with a parental history of hypertension is a cornerstone of early detection of functional and morphologic abnormalities of the arterial wall that may be responsible for many cardiovascular and cerebro-vascular complications in their future life.

**Subjects and Methods:** The study includes sixty subjects (ages 15-30 years), all were clinically healthy by applying exclusion criteria, full history and clinical examination. They are divided based on their family history of hypertension into two groups, group-I 30 offspring with a parental history of hypertension and group-II 30 off-spring of normotensive parents. All subjects were evaluated to obtain systolic, diastolic and pulse pressure readings then, M-mode echocardiography is done to study their aortic elastic properties.

**Results:** After collection of both clinical (blood-pressure) and Echocardiographic data, analyses of the results revealed a significant elevation of all blood pressure parameters in group-I than group-II with systolic Bp of mean ± SD (118.5±9.7 in group-I versus 106±4.9mmhg in group-II), diastolic Bp (66.8±5.7 for group-I versus 62.8±8.0mmhg in group-II) and a net increase in pulse pressure in group-I than group-II (51.6±10.5 versus 43.1±6.2). Comparing aortic diameters of two groups revealed that, a non-significant increase in systolic diameter in group-I (p=non-significant), significant increased diastolic diameter in group-I with mean ± SD (29.8±2.3 versus 28.0±1.3mm in group-II, p=0.01). Group-II subjects exhibit an increased Ao-diameter change property with mean ± SD (3.7±0.4 versus (2.6±0.5mm in group-I) reflecting impression of enhanced their aortic elastic feature. Comparing aortic stiffness parameters in between the two groups revealed a significant (p=0.001) difference in all parameters. Group-I showed decreased aortic strain, decreased distensibility and increased aortic stiffness in relation to group-II with Ao-strain of mean ± SD (8.9±1.8 in group I versus 13.4±1.6 for group-II), Ao-distensibility (3.1±0.8 in group-I versus 5.0±1.1cm² dyne⁻¹ in group-II) and Ao-stiffness is (0.21±0.02 in group-I versus 0.12±0.02) in group-II. In a trial to study the effect of blood pressure on aortic stiffness, It was found that, systolic blood pressure is positively correlated to increased aortic stiffness, with p-value of 0.001 and coefficient correlation r 0.66 and is negatively correlated to both aortic strain and distensibility (p value 0.001, r=−0.61 and p 0.001 and r =−0.57) respectively. Correlation made to study the effect of age and gender on Ao elastic properties revealed that, there’s a positive age related increased aortic stiffness (p value=0.02, r 0.28) and a negative correlation to aortic distensibility (p=0.01, r −0.32). Detection of the effect of gender variation on the results was obvious in group-I as males were found to have a significantly (p=0.001) higher Ao stiffness than females with mean ± SD (0.20±0.002) in males versus (0.14±0.002) in females. Females are found to have a significant higher aortic strain and distensibility (p=0.001 for strain and 0.03 for distensibility) with mean ± SD Ao strain (12.2±2.3 for females and 9.7±2.9 for males), however, Ao distensibility was (4.4±0.9 for females and 3.6±1.7 for males).

**Conclusion:** Group-I was found to have a higher PP and less change in Ao diameters between systole and diastole and this is reflected on increased Ao stiffness parameters in their results with lower distensibility and strain. Age is found to be highly correlated to increased Ao stiffness and decreased distensibility. Also, males possessing a higher than females Ao stiffness results.

**Key Words:** Aortic stiffness – Ao distensibility - Offspring – Echocardiography.

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Introduction

There is a growing awareness that abnormal large artery function plays an important role in the pathogenesis of cardiovascular disease. Investigation of arterial stiffness, specially of the large arteries, has gathered pace on recent years with the development of readily available non-invasive assessment techniques. The use of ultrasound to relate the changes in diameter or area of an artery to distending pressure gives important idea about arterial stiffness. Increased arterial stiffness, with an associated increase in the amplitudes of the forward and reflected pressure waves, is a major determinant of increased systolic and pulse pressure [1].

Arterial stiffening is associated with a number of known cardiovascular disease risk factors, raising the possibility that increased arterial stiffness may be a surrogate for advanced atherosclerotic vascular disease. However, prior studies have suggested that aortic stiffening can occur in the absence of atherosclerosis [2]. Therefore, one goal of this study was to detect early changes in arterial stiffening in aortocentral pressure in offspring of known hypertensive patients aiming to direct the attention towards prevention of burden of risk factors for cardiovascular disease based on the idea that, the reflected wave returns to the central aorta in diastole and therefore enhances diastolic perfusion pressure in the coronary circulation [3]. Partial wave reflection also returns a portion of the pulsatile energy content of the wave form to the central aorta where it is dissipated by viscous damping. Loss of this apparently protective function of wave reflection could contribute to the pathogenesis of a growing spectrum of cardiovascular and non cardiovascular accompaniments of a potential microvascular etiology, [4] including white matter lesions of the brain [5] and renal dysfunction [6,7].

The aorta is not only a conduit delivering blood to the tissues but is also an important modulator of the entire cardiovascular system, its elastic properties also affecting left ventricular function and coronary blood flow. Data from the Framingham Heart Study have determined how systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) change with advancing age. DBP is largely determined by peripheral arterial resistance, increases until middle age and then tends to fall. In contrast, SBP and PP are influenced more by the stiffness of large arteries, as well as, peripheral pulse wave reflection and the pattern of left ventricle ejection increase continuously with age [8,9].

The elastic properties of Aorta acts as buffering of the intermittent pulsatile output from the heart to provide a steady flow to the capillary beds. By virtue of its elastic properties, the aorta influences left ventricular function and structure and coronary blood flow [8].

Windkessel theory treats the circulation as a central elastic reservoir (the large arteries) into which the heart pumps and from which blood travels to the tissues through relatively non-elastic conduit (peripheral arteries). The elasticity of the proximal large arteries is the result of the high elastin to collagen ratio in their walls which progressively declines toward the periphery. The increase in arterial stiffness that occurs with age is largely the result of progressive elastic fiber degeneration [10].

The elasticity of a given arterial segment is not constant but instead depends on its distending pressure. As distending pressure increases, there is greater recruitment of relatively inelastic collagen fibers and consequently, a reduction in its elasticity [11].

The background level of distending pressure in the circulation is determined by mean arterial pressure (MAP). This is important because MAP must be taken into account whenever measurement of arterial stiffness are made so that anticipated effects of distending pressure can be differentiated from real differences in the elasticity of the arterial wall. In addition to collagen and elastin, the endothelium and arterial wall smooth muscle bulk and tone also influence elasticity [12,13].

It is well known that aortic elastic properties are important determinants of blood pressure and left ventricular function. Arterial stiffness has been considered an independent predictor of cardiovascular mortality in patients with cardiovascular disease and even in the general population [14,15].

Many studies demonstrated that the arterial stiffness measurements correlate significantly with those of endothelial function. They proposed that an increase in large-conduit vessel stiffness could represent either a cause or a consequence of endothelial dysfunction and might explain why elevated pulse pressure is a new cardiovascular risk factor [16].
Because increased arterial stiffness is an independent predictor of morbidity and mortality from cardiovascular disease and aortic stiffness is more predictive than the stiffness of other arterial regions [17].

The vascular dynamics of children with a parental history of hypertension has not been defined. A number of genetic influences on arterial stiffness have also been identified. Thus, polymorphic variation in the Fibrillin-I, angiotensin-II type-I receptor and endothelin receptor genes are related to stiffness. The angiotensin converting enzyme I/D polymorphism have been reported to associates with increased arterial stiffness but not consistently [18-20].

Systemic arterial hypertension is associated with functional and morphologic abnormalities of the arterial wall. Hypertensive adults have a twofold increase in carotid and aortic stiffness when compared to normotensive cohorts. Despite extensive research in the area of vascular dynamics, little has been done to characterize the compliance of elastic vessels in children with a parental history of hypertension. The Bogalusa heart group reported a significant elevation of carotid stiffness in adolescents with increased systolic blood pressure levels [21].

Impaired arterial compliance is an independent predictor of cardiovascular (CV) disease risk and mortality [22-24]. Risk factors for CV disease mediate their effects by adversely altering the structure, endothelial function and dynamic properties of the vasculature. The generalized structural and functional changes in the arterial circulation contribute to alterations in regional blood flow, progression of atherogenesis and microvascular abnormalities [25].

Some studies have shown that alterations in the pulsatile behavior of the vasculature may be a sensitive marker of arterial injury related to CV risk factors [26]. But changes in pulsatile function are inhomogeneous within localized arterial segments of elastic and muscular arteries. In contrast to the marked heterogeneity of the physical characteristics of localized arterial segments, consistent and predictable changes occur in the arterial pulse contour regardless of the site of measurement. These changes reflect alterations in total arterial compliance and can be quantified with the pulse contour analysis technique, which assesses not only the physiological behavior of the large conduit arteries that serve a capacitance function but also that of the smaller arteries, which represent the predominant site of reflected waves or oscillations in the arterial bed [27].

Subjects and Methods

Participants:
A total of sixty subjects (ages 15-30 years) were studied and divided based on their family history of hypertension. Group-(I) included 30 offspring with a parental history of hypertension and group-(II) 30 off-spring of normotensive parents with percentage of M/F ratio 40% in both groups. In group-I, only one parent of each subject studied had hypertension verified by the investigators and defined as a systolic blood pressure above 140mmHg and diastolic blood pressure above 90mmHg on at least three different evaluations.

All subjects in the study were clinically healthy. Exclusion criteria were obesity (defined as 20% overweight from ideal bodyweight), congenital or acquired cardiomyopathies and any other chronic medical illness. Height and weight were obtained with a clinical Detecto-scale. Dubois’s nomogram was used to calculate body surface area from height and weight. Blood pressure was determined using a mercury sphygmomanometer. The first and fourth Korotkoff sounds were used to identify systolic and diastolic blood pressure, respectively. All subjects underwent full history and routine clinical examination.

Methods:
The participants were asked to refrain from medications containing any sympathomimetic, sodium or caffeine agents and smoking or strenuous exercise for 48 hours before the study. After a light breakfast following overnight fasting, the subject is asked to rest on a bed in the supine position for 15 minute and then a trans-thoracic echocardiography is performed using a commercially available GE vivid 3 echo machine equipped with 2.5-3.5MHz transducer. The internal aortic root diameters were measured in parasternal long-axis view at 3cm above the aortic valve using two-dimensional guided M-mode trans-thoracic echocardiography. The arterial pressure was measured simultaneously at the brachial artery using sphygmomanometer. The aortic systolic diameter was measured at the full opening of the aortic valve and the diastolic diameter was measured at the peak of QRS. Three consecutive beats were routinely measured and averaged.
Assessment of Aortic stiffness parameters:

Four formulas were calculated as indices of aortic elastic properties as follows:

- Aortic diameter change = SAD – DAD
- Ao Strain index = (SAD – DAD) x 100 / DAD
- Aortic Destinsibility = 2 X (SAD – DAD) / (PP X DAD) in \( \text{cm}^2 \text{ dyne}^{-1} \)
- Aortic stiffness index = \( \ln \) (SBP/DBP) / (SAD - DAD) / DAD

Where, SAD is systolic aortic diameter, DAD is diastolic aortic diameter, \( \ln \) is the natural logarithm, PP is the pulse pressure, SBP is the systolic blood pressure and DBP is the diastolic blood pressure.

Data were collected and analyzed by Statistical Package for Social Sciences (SPSS) version 10. Data are expressed as mean ± (SD) for aortic elastic parameters to both groups. Numbers and percentages are compared using Chi-square and the Student t test. Pearson’s correlation was made for the effect of age on the aortic elastic parameters. A probability level of \( p \)-value \( \leq 0.05 \) was considered as statistically significant in all results obtained.

### Results

**Grouping based as:**

- Group (I): 30 healthy individuals with parental history of systemic hypertension and
- Group (II): 30 healthy individuals with no parental history of systemic hypertension as controls.

Demographic data of all subjects as regard age, body mass index and sex revealed no significant variation between two groups and the sex distribution is exactly the same with male percentage of 76.6% in both. As shown in Table (1).

### Blood pressure measurements:

Comparison of blood pressure in between the two groups resulted in; there a significant increased systolic blood pressure I group-I than group-II with mean ± SD (118.5±9.7 in group-I versus 106±4.9mmhg in group-II with \( p=0.001 \)). Also, a significant high diastolic blood pressure in group-I than group-II with mean ± SD (66.8±5.7 for group-I versus 62.8±8.0mmhg in group-II, \( p=0.03 \)). This resulted in significant increase in pulse pressure of group-I than group-II with mean ± SD (51.6±10.5 in group-I versus 43.1±2.2mmhg in group-II, \( p=0.001 \)). As shown in Table (2) and Fig. (1).

### Table 1: Demographic data of all groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.8 ± 5.0</td>
<td>21.0 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>17.3 ± 1.0</td>
<td>17.4 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/18</td>
<td>12/18</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Bl.pr.</td>
<td>118.5±9.7</td>
<td>106.0±4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic Bl.pr.</td>
<td>66.8±5.7</td>
<td>62.8±8.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>51.6±10.5</td>
<td>43.1±6.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Figure 2: Graphic presentation of Blood pressure results in both groups.
M-mode Ao diameter:

A- Ao diameters:

Comparing aortic diameters of the two groups revealed that, a non-significant increase in systolic diameter in group-I ($p=\text{non-significant}$), significant increased diastolic diameter in group-I with mean ± SD (29.8±2.3) versus (28.0±1.3mm) in group-II with $p=0.01$. And a net result of increased Ao-diameter change in group-II with mean ± SD (3.7±0.4) versus (2.6±0.5mm) in group-I reflecting enhanced aortic elastic property in the control subjects. As shown in Table (3) and Fig. (2).

Table 3: Comparison of blood pressure between group I and group II.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Ao D.</td>
<td>32.4±2.5</td>
<td>31.8±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic Ao D.</td>
<td>29.8±2.3</td>
<td>28.0±1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Ao-diam.change</td>
<td>2.6±0.5</td>
<td>3.7±0.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 3: Graphic presentation of Ao diameters results in both groups.

B- Aortic elastic parameters:

Comparison of the three calculations related to aortic elastic function in between the two groups revealed a significant ($p=0.001$) difference in all parameters, in the form of, the group-I showed decreased aortic strain, decreased distensibility and increased aortic stiffness in relation to group-II with Ao-strain of mean ± SD (8.9±1.8) in group I versus (13.4±1.6) for group-II, Ao-distensibility (3.1±0.8) in group-I versus (5.0±1.1cm² dyne⁻¹) in group-II and Ao-stiffness is (0.21±0.02) in group-I versus (0.12±0.02) in group-II. As shown in Table (4) and Fig. (3).

Table 4: Comparison of Ao stiffness parameters between group I and group II.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao Strain</td>
<td>8.9±1.8</td>
<td>13.4±1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Ao Destensibility</td>
<td>3.19±0.8</td>
<td>5.0±1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Ao Stiffness</td>
<td>0.21±0.02</td>
<td>0.12±0.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 4: Graphic presentation of Ao elastic properties results in both groups, (A) showed increased strain and distensibility in group-II, (B) showed increased Ao-stiffness index in group-I.

Effect of Blood pressure on Ao elastic properties:

It was found that, systolic blood pressure is positively correlated to increased aortic stiffness, with $p$-value of 0.001 and coefficient correlation $r = 0.66$ and is negatively correlated to both aortic strain and distensibility ($p$ value 0.001, $r = -0.61$ and $p = 0.001$ and $r = -0.57$) respectively. Pulse pressure is also of major positive correlation to increased aortic stiffness ($p = 0.001$ and $r = 0.72$) and is negatively correlated to aortic strain and distensibility ($p = 0.001$, $r = -0.49$ and ($p = 0.001$ and $r = -0.75$) respectively. As shown in Fig. (4).
Aortic Elastic-Properties in Offspring of Hypertensive Patients

Effect of Age and Gender on Ao elastic properties:
Correlations were made as regard the effect of age on aortic elastic parameters revealed that, there’s a positive age related increase aortic stiffness with \( p = 0.001 \) and correlation coefficient 0.69 and a negative correlation to aortic distensibility with \( p = 0.01 \) and correlation coefficient –0.66 as shown in Figs. (6,7).

Detection of the effect of gender variation on the results was obvious in group-I as males were found to have a significantly \( (p=0.001) \) higher Ao stiffness than females with mean ± SD (0.20±0.002) in males versus (0.14±0.002) in females. In contrary, females are found to have a significant higher aortic strain and distensibility \( (p=0.001 \text{ for strain and } 0.03 \text{ for distensibility}) \) with mean ± SD Ao strain (12.2±2.3) for females and (9.7±2.9) for males. However, Ao distensibility was (4.4±0.9) for females and (3.6±1.7) for males. As shown on Fig. (8).

**Figure 5:** Graph shows a positive correlation between SBP and Ao Stiffness, \( p=0.001 \) and coefficient correlation 0.66.

**Figure 6:** Graph shows a positive correlation between Age and increased Ao stiffness Correlation coefficient =0.69, Slope, \( p=0.01 \).

**Figure 7:** Graph shows a negative correlation between Age and Ao distensibility Correlation coefficient=–0.66, Slope, \( p=0.01 \).

**Figure 8:** Male versus female Ao elastic properties (A): Females having higher strain & distensibility, (B) Males are higher Ao stiffness.

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Discussion

The ability to identify alterations in the structure and function of the vasculature due to adverse anthropometric, haemodynamic and metabolic factors is crucial to CV risk assessment at a pre-clinical stage. The earliest change in the structure and function of the vasculature involves a diminution in the change in systolic to diastolic diameters. This change reflects a change in the stiffness or compliance characteristics of the arterial blood vessels [28].

As far as, arterial stiffness is an independent predictor of mortality from cardiovascular disease and aortic stiffness is more predictive than the stiffness of other arterial regions, we investigated the vascular elastic properties of the aorta. Many methodologies were investigated to assess aortic stiffness such as pulse wave velocity, arterial pressure waveforms and aortic diameter changes (strain and distensibility) [16].

Measurement of pulse wave velocity that has been used in previous studies to investigate arterial stiffness and measuring the distance that the pulse wave traveled had some disadvantages, such as having to correct or age and the effects of fat, breast size and thoracic abnormalities. In this respect, it has been suggested that aortic strain and distensibility should be calculated from the aortic diameters measured by echocardiography and blood pressure obtained by sphygmomanometry. Thus, we used the above-mentioned formula to calculate the aortic elasticity parameters [29].

We studied the aortic elastic properties in offspring of hypertensive patients to detect their likelihood susceptibility for being hypertensive in their future aiming to prevent prospective CV risk in a pre-clinical stage. Our results revealed that, subjects with parental history of hypertension was found to have higher pulse pressure, less distensibility, less aortic strain and consequently higher aortic stiffness indices than those of non-hypertensive parents. This was supported by Shirakawa et al [30] who suggested that a family history of hypertension had an additive impact on the age-associate increase in the risk of hypertension. Tozawa et al [31] showed that the greater the number of family members with hypertension was, the greater the prevalence of hypertension and BP in the probates, independent of conventional risk factors for hypertension.

Meaney et al [32] studied 100 non-obese offspring of hypertensive or normotensive parents by means of an ultrasound technique and reported that carotid stiffness was significantly higher in the offspring of the hypertensive parents, without adjustment for BP, which was already higher in this group. Prospective study provided evidence that increased aortic stiffness precedes hypertension [33].

In a trial to correlate Age-related effect on arterial stiffness, our study detect a significant positive correlation with increased stiffness parameters with age and this is supported by the findings of McVeigh et al [34] who noticed that, the rise in BP with aging, even within the normal range, was associated with a reduction in large arterial compliance estimates. Although impaired arterial compliance is considered an antecedent factor for hypertension, the early phase of high BP in youth is influenced by increases in sympathetic nervous system activity and peripheral vascular resistance resulting in arterial stiffness. The manifestation of later-phase hypertension is influenced more by increases in central vessel stiffness than by sympathetic activity [35]. Other researches explained this phenomenon, as the sustained elevation in BP is known to produce mechanical stress and to stimulate arterial smooth muscle cell hyperplasia and hypertrophy as well as collagen synthesis, resulting in impaired arterial compliance [37], which may further increase BP and start a vicious cycle [22,35].

We investigated gender effect on aortic elastic properties, and found that, there's a strong tendency for increased arterial stiffness in males than females. These differences between the sexes in the results of arterial distensibility have been explained by many authors and are attributed to the smaller body height and related size of the arterial tree in women; However, height is suggested to influence arterial wave reflections [27,38]. Others suggested that he most plausible factor is the role of steroid sex hormones in vascular protection and arterial function. Several studies have shown that vascular smooth muscle cells contain functional estrogen receptors and that estrogens have short-term vascular effects, potentiating endothelium-dependent vasodilation in conductive and resistive arteries of premenopausal women (18-20) and decreasing arterial stiffness and increasing arterial compliance (21,22).
References


33- Dernellis J, Panaretou M: Aortic stiffness is an independent predictor of progression to hypertension in no hypertensive subjects. Hypertension 2005; 45: 426-431.


Association of High Sensitivity C-Reactive Protein with the Presence and Extent of Coronary Artery Disease in Acute Coronary Syndrome

INAS IBRAHIM EWEDA, MD; SAMIR SALEH WAFA, MD; JOSEPH ADLY YOUSSEF, MBBch

Objective: In an effort to better determine risk of heart disease and prevent clinical events, many physicians began to measure C-reactive protein (CRP) as a routine part of global risk assessment. The aim of this case-control study was to assess the association of high sensitivity CRP (hs-CRP) level with the occurrence and extent of coronary disease.

Methods: This study included sixty patients selected from the emergency room and the catheterization laboratory, twenty-five with the diagnosis of acute coronary syndrome (ACS), twenty-five with chronic stable angina (CSA) and ten subjects with normal coronary angiography performed to exclude symptomatology. The sixty subjects were subjected to data recording, full clinical examination, coronary angiography, hs-CRP measurement. Data were collected, revised and analyzed statistically.

Results: The mean level of hs-CRP was 3.61±3.25 mg/dl in ACS group, 1.46±1.59 mg/dl in the CSA group and 0.8±0.46mg/dl in normal subjects, the difference was statistically highly significant (p<0.01). With comparison between levels of hs-CRP and the risk factors of coronary artery disease, it appeared to be insignificant apart from family history of coronary artery disease and previous history of myocardial infarction (p<0.05).

Conclusion: hs-CRP is significantly elevated in patients with acute coronary syndrome when compared with those chronic stable angina and normal subjects.

Key Words: High sensitivity C-reactive protein – Acute coronary syndrome.

Introduction

Up to half of all events associated with cardiovascular disease are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors, including dyslipidemia [1]. As a result, attention has increasingly turned to the role of other factors, such as inflammation, in the development of atherosclerosis and cardiovascular disease [2,3]. These efforts led to the search for inflammatory biomarkers to improve the detection of coronary and cardiovascular risk among seemingly healthy individuals [4]. Prominent among the possible candidates for a clinically useful biomarker of cardiovascular disease risk is C-reactive protein (CRP) as measured by high-sensitivity (hs) assay [5].

CRP is a critical component of the immune system, a complex set of proteins that our bodies make when faced with a major infection or trauma. CRP was discovered nearly 80 years ago by scientists exploring the human inflammatory response. The role that CRP plays in heart disease, however, has only recently been uncovered.

The human body makes CRP but in different amounts depending on a variety of factors, including genetics as well as lifestyle habits. On average, individuals who smoke, have high blood pressure, are overweight, and fail to exercise tend to have high levels of CRP, whereas thin athletic individuals tend to have lower levels. Nonetheless, almost half of the variation in CRP levels between different people is inherited and thus reflects levels that your parents and grandparents have passed on to you through their genes [5]. This is not surprising given the fundamental role that CRP plays in inflammation, an extremely important process for wound healing, for warding off bacteria and viruses, and for many key processes critical for survival.
Research over the past decade has shown that too much inflammation in some circumstances can have adverse effects, particularly on the blood vessels that carry oxygen and nutrients to all the tissues of the body. Scientists now understand that atherosclerosis (the process that is associated with cholesterol accumulation in the arteries) is in many ways an inflammatory disorder of the blood vessels, just as arthritis is an inflammatory disorder of the bones and joints [1].

Inflammation is established as an important contributor to atherogenesis and acute atherothrombosis. Researchers and clinicians have thus turned to biochemical markers of inflammation as possible noninvasive indicators of underlying atherosclerosis, the risk of first or recurrent cardiovascular events, and the success of therapeutic and preventive interventions. High sensitivity CRP is the most extensively studied of these markers and is associated with the risk of adverse cardiovascular outcomes in apparently healthy individuals and in patients with established coronary artery disease [6].

A relationship between unstable angina and elevated serum CRP levels was shown more than 30 years ago [7]. More recently, it has been established that elevated serum CRP is associated with a poor prognosis in unstable angina patients [8] and that it may predict future risk for myocardial infarction or stroke in apparently healthy men [9]. It has been suggested that increased CRP which is synthesized primarily in the liver in response to interleukin-6 and other cytokines, may not only be a marker of low level inflammation but may directly enhance inflammation in plaques [10,11]. This amplification may be mediated by its involvement in binding to complement C1q when ligand bound or in an aggregate state and in activated endothelial cells with upregulation of chemokines and adhesion molecules [12-13].

CRP is a powerful predictor of risk, particularly when combined with cholesterol evaluation. Some physicians choose to measure CRP along with a panel of other "novel" risk factors including homocysteine and lipoprotein (a). Others may elect to measure CRP along with more expensive tests that measure specific cholesterol subfractions. However, in all comparisons the predictive value for CRP has been substantially greater than that observed for these alternative "novel" markers of risk. Further, only CRP has proven to add important prognostic information to that already available from standard cholesterol screening [1].

Subjects and Methods

This study included 60 patients, they were divided in three groups, group A was formed of 25 patients with acute coronary syndrome, group B was formed of 25 patients with chronic stable angina and group C was the control group formed of 10 subjects with normal coronary angiography performed to exclude symptomatology. All of the subjects were subjected to data recording, coronary angiography and high sensitivity C-reactive protein measurement.

Coronary angiography:

Patients underwent quantitative coronary angiography which was performed with a computer-assisted analysis system. Stenosis was expressed as percent diameter narrowing using the nearest normal appearing region as the reference. Significant coronary artery disease was defined as a stenosis diameter greater than or equal to 50% in one or more major epicardial artery.

High sensitivity CRP measurement:

Blood samples were obtained from all patients before coronary angiography. Peripheral venous blood was drawn into collection tubes with citrate. Every blood sample was centrifugated to separate the serum which was isolated in special tubes that were kept frozen. Later, hs-CRP levels were measured using automated photoanalyzer (Dimension XP and clinical chemistry system, DAD BEHRING). The reagent used was C-reactive protein extend range (RCRP) flex reagent cartridge, the reference range was 0.5mg/dl.

Statistical analysis:

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as proportions. Student's t test was used for analysis of continuous data. Analysis of variance (ANOVA) and Post Hoc test were used for analysis of data. Chi-square test was used for comparisons of proportions. All data were analyzed with SPSS 10.0 for Windows. A p value <0.05 was considered statistically significant (S), p<0.01 was considered highly significant (HS) and p>0.05 was considered non significant (NS).

Results

The mean age of the patients was 49.48 years in ACS, 54.24 years in CSA and 56.3 years in the control subjects p<0.05. The number of males in
ACS was 100%. The number of those with smoking habits was highest in ACS group \( p < 0.05 \).

**Table 1:** Basic characteristics of the patients and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>( p )</th>
<th>( \text{Sig.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.48±8.07</td>
<td>54.24±8.06</td>
<td>56.3±8.31</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Male</td>
<td>25 (100%)</td>
<td>20 (80%)</td>
<td>5 (50%)</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>DM</td>
<td>10 (40%)</td>
<td>12 (48%)</td>
<td>3 (30%)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>HTN</td>
<td>13 (52%)</td>
<td>18 (72%)</td>
<td>7 (70%)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>SM</td>
<td>22 (88%)</td>
<td>13 (52%)</td>
<td>3 (30%)</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6 (24%)</td>
<td>13 (52%)</td>
<td>2 (20%)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>FH of CAD</td>
<td>12 (48%)</td>
<td>12 (48%)</td>
<td>1 (10%)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
<td>0 (0%)</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

When the age was studied there was significant statistical difference between the three groups, the ANOVA (analysis of variance) test was positive so the post Hoc test was conducted to determine the LSD (Least Significance Difference). The following three tables will show the comparison between every two groups as regards the age, there was a significant difference between group A and the other groups B and C but there was no significant difference between group B and C.

**Table 2:** Post Hoc test for age among groups A and B.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group A</th>
<th>Group B</th>
<th>Mean difference</th>
<th>( p )</th>
<th>( \text{Sig.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>49.48±8.07</td>
<td>54.24±8.06</td>
<td>-4.76</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

**Table 3:** Post Hoc test for age among groups A and C.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group A</th>
<th>Group C</th>
<th>Mean difference</th>
<th>( p )</th>
<th>( \text{Sig.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>49.48±8.07</td>
<td>56.3±8.31</td>
<td>-6.82</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

**Table 4:** Post Hoc test for age among groups B and C.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group B</th>
<th>Group C</th>
<th>Mean difference</th>
<th>( p )</th>
<th>( \text{Sig.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>54.24±8.06</td>
<td>56.3±8.31</td>
<td>-2.06</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

The number of affected vessels by coronary angiography was compared with hs-CRP in ACS group, it was found that the level of hs-CRP was statistically significantly higher in multiple vessel disease.

**Table 6:** Comparison between number of affected vessels as regarding hs-CRP in group A (ACS).

<table>
<thead>
<tr>
<th></th>
<th>Single vessel</th>
<th>Multiple vessel</th>
<th>( p )</th>
<th>( \text{Significance} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>2.42±2.01</td>
<td>5.09±3.75</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

The levels of hs-CRP was compared with the risk factors of ischemic heart disease (including age, sex, etc…), it was insignificant apart from family history (FH) of ischemic heart disease and previous history of myocardial infarction (MI).

**Table 7:** Comparison between the level of hs-CRP and presence of family history of ischemic heart disease and history of previous myocardial infarction.

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>( p )</th>
<th>( \text{Significance} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP (FH)</td>
<td>3.33±3.04</td>
<td>1.74±2.24</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>hs-CRP (MI)</td>
<td>3.84±2.91</td>
<td>1.81±2.36</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>
Discussion

In this study, there was a highly significant statistical difference in the level of hs-CRP between the patients and the control group. Further analysis showed that the statistical difference was highly significant between patients with acute coronary syndrome and those with chronic stable angina, and also between the acute coronary syndrome group and the control group. In the meantime, there was no significant statistical difference between chronic stable angina group and the control group.

The level of hs-CRP was higher in certain subgroups (p<0.05), for example, patients with multiple vessel disease and those with history of previous myocardial infarction and positive family history of ischemic heart disease.

In another study [14], they demonstrated a modest elevation of serum hs-CRP in autopsy samples of sudden coronary death, regardless of the apparent mechanism of death. There were significant elevations of serum hs-CRP compared with controls in patients dying with acute coronary thrombi associated with plaque rupture or erosion as well as patients dying with stable plaque without evidence of thrombi. This study also demonstrated marked elevations of serum hs-CRP in patients with acute myocardial necrosis and inflammatory conditions. These data in patients with myocardial infarction and inflammatory conditions were presented to validate the postmortem method of hs-CRP measurement as well as highlight the increase in serum hs-CRP that results with myocardial necrosis, which accompanies underlying coronary artery disease with thrombosis. They also correlated the serum levels with histologic staining for CRP in fatal lesions. There was a positive correlation between the intensity of CRP staining with serum levels independent of mechanism of death (rupture, erosion and stable plaque).

Elevated hs-CRP has been shown to be a strong predictor of future cardiovascular risk in patients with established coronary heart disease, with or without a previous myocardial infarction. In the Scandinavian Simvastatin Survival Study, elevated hs-CRP levels predicted mortality in patients with stable ischemic heart disease [15]. Blake and Ridker [16] have shown that elevated hs-CRP can predict risk of cardiovascular events (including death, acute myocardial infarction, and need for revascularization procedures) in patients with acute coronary syndrome.

Recently, Ridker and Cook [17] suggested that the scope of hs-CRP values be extended from less than 0.5 mg per liter (very low) to greater than 10 mg per liter (very high). This extension of scope would provide clinicians with additional prognostic information on cardiovascular disease. The joint guidelines from the Centers for Disease Control and Prevention and the American Heart association state that the optimal use of hs-CRP is to help guide the evaluation and therapy for primary coronary heart disease prevention for patients at intermediate risk, (10%-20% coronary heart disease risk over 10 years) [3].

High sensitivity C-reactive protein, a marker of inflammation, is a strong predictor of future cardiovascular events in individuals both with and without overt cardiovascular disease. Recent trials have suggested that hs-CRP may assist in stratifying risk inpatients presenting with coronary artery disease, particularly those with acute coronary syndrome [18]. Further studies examining hs-CRP levels may help elucidate new therapeutic strategies for the secondary prevention of cardiovascular disease. High sensitivity CRP also adds prognostic information in individuals with overt coronary disease.

References


Tissue Doppler Echocardiographic Detection of Right Ventricular Infarction and Location of Right Coronary Artery Lesion

M W AFAEE, MD; ISLAM A EL SHERBENY, MD; MAHA H EL SEBAIE, MD; SAYED NABEH, MSc

Background: Diagnosis of right ventricular myocardial infarction (RVMI) is important for adequate treatment of patients with inferior myocardial infarction (MI). Tissue Doppler imaging (TDI) is an echocardiographic technique that enables measurement of myocardial velocities and makes the quantitative assessment of the systolic and diastolic movements of myocardial walls possible and is an indicator of global and regional left as well as right ventricular function.

Aim of the Work: To assess the use of right ventricular myocardial indices obtained by TDI in the diagnosis of right ventricular infarction and its relation to infarct related artery in patients with inferior myocardial infarction.

Subjects and Methods: We studied 32 patients (14 patients with inferior MI, 18 patients with inferior MI associated with RVMI) and 16 healthy subjects; all of them had 12-Lead electrocardiogram, standard echocardiographic study, TDI study of tricuspid annulus both at right ventricular free wall and interventricular septum, measuring myocardial systolic velocity (Sm), myocardial diastolic velocities (Em) and (Am), isovolumic relaxation time (IVR), isovolumic contraction time (IVC), ejection time (ET) and calculation of myocardial performance index (MPI), coronary angiography was done for patients group within one month.

Results: Patients with inf. MI and associated RVMI had significant reduction in Sm, Em, Am and ET at right ventricular free wall and septal level, with increase MPI and prolonged IVR at right ventricular free wall. In patients with proximal right coronary artery (RCA) Sm, Em and ET were reduced with prolonged MPI at right ventricular free wall. Stepwise logistic regression analysis of confounding variables showed that Sm and MPI were independent predictors for diagnosis of RVMI and proximal RCA from receiver operating characteristic curve (ROC) for diagnose of RVMI and proximal RCA the best cut of value of Sm and MPI were Sm <12cm/sec and MPI >0.7.

Conclusion: Measurement of right ventricular myocardial velocities and calculation of MPI is useful in diagnosis of right ventricular infarction and detection of patients with proximal (RCA) lesion.

Key Words: Tissue Doppler – Right ventricular infarction.

Introduction

Diagnosis of right ventricular infarction is important for adequate treatment of patients with inferior myocardial infarction [1] in those patients, the risk of in hospital death is high and major complications are greater [2,3], diagnosis of those patients depend on clinical data, ECG, as well as echocardiography.

Although the clinical triad of hypotension, absence of pulmonary congestion and elevated jugular venous pressure is quite specific, the sensitivity is only 10 to 25% [1]. Even when using additional chest leads electrocardiographic study, remains insufficient when compared with autopsy-proven MI. Two-dimensional echocardiography are used and may observe a hypo kinetic or a kinetic segment of the right ventricle [4], but these methods are occasionally insufficient due to complex shape of the right ventricle.
Tissue Doppler imaging (TDI) is an echocardiographic technique that enables myocardial velocities and makes the quantitative assessment of the systolic and diastolic movements of myocardial walls possible. And has been demonstrated to be an indicator of global and local left as well as right ventricular function [4].

**Aim of the work:**

The purpose of the present work was to assess the use of right ventricular myocardial indices obtained by TDI in the diagnosis of RVMI and its relation to the infarct-related artery (IRA) in patients with acute inferior MI.

**Patients and Methods**

We included 32 patients with inferior MI who referred to coronary care unit Zagazig University with acute inferior MI and 16 healthy age matched individual as control group. Patients were included in this study if they had:

- Inferior MI with (classic Chest pain, ST segment elevation of ≥0.1mV in two or more inferior leads, II, III, AVF and elevated cardiac enzyme), RVMI defined as ST-segment elevation of ≥0.1mV in V3R, V4R. We excluded patients with; previous MI, valvular disease, bundle-branch block, atrial fibrillation, primary or secondary pulmonary hypertension and cardiomyopathy. Our patients were classified according to presence or absence of right ventricular infarction into two groups; group I (Inferior wall MI; 14 patients), group II (inferior wall MI with right ventricular infarction; 18 patients) and group III (16 control subjects), also our patients were reclassified according to angiographic finding into three groups; group A (with proximal RCA lesion; 14 patients), group B (with distal RCA lesion; 6 patients) and group C (with LCX lesion; 8 patients). In our study four patients died from sudden cardiac death and cardiogenic shock before coronary angiography.

**Every patient was subjected to:**

- Careful history taking.
- Thorough clinical examination: General and (local cardiac examination).
- Standard 12-lead ECG and right pericardial lead (V3R and V4R).
- Blood sample for laboratory examination.

V- Conventional echocardiography: Echocardiographic examination were performed within 2 days after the onset of symptoms for each patient in supine and left lateral position using Hewlett Packard SONOS 5500 with 2.5MHz transducer. All standard views were obtained according to recommendation of American Society of Echocardiography [5].

VI- Tissue Doppler echocardiography: The TDI recordings were obtained by optimizing (minimizing) the gain and reducing the noise with the use of low wall filter settings (decrease Nequist scale i.e., 50Hz). From the apical four-chamber view, the TDI cursor was placed to the right ventricular free wall and the interventricular septum at the level of the tricuspid annulus in such a way that the annulus moved along the sample volume line.

1- A major positive (Sm) wave recorded with the movement of the annulus toward the cardiac apex during systole.

2- Two major negative velocities with the movement of the annulus toward the base of the heart during diastole, one during the early phase of diastole (Em) and another during the late phase of diastole (Am).

3- Sm duration was measured as the ejection time (ET).

4- Isovolumetric relaxation time (IVR) is the time between the end of the Sm and the beginning of the Em.

5- Isovolumetric contraction time (IVC) is the time between the end of Am and the beginning of Sm.

6- The right ventricular MPI was calculated as (IVR+IVC)/ET, by using the previous values obtained from the right ventricular free wall.

iv- Coronary angiography:

Coronary angiography was performed to detect the IRA within the first month after the MI. Significant coronary disease was defined as ≥70% stenosis.

**Statistics:**

Continuous variables were expressed as mean, standard deviation and were compared by t-test. Categorical variables were expressed as percentages and comparison was generated by chi square test. Stepwise logistic regression analysis to determine
factors that were independently associated with RVMI and proximal RCA. A cut off value for Sm and MPI was detected by ROC analysis sensitivity, specificity, PPV and NPV were done by standard tests.

**Results**

Demographic and lab. Data; (Table 1 and Fig. 1): there were significant decrease of systolic and diastolic blood pressure in group II ($p=0.001$) and significant increase of neck vein congestion and cardiac enzyme level in the same group ($p=0.001$).

Conventional echo data; (Table 2) RVD, Tricuspid Regurge, Mean pulmonary artery pressure and pulmonary artery systolic pressure were higher in group II, at mitral valve level the E wave and A wave were significantly lower with significant decrease of E/A ratio in group II ($p=0.001$).

TDI of right ventricular free wall; (Table 3) The mean systolic and diastolic velocities (Sm), (Em) and (Am) waves were reduced in group II ($p=0.001$). There were significant increase of IVR, IVC and MPI in group II ($p=0.001$). And significant decrease of ET in the same group.

TDI at interventricular septum; (Table 4) There were significant decrease of (Sm), (Em) and (Am) in group II ($p=0.001$). With significant decrease of Em/Am ratio in the same group ($p=0.001$). The IVC was increased in group II ($p=0.001$). With significant decrease of ET in the same group ($p=0.001$) but IVR did not show significant difference between examined groups ($p=0.5$).

Comparison based on angiographic finding (TDI of right vent. Free wall); (Table 5) The mean (Sm) and (Em), velocities were significantly decreased in group A ($p=0.001$) the mean IVR and MPI were significantly high in group A and significant decrease of ET in group A ($p=0.009$).

TDI at interventricular septum; (Table 6) The Sm and Em were significantly decrease in group A ($p=0.019$). And significant decrease of Em/Am in group A ($p=0.007$). And significant increase of IVC in the same group ($p=0.0015$).

Stepwise logistic regression analysis of confounding variables showed that Sm and MPI have a significant association with RVMI and proximal RCA (Table 7) with a ROC analysis cut of value of Sm and MPI were: Sm <12mm and MPI >0.7mm.

MPI of >0.70 and Sm <12cm/sec can diagnose RVMI, with high sensitivity (92.3%) and (85.7%), the MPI of >0.70 and Sm <12cm/sec can diagnose proximal RCA, with high specificity (87.5%) and (81.3%) (Table 8).
**Table 1**: Demographic and lab. data of examined groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n=14)</th>
<th>Group II (n=18)</th>
<th>Group III (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.7±10.4</td>
<td>56.1±6.2</td>
<td>53.6±8.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Gender male</td>
<td>11 (78.6%)</td>
<td>12 (60.7%)</td>
<td>12 (75%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (21.4%)</td>
<td>6 (33.3%)</td>
<td>4 (25%)</td>
<td>0.73</td>
</tr>
<tr>
<td>DM</td>
<td>8 (73.1%)</td>
<td>9 (50.0%)</td>
<td>9 (56.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>HTN</td>
<td>9 (64.3%)</td>
<td>14 (77.8%)</td>
<td>9 (60%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (71.4%)</td>
<td>11 (61.1%)</td>
<td>12 (75%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Dysplidemia</td>
<td>10 (71.4%)</td>
<td>10 (55.6%)</td>
<td>10 (62.5%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Troponin T</td>
<td>0.56±0.36</td>
<td>1.03±0.6*</td>
<td>0.004±0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>CK-MB g/ml</td>
<td>65.3±19.5</td>
<td>88.6±37.7*</td>
<td>20±5.1</td>
<td></td>
</tr>
</tbody>
</table>

DM = Diabetes mellities.
SBP = Systolic blood pressure.
HTN = Hypertension.

*p<0.05 when compare with group I.
**p<0.05 when compare with group I, II.

p-value ≤0.05 is Significant.

**Table 2**: Conventional echo finding.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n=14)</th>
<th>Group II (n=18)</th>
<th>Group III (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF%</td>
<td>58.2±7.05</td>
<td>57.6±10.1</td>
<td>65.6±9.3*</td>
<td>0.03</td>
</tr>
<tr>
<td>LVESSD (mm)</td>
<td>39.1±3.6</td>
<td>38.5±2.1</td>
<td>36.8±4.7</td>
<td>0.3</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>53.2±4.1</td>
<td>53.6±5.4</td>
<td>56.9±4.3</td>
<td>0.06</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>37.1±3.2</td>
<td>37.5±2.2</td>
<td>37.4±3.2</td>
<td>0.93</td>
</tr>
<tr>
<td>AOE (mm)</td>
<td>34.3±1.5</td>
<td>35.1±1.02</td>
<td>34.6±1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>25.3±1.86</td>
<td>29.9±2.65*</td>
<td>22.1±1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>10.6±1.3</td>
<td>10.9±2.09</td>
<td>10.9±1.2</td>
<td>0.59</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.6±1.2</td>
<td>11.0±9.3</td>
<td>10.8±7.1</td>
<td>0.5</td>
</tr>
<tr>
<td>TR no (%)</td>
<td>10 (71.4%)</td>
<td>15 (83.3%)*</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>27.2±2.1</td>
<td>34.5±2.2*</td>
<td>28.2±1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>37±2.9</td>
<td>44.9±2.7*</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>E wave (cm/sec)</td>
<td>71.6±9.1</td>
<td>52.1±6.7*</td>
<td>89.1±4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>A wave (cm/sec)</td>
<td>65.3±8.1</td>
<td>61.5±4.3*</td>
<td>79.9±4.8</td>
<td>0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.116±0.17</td>
<td>0.85±0.1*</td>
<td>1.119±0.07</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LVESESD = Left ventricular end systolic dimension.
LVEDD = Left ventricular end diastolic dimension.
LA = Left atrium.
AOE = Aortic excursion.
RVD = Right ventricular dimension.
IVST = Interventricular septal thickness.
PWT = Posterior wall thickness.
TR = tricuspid regurg.
MPAP = Mean pulmonary artery pressure.
PASP = Pulmonary arterial systolic pressure.

*p-value ≤0.05 is Significant.
Table 8: The sensitivity and specificity of Sm <12 cm/sec and RCA diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm &lt;12 cm/sec</td>
<td>85.7</td>
<td>61.3</td>
<td>50.0</td>
<td>90.5</td>
</tr>
<tr>
<td>MPI &gt;0.7</td>
<td>92.3</td>
<td>67.7</td>
<td>54.5</td>
<td>95.5</td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm &lt;12 cm/sec</td>
<td>64</td>
<td>81.3</td>
<td>75.0</td>
<td>72.2</td>
</tr>
<tr>
<td>MPI &gt;0.7</td>
<td>71.4</td>
<td>87.5</td>
<td>83.3</td>
<td>77.8</td>
</tr>
</tbody>
</table>

Discussion

The management and prognosis of right ventricular infarction differs substantially from that of left ventricular infarction [6]. Myocardial velocities and myocardial performance index (MPI), which are parameters assessing left ventricular function, can give information about right ventricular function as well [7,8]. So the present study was designed to test the use of the right ventricular myocardial indices obtained by pulsed-wave TDI in the diagnosis of RVMI and its possible usefulness in determining the infarct-related artery (IRA) in patients with acute inferior MI.

In our study the examined groups were age and gender matched, with no significant difference in CAD risk factors. Patients with associated inferior infarction presented with low systolic and diastolic blood pressure with congested neck veins because of reduced right ventricular contractility which lead to serious deterioration of both ventricular functions. With the concern to laboratory finding: The troponin level and CK-MB were significantly higher in those patients which reflect gross myocardial damage and bigger area of infarction, in conventional echo: Right ventricular diastolic dimension, TR and MPAP were greater in group with inferior and RVMI this is in agreement with Kidawa et al and Hisham et al [9,10]. The early filling E wave, late filling A wave and E/A ratio were significant lower in group with inferior and RVMI due to marked septal affection and more proximal coronary artery lesion with left ventricular dysfunction; this is agreement with Badran et al [11].

As regard tissue Doppler findings: We found that patients with inferior MI and RVMI had reduced peak Sm, Em, Am and ET when measured at RV free wall and septal level due to decreased systolic and diastolic function of right ventricle caused by greater damage; this is in agreement with Hisham et al, Badran et al and Zaborska et al [10,11,12] and disagree with Kidawa et al [9] who showed non significant difference mostly because they measured TDI velocities on the second day after primary coronary angioplasty in which the effective treatment may cause early recovery of right ventricular function. In the same patients IVC was prolonged at (RV) free wall and septal site but IVR was prolonged at RV free wall only, therefore; TDI of the septum may not be a good discriminator of RVMI, mostly because the tricuspid annular velocities at septal level could be affected by left ventricular function as the inter-ventricular septum has been considered to be a part of the left ventricle. Also myocardial performance index MPI of RV free wall was significantly high in patients who had additional RVMI. This index (MPI) is simple and useful method that is independent of heart rate [13], is unaffected by the geometric shape of the ventricle [14] with an excellent reproducibility between observer. In agreement with this result Tei et al [7] had shown that the right ventricular MPI is increased in patients with primary pulmonary hypertension. Eidem et al [15] also showed MPI increased significantly in patients with severe right ventricular insufficiency. Ozdemir et al [16] showed that MPI increased in patients with RVMI.

As regard angiographic data: Patients who had proximal RCA had decrease in Sm, Em at RV free wall and tricuspid annulus [11,12]. With decrease in E/A ratio of tricuspid annulus. This is agree with Ozdemir et al [16] and disagree with Kidawa et al [9]. 2006. This group of patients had prolonged IVR and reduced ejection time ET of right ventricular (RV) free wall, MPI of RV free wall was significantly high in patients who had proximal
RCA more than patient who had distal RCA or LCX; this is agree with Ozdemir et al, 2003 [16]. As MPI is an indicator of both systolic and diastolic functions, so increased MPI in patients with RVMI and proximal RCA suggests that systolic and diastolic RV functions are more deteriorated in those patients.

**Conclusion**

Measurement of right ventricular myocardial velocities and calculation of MPI is useful in diagnosis of right ventricular infarction and detection of patients with proximal (RCA) lesion.

**Clinical implication:** In patients with inf (MI) additional RVMI and proximal RCA lesion could be detected by the non invasive diagnostic tool (TDI) with high sensitivity and specificity and point to patients with high risk of major in hospital complications who need appropriate management.

**Study limitation:** Lake of true golden standard for diagnosis of RVMI and the use of ECG for this purpose.

**References**

Genetic Profile of Modifiable Risk Factors for Myocardial Infarction

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Myocardial infarction (MI) is the leading cause of death in North America and Europe and in many other countries in recent years. Framingham Study has identified a number of risk factors for CAD, but searching for new risk factors is going on. The association of certain genes with the traditional risk factors may have a strong predictive value in the near future. This will help the health system to early detect patients with possible high risk according to their genotypes, even before the appearance of the traditional risk factors.

Platelet glycoprotein Ia/IIa complex, an integrin platelet receptor, is expressed at low density on the platelet surface, with a wide variation within normal persons that results in variability of response to collagen. Gene polymorphism of α2 & β1 (the 2 polypeptide chains that form the Ia/IIa complex) results in variable receptor density and is associated with the occurrence of MI.

Plasminogen activator inhibitor (PAI-1) is a major regulator of the fibrinolytic system. An increased plasma level of PAI-1 results in less plasmin degradation of fibrin and thus, would be expected to be prothrombotic. Insertion or deletion of guanine (G) base at the promoter region of PAI-1 gene (i.e. gene polymorphism) influences the level of PAI-1. High levels of PAI-1 was observed in subjects with 4G/4G genotypes, intermediate levels in 4G/5G subjects and lowest levels in subjects with the 5G/5G genotype.

In this work, we tried to study the relation between the traditional risk factors for coronary artery disease and the genetic profile of patients who have already sustained an MI.

To achieve this goal, we studied 57 pts with uncomplicated acute MI including 49M and 8F (mean age: 54.7 yrs). Besides clinical evaluation, all patients were subjected to routine laboratory measurements, followed by DNA extraction from a peripheral venous sample. Platelet receptor (α2 β1) gene polymorphism was studied using restriction fragment length polymorphism (RFLP)-technique. Two sites in the intron G of α2 gene are of particular interest: Bgl II site (“A” at position 3160) which is associated only with allele 1 and Nde I site (“T” at position 3090), present in alleles 1 and 2, but absent in allele 3. For PAI-1 genotyping, a mutated oligonucleotide was used to insert a site for the restriction enzyme (Bsi Y1) in the product of amplification by PCR technique. Such restriction site enables the identification of the extra G base.

Among smoker group, pts who carried both the Platelet receptor genotype-1 and the PAI-1 genotype “5G” represented the highest percentage (50%) as compared to the other genotypes (33.3 and 16.7% for 4G and 4G/5G, respectively) - (p<0.05). Diabetics and dyslipidemics showed a higher distribution within platelet receptor genotype-1 if they carried simultaneously the heterozygous 4G/5G genotype as compared to other types of PAI-1 gene polymorphism (66.6, 88.9 and 90% for DM, high LDL-C and high TG, respectively) - (p<0.05). Pts carrying both Platelet receptor genotype-1 as well as heterozygous 4G/5G are more likely to have multiple risk factors (62.5%) than the homozygous 4G or 5G genotypes (18.8% for each) - (p<0.05).

We concluded that distribution of different risk factors differs according to genotypes, especially when considering gene-gene interaction. Among pts with MI, simultaneous presence of platelet receptor genotype-1 and PAI-1 4G/5G is associated with higher prevalence of diabetes and dyslipidemia, whereas patients carrying both Platelet receptor genotype-1 as well as the homozygous 4G or 5G genotypes are more likely to have single risk factors. The latter genotype combination may have a possible predictive value for developing MI in apparently low risk patients.

Key Words: Genetic profile – Myocardial infarction.

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Genetic Profile of Modifiable Risk Factors for Myocardial Infarction

Introduction

Myocardial infarction (MI) is the leading cause of death in North America and Europe and in many other countries in recent years. With the elderly representing an increasing proportion of the population who have a high incidence of and mortality from acute MI, it probably will remain the leading cause of death over the next several decades. Moreover, the increased incidence of diabetes and obesity stemming from a global shift to a Western diet and lifestyle will increase the sequelae of coronary artery disease (CAD) in the future [1].

Starting in 1948, the Framingham Study has identified a number of risk factors for CAD. Cigarette smoking was first addressed in 1960 and then dyslipidemia and hypertension followed. Later on, diabetes and Family history of premature CAD have been recognized among the traditional risk factors [2]. Those at highest multifactorial risk should be targeted for lifestyle intervention and hand in hand with drug therapies. Unfortunately, almost one half of patients who develop myocardial infarction do not have overt dyslipidemia. Therefore, new risk factors have been searched for over the last decade, e.g. homocysteine, Lp(a), fibrinogen and CRP [3,4].

CAD has long been known to 'run in families'. A small proportion of cases can be attributed to rare, highly penetrant, monogenic effects (e.g. LDLR, APOB and ABCG5 mutations), but most are multifactorial in aetiology, involving numerous environmental and heritable risk factors. The identification of specific susceptibility genes will add to our knowledge of the molecular pathophysiology of CAD, refine the identification of high-risk individuals and suggest areas of research for drug discovery [5].

Furthermore, recent advances in genetic and genomic approaches have allowed both genome-wide linkage mapping and large-scale gene-association studies to take place. Activation of platelets, thrombin generation and thrombus formation represent the dynamic process that lead to acute coronary thrombosis. Various gene polymorphisms may affect the progress of these events in the context of acute MI [6].

Platelet glycoprotein Ia/IIa complex, an integrin platelet receptor, is expressed at low density on the platelet surface, with a wide variation within normal persons that results in variability of response to collagen. Gene polymorphism of α2 & β1 (the 2 polypeptide chains that form the Ia/IIa complex) results in variable receptor density and is associated with the occurrence of MI [7].

Plasminogen activator inhibitor (PAI-1) is a major regulator of the fibrinolytic system. An increased plasma level of PAI-1 results in less plasmin degradation of fibrin and thus, would be expected to be prothrombotic. Insertion or deletion of guanine (G) base at the promoter region of PAI-1 gene (i.e. gene polymorphism) influences the level of PAI-1. High levels of PAI-1 was observed in subjects with 4G/4G genotypes, intermediate levels in 4G/5G subjects and lowest levels in subjects with the 5G/5G genotype [8].

In this work, we tried to study the relation between the traditional risk factors for coronary artery disease and the genetic profile of patients who have already sustained an MI. The relation between the number of risk factors will be assessed in relation to various genotypes as regards PAI-1 4G/5G and platelet receptor α2 polymorphisms.

Methods

Study population:

We studied 57 patients with uncomplicated acute MI including 49M and 8F (mean age: 54.7 yrs), admitted to the Critical Care Department of Cairo University from May 2003 to May 2005.

Assessment of risk factors:

Besides proper history taking and thorough clinical evaluation, patients included in the study were subjected to routine laboratory investigations including fasting blood sugar, serum low density lipoprotein-cholesterol (LDL-C) and serum triglycerides (TG). Patients identified as ex-smoker are those who have completely given up smoking for at least 5 years.

Platelet receptor genotyping:

DNA extraction was performed from a peripheral venous sample, using QIAamp Blood Mini Kit (Qiagen).

The following primers were used:

5’ GATTAAACTTTCCCAGACTGCTTC 3’
5’ CATAGGTGTGTGGGAACAGGTGG3’

Amplification of intron G was carried out. Fifty microliters of polymerase chain reaction contained 25µl master mix, 5µl of genomic DNA and 12pmol of each primer.
Samples were incubated at 95°C for 5 minutes, followed by 30 cycles of:
- Danaturation at 95°C for 1 minute.
- Annealing at 60°C for 1 minute.
- Extension at 72°C for 1 minute and final extension at 72°C for 7 minutes.

The amplification product contains sites upon which the restriction enzymes Bgl II and Nde I act.

Nde I is a restriction endonuclease enzyme derived from Neisseria denitrificans. It recognizes the sequence 5’-CA/TA TG-3’.

Bgl II is derived from Bacillus globigii and recognizes the sequence 5’-A/GA TCT-3’.

Ten microliters of the PCR product was digested with 10 units restriction enzyme (both Nde I and Bgl II were used separately at 37°C overnight) and run by electrophoresis in a 2% agarose gel and visualized directly by ethidium bromide staining.

To achieve an easy and rapid evaluation of the common guanosine insertion/deletion polymorphism at position -675 of the PAI-1 gene, a protocol based on PCR technique and a restriction enzyme was developed by Margaglione et al., 1997. A mutated oligonucleotide was used to insert a site for the Bsi YI restriction enzyme in the product of amplification. Bsi YI is generated from Bacillus species and recognizes the sequence 5’-CCNNNNN/NNCC-3’. Such restriction site enables the identification of the extra G base. Two primers (oligonucleotides) were used; a 22 (−697/−676) forward oligonucleotide, with a C>−681A substitution: 5’ CACAGAGAGTCTGGCCACGT 3’ and a 21 (−598/−619) reverse oligonucleotide: 5’ CCAACAGAGGACTCTTGGTCT 3’

PCR was performed in a final volume of 50µl that contained 25µl master mix, 5µl of genomic DNA and 15pmol of each primer.

DNA was amplified for 30 cycles, each cycle composed of:
- Denaturation at 95°C for 1 minute.
- Annealing at 60°C for 1 minute, then.
- Extension at 72°C for 2 minutes.

Then, 20µl of the amplification products (99bp for the 5G and 98 for the 4G) were digested for 150 minutes with 1 unit of the Bsi YI restriction enzyme and the fragments (a single one of 98bp for the 4G allele and 2 fragments of 77 and 21 bp respectively for the 5G allele) were fractionated by 4.5% agarose gel electrophoresis and identified by ethidium bromide staining [10].

DNA extraction was performed from a peripheral venous sample, using QIAamp Blood Mini Kit (Qiagen).

Detection of this polymorphism is commonly carried out by allele specific oligonucleotide melting technique. This method needs to be carefully optimized so that, under stringent conditions only perfectly matched probes will bind to the target allele.

To achieve an easy and rapid evaluation of the common guanosine insertion/deletion polymorphism at position -675 of the PAI-1 gene, a protocol based on PCR technique and a restriction enzyme was developed by Margaglione et al., 1997. A mutated oligonucleotide was used to insert a site for the Bsi YI restriction enzyme in the product of amplification. Bsi YI is generated from Bacillus species and recognizes the sequence 5’-CCNNNNN/NNCC-3’. Such restriction site enables the identification of the extra G base. Two primers (oligonucleotides) were used; a 22 (−697/−676) forward oligonucleotide, with a C>−681A substitution: 5’ CACAGAGAGTCTGGCCACGT 3’ and a 21 (−598/−619) reverse oligonucleotide: 5’ CCAACAGAGGACTCTTGGTCT 3’

PCR was performed in a final volume of 50µl that contained 25µl master mix, 5µl of genomic DNA and 15pmol of each primer.

DNA was amplified for 30 cycles, each cycle composed of:
- Denaturation at 95°C for 1 minute.
- Annealing at 60°C for 1 minute, then.
- Extension at 72°C for 2 minutes.

Then, 20µl of the amplification products (99bp for the 5G and 98 for the 4G) were digested for 150 minutes with 1 unit of the Bsi YI restriction enzyme and the fragments (a single one of 98bp for the 4G allele and 2 fragments of 77 and 21 bp respectively for the 5G allele) were fractionated by 4.5% agarose gel electrophoresis and identified by ethidium bromide staining [10].

PAI-1 Genotyping:
DNA extraction was performed from a peripheral venous sample, using QIAamp Blood Mini Kit (Qiagen).

Detection of this polymorphism is commonly carried out by allele specific oligonucleotide melting technique. This method needs to be carefully optimized so that, under stringent conditions only perfectly matched probes will bind to the target allele.

Data management and statistical analysis:
All collected data were revised for completeness and logical consistency. They were coded and entered on computer for analysis. A database was
developed on "Excel" for data entry. Data was then transferred to SPSS version 11 for analysis.

Simple frequencies were used for data checking. Bivariate relationships are displayed in cross tabulations and graphs to illustrate simple data. Appropriate statistical test of significance "Chi square" was used to test the null hypothesis in comparison of risk factors among the studied group.

Results

Out of the 57 pts included in this study, 56.1% (n=32) were smokers, 40.4% (n=23) were diabetic, 42.1% (n=24) were hypertensive, 29.8% (n=17) had high LDL-C and 35.1% (n=20) had hypertriglyceridemia (Table 1, Fig. 3).

Table 1: Percent distribution of modifiable risk factors within the study population.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>32</td>
<td>56.1</td>
</tr>
<tr>
<td>Diabetic</td>
<td>23</td>
<td>40.4</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>24</td>
<td>42.1</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>17</td>
<td>29.8</td>
</tr>
<tr>
<td>High TG</td>
<td>20</td>
<td>35.1</td>
</tr>
</tbody>
</table>

LDL-C = Low density lipoprotein cholesterol.
TG     = Triglycerides.

Figure 3: Percent distribution of modifiable risk factors within the study population.

(DM = Diabetes mellitus, HTN = Hypertension, LDL-C = Low density lipoprotein cholesterol, TG = Triglycerides).

Table (2) and Fig. (4) show the percent distribution of different genotypes of platelet receptor α2 polymorphism:

Table 2: Percent distribution of different genotypes of platelet receptor α2 polymorphism.

<table>
<thead>
<tr>
<th>Platelet receptor genotype</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype-1</td>
<td>24</td>
<td>42.1</td>
</tr>
<tr>
<td>Genotype-2</td>
<td>21</td>
<td>36.8</td>
</tr>
<tr>
<td>Genotype-3</td>
<td>12</td>
<td>21.1</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 4: Percent distribution of different genotypes of platelet receptor α2 polymorphism.

Table 3: Percent distribution of different genotypes of PAI-1 polymorphism.

<table>
<thead>
<tr>
<th>PAI-1 genotype</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>4G</td>
<td>19</td>
<td>33.3</td>
</tr>
<tr>
<td>5G</td>
<td>18</td>
<td>31.6</td>
</tr>
<tr>
<td>4G/5G</td>
<td>20</td>
<td>35.1</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 5: Percent distribution of different genotypes of PAI-1 polymorphism.
Distribution of platelet receptor genotypes within various modifiable risk factors for CAD was assessed. Percentage of both genotype 1 and 2 among smokers was significantly higher than genotype 3 ($p<0.05$), whereas the distribution of the three genotypes did not differ significantly within the other risk factors (Table 4, Fig. 6).

4G/5G was also higher among dyslipidemic patients as compared to the other 2 genotypes with statistically significant difference ($p<0.05$), (Table 5, Fig. 7).

**Table 4:** Percent distribution of Platelet Receptor Genotype according to modifiable risk factors.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>PL-REC Genotype</th>
<th>G-1</th>
<th>G-2</th>
<th>G-3</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker (N=32)</td>
<td>N %</td>
<td>12</td>
<td>12</td>
<td>25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetic (N=23)</td>
<td></td>
<td>11</td>
<td>7</td>
<td>5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hypertensive (N=24)</td>
<td></td>
<td>12</td>
<td>10</td>
<td>8.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>High LDL-C (N=17)</td>
<td></td>
<td>9</td>
<td>2.9</td>
<td>2.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>High TG (N=20)</td>
<td></td>
<td>10</td>
<td>5</td>
<td>25</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

$G =$ Genotype. $TG =$ Triglycerides. $LDL-C =$ Low density lipoprotein-cholesterol. $PL-REC =$ Platelet receptor.

**Table 5:** Percent distribution of PAI-1 Genotype according to modifiable risk factors.

<table>
<thead>
<tr>
<th>PAI-1 Genotype</th>
<th>4G N %</th>
<th>5G N %</th>
<th>4G/5G N %</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker (N=32)</td>
<td>9 28.1</td>
<td>14 43.8</td>
<td>9 28.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetic (N=23)</td>
<td>11 47.8</td>
<td>2    8.7</td>
<td>10 43.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertensive (N=24)</td>
<td>8    33.3</td>
<td>7    29.2</td>
<td>9 37.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>High LDL-C (N=17)</td>
<td>6    35.3</td>
<td>1    5.9</td>
<td>10 58.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>High TG (N=20)</td>
<td>6    30.0</td>
<td>2    12</td>
<td>10 60.0</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

$G =$ Genotype. $LDL-C =$ Low density lipoprotein-cholesterol. $TG =$ Triglycerides. $PAI-1 =$ Plasminogen activator inhibitor type 1 gene.

**Figure 6:** Percent distribution of Platelet Receptor Genotype according to modifiable risk factors.

(DM = Diabetes mellitus, G = Genotype, HTN = Hypertension, LDL-C = Low density lipoprotein-cholesterol, PL-REC = Platelet receptor, TG = Triglycerides).

Distribution of PAI-1 genotypes within various modifiable risk factors for CAD was also assessed. Percentage of both genotypes 4G and 4G/5G among diabetics was significantly higher than 5G genotype ($p<0.05$). The percentage of heterozygous genotype 4G/5G was also higher among dyslipidemic patients as compared to the other 2 genotypes with statistically significant difference ($p<0.05$), (Table 5, Fig. 7).

Then, we assessed percent distribution of multiple genotypes according to risk factors. Distribution of both Platelet receptor and PAI gene polymorphisms was assessed within different risk factors. Among smoker group, pts who carried both the Platelet receptor genotype-1 and the PAI-1 genotype "5G" represented the highest percentage
as compared to the other genotypes. Diabetics and dyslipidemics showed a higher distribution within platelet receptor genotype-1 if they carried simultaneously the heterozygous 4G/5G genotype as compared to other types of PAI-1 gene polymorphism (Table 6, Fig. 8).

Table 6: Percent distribution of multiple genotypes according to risk factors. Percentages were calculated for each single risk factor within every platelet receptor genotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Risk Factors</th>
<th>PL-REC 1</th>
<th>PL-REC 2</th>
<th>PL-REC 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4G</td>
<td>5G</td>
<td>4G/5G</td>
<td>4G</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>p value</td>
<td>33.3%</td>
<td>50%</td>
<td>16.7%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>p value</td>
<td>27.3%</td>
<td>0.0%</td>
<td>66.7%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>p value</td>
<td>16.7%</td>
<td>33.3%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>High LDL-C</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>p value</td>
<td>11.1%</td>
<td>0.0%</td>
<td>88.9%</td>
<td>80%</td>
</tr>
<tr>
<td>High TG</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>p value</td>
<td>10%</td>
<td>0.0%</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Table 6: Percent distribution of multiple genotypes according to risk factors. Percentages were calculated for each single risk factor within every platelet receptor genotype.

Figure 8: Percent distribution of Platelet receptor and PAI-1 genotypes within modifiable risk factors.

The presence of single versus multiple risk factors was assessed in the patients included in the study according to their genotypes. Patients carrying both Platelet receptor genotype-1 as well as heterozygous 4G/5G are more likely to have multiple risk factors than the homozygous 4G or 5G genotypes. This difference is statistically significant (Table 7, Fig. 9).
In this study, we focused on a group of patients with CAD who have already sustained MI. We tried to assess their genetic background as regards two important genes that may be involved in the pathophysiology of arterial thrombosis; namely platelet receptor α2 and PAI-1 gene polymorphisms.

In the present study, genotype-1 of platelet receptor polymorphism showed the highest percentage followed by genotype-2 and genotype-3. This is different from the distribution described by previous studies in the normal population with a higher prevalence of genotype-2 followed by genotype-1 then genotype-3 [11]. This may reflect an association between genotype-1 and AMI. However, further studies should be carried on to verify the distribution of these alleles in the normal Egyptian population.

The significance of the α2 alleles in arterial thrombosis has been evaluated in several studies. The initial report described a correlation between allele 1 (high receptor density) and risk for myocardial infarction [11]. In a larger study on patients undergoing angiography, an association between allele 1 and myocardial infarction was observed in younger patients [12]. Gene polymorphism of α2 results in variable receptor density and is associated with the occurrence of MI. The number of α2 molecules per platelet varies by an order of magnitude and correlates precisely with quantitative estimates of platelet adhesion to type I or type III collagens. The high frequency genotype 1 of the α2 gene shows high receptor density whereas genotype 2 and 3 show low receptor density [7]. High density of platelet integrin receptors may result in enhancement of platelet aggregation that plays an important role in the pathogenesis of acute coronary syndrome.

In our study, the prevalence of different PAI-1 genotypes was comparable (35.1, 33.3 and 31.6% for 4G/5G, homozygous 4G and homozygous 5G respectively).

The sequence length polymorphism (4G/5G) in the promoter region of the PAI-1 gene was identified by Dawson et al, 1993. This polymorphism contributes to PAI-1 expression since individuals with the 4G/5G genotype have 25% higher PAI-1 levels than those with the 5G/5G genotype [13].

PAI-1 is a major regulator of the fibrinolytic system. An increased plasma level of PAI-1 results in less plasmin degradation of fibrin and thus, would be expected to be prothrombotic. PAI-1 levels are regulated by genetic and environmental factors. In addition, increased PAI-1 could potentiate plaque formation not only through its effects on the fibrinolytic system in blood, but also by enhancing persistence and propagation of microthrombi, known to contain clot-associated mitogens.

### Table 7: Percent distribution of genotypes according to number of risk factors.

<table>
<thead>
<tr>
<th>No. of risk Genotype</th>
<th>Single risk (N:24)</th>
<th>Multiple risks (N:31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL-REC 1 4G</td>
<td>3 42.9%</td>
<td>3 18.8%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5G</td>
<td>4 57.1%</td>
<td>3 18.8%</td>
<td></td>
</tr>
<tr>
<td>4G/5G</td>
<td>0 0.0%</td>
<td>10 62.5%</td>
<td></td>
</tr>
<tr>
<td>PL-REC 2 4G</td>
<td>4 33.3%</td>
<td>5 55.6%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>5G</td>
<td>4 33.3%</td>
<td>1 11.1%</td>
<td></td>
</tr>
<tr>
<td>4G/5G</td>
<td>4 33.3%</td>
<td>3 33.3%</td>
<td></td>
</tr>
<tr>
<td>PL-REC 3 4G</td>
<td>2 40.0%</td>
<td>2 33.3%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>5G</td>
<td>3 60.0%</td>
<td>2 33.3%</td>
<td></td>
</tr>
<tr>
<td>4G/5G</td>
<td>0 0.0%</td>
<td>2 33.3%</td>
<td></td>
</tr>
</tbody>
</table>

PL-REC = Platelet receptor gene.
4G, 5G, 4G/5G = PAI-1 genotypes.
LDL-C = Low density lipoprotein-cholesterol.
TG = Triglycerides.

### Figure 9: Percent distribution of genotypes according to number of risk factors.

(DM = Diabetes mellitus, G = Genotype, 4G, 5G and 4/5 are PAI-1 genotypes, HTN = Hypertension, LDL-C = Low density lipoprotein-cholesterol, PL-REC = Platelet receptor, TG = Triglycerides).

**Discussion**

In this study, we focused on a group of patients with CAD who have already sustained MI. We tried to assess their genetic background as regards two important genes that may be involved in the pathophysiology of arterial thrombosis; namely platelet receptor α2 and PAI-1 gene polymorphisms.

In the present study, genotype-1 of platelet receptor polymorphism showed the highest percentage followed by genotype-2 and genotype-3.
exacerbating "atherothrombosis", would be favored by PAI-1 overproduction [14].

The 4G polymorphism has been associated with MI at young age in a study that patients after their first MI. These men were younger than 45 years of age and had genetic analysis and their PAI-1 levels measured 4 to 6 months after the index event. The frequency of the 4G allele was significantly higher among young post-infarction patients than among control subjects. PAI-1 activity was significantly higher in the control group, who were homozygous for the 4G allele [13]. In the present study, patient’s age was of wide range (34-76 years). This may explain why the genotype distribution in our results is not consistent with the aforementioned study.

On the other hand, in a meta-analysis, there was a weak association of the 4G/4G genotype and myocardial infarction; particularly in high risk groups. This study was specifically designed to explore the potential effect of PAI-1 genotype on responses to the acute phase stimulus as represented by AMI. There were no significant differences observed in the levels of PAI-1 activity or antigen between the three PAI-1 genotypes during the course of AMI or at follow-up [15].

Similarly, Ossei-Gerning et al, 1997 showed no relationship has been found between either PAI-1 levels or genotype and the presence of atheroma, characterized by coronary angiography [16]. An important question should be raised here: Is it important to consider gene-gene interaction i.e. the interaction between PAI-1 gene and other genes like, for instance, platelet receptor genes in the context of CAD?

Among patients who smoke: platelet receptor genotype-1 and PAI-1 4G/5G is associated with higher incidence of diabetes and dyslipidemia.

In the present study, simultaneous presence of platelet receptor genotype-1 and PAI-1 4G/5G is associated with higher incidence of diabetes and dyslipidemia.

The regulation of PAI-1 expression through the 4G/5G polymorphism is modified by plasma triglyceride levels [20] and perhaps insulin as well [21]. In vitro work has shown proinsulin increase expression of PAI-1 mRNA in bovine aortic endothelial cells, an effect not mediated via the insulin or insulin-like growth factor receptor [22]. Nordt et al, 1998 showed that intravenous infusion of proinsulin in rabbits leads to an increase in plasma PAI-1 activity and increased PAI-1 mRNA in aorta and liver.

Allison et al, 1999 studied activation of PAI-1 protein and mRNA expression by native LDL (nLDL), UV-oxidized LDL (uvLDL) and triglyceride (TG)-enriched LDL in human umbilical vein endothelial cells (HUVECs) by using different incubation times and a wide range of lipoprotein concentrations. The results indicate that the TG content of the LDL particle influences PAI-1 expression in endothelial cells. Low concentrations of uvLDL enhanced PAI-1 protein and mRNA expression in the HUVECs after an 18-hour incubation but did not influence the VLDL-inducible transcription factor [24].

We tried to assess the distribution of patients who have either single or multiple risk factors among various genotypes. Our results showed that Patients carrying both Platelet receptor genotype-1 as well as the homozygous 4G or 5G genotypes are more likely to have single risk factors than heterozygous 4G/5G. Adding the fact that all the patients included in the study have already sustained MI, we can draw the conclusion of the potential importance of this gene-gene interaction may be a possible new predictor of developing MI in an apparently low risk group. Further studies on larger population of MI and CAD patients are needed to confirm such a hypothesis.

In conclusion, this study is an attempt to stress the importance of certain genes that may play a role in the pathophysiology of arterial thrombosis in patients with CAD. Distribution of different risk factors differs according to genotypes, especially when considering gene-gene interaction. Among pts with MI, simultaneous presence of platelet receptor genotype-1 and PAI-1 4G/5G is associated
with higher incidence of diabetes and dyslipidemia, whereas patients carrying both Platelet receptor genotype-1 as well as the homozygous 4G or 5G genotypes are more likely to have single risk factors. The latter genotype combination may have a possible predictive value for developing MI in apparently low risk pts.

Acknowledgement:
We acknowledge the great effort of Chemists: Soheir Mahmoud, Yasser Ramadan and Yasser Salah in accomplishing this work.

References
The Relation between Microalbuminuria and Coronary Collateral Vessels Development in Patients with Acute Coronary Syndrome

WALID MAAMOUN, MD*; ADEL HASAN, MSc**

**Background**: It has been shown that Microalbuminuria (MA) is independently associated with all cause mortality and cardiovascular morbidity and mortality in the general population [2,3], and in the general population [5,6]. As the association between proteinuria and cardiovascular events is well described [7], some recent studies proved that CAD patients with microalbuminuria had much greater atherosclerotic burden in the form of multi-vessel disease than those without microalbuminuria, the actual pathogenic mechanism is not well established but suggested to be found in endothelial dysfunction [8]. Coronary collateral vessels (CCVs) can provide a perfusion reserve in case of increased myocardial oxygen demand and the most important element in the cascade of collateral growth is the endothelium [9]. We hypothesized that in patients with ACS, microalbuminuria which has been suggested as a marker of systemic vascular disease and endothelial dysfunction [10,11] affects the CCVs.

**Methods**: The subjects, 100 non-diabetic non-hypertensive patients (91 men and 9 women: mean age 54.4±10.4) who were presented as a case of acute coronary syndrome; were classified as microalbuminuria-negative (<20 mg/L) and microalbuminuria-positive (>20mg/L) after measuring the level of urine albumin by spot urine examination in first day of admission. Coronary angiography was done later with assessment of the CCVs on the basis of Rentrop classification: 0= no filling of any collateral vessels, 1= filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2= partial filling of the epicardial artery by collateral vessels, and 3= complete filling of the epicardial artery by collateral vessels.

**Results**: There were no significant differences between both groups as regard the baseline clinical characteristics. CCVs development was poorer in Microalbuminuria-positive patients than microalbuminuria-negative patients (33% vs 62%; \( p=0.007 \)). Patients with microalbuminuria compared with the normalbuminuria had increased prevalence of two and three vessel disease (67% vs 46%, \( p=0.005 \)).

**Conclusion**: Non diabetic non hypertensive ACS Patients with microalbuminuria had poorer CCVs development than those without microalbuminuria. The results indicate that microalbuminuria exhibits a significant association with the CCVs development.

**Key Words**: Microalbuminuria – Coronary collateral vessels – Acute coronary syndrome.
development negatively. The purpose of this study was to evaluate the relation between microalbuminuria and development of CCVs in non-diabetic non-hypertensive patients.

**Methods**

**Study population:**

We studied 100 non-diabetic non-hypertensive patients (91 men and 9 women: mean age 54.4±10.4) who were presented as a case of acute coronary syndrome; angiographically documented, in the University of science and technology hospital between November 2008 and June 2009. Patients with previous revascularization or heart failure (EF less than 40%) were excluded from the study. Patients with renal disease, acute or chronic inflammatory diseases, those on statin and ACE-I/ARBs therapy were also excluded from the study, as these conditions may influence collateral development and the level of microalbumin in urine. Patients with coronary artery stenosis less than 75% were excluded from the study for insufficient development of CCVs.

We collected data on well recognized cardiovascular risk factors such as age, dyslipidaemia, obesity and smoking. We also collected data on microalbuminuria (MA). Urine albumin was measured at the same day of admission by spot urine examination. Patients with albumin levels more than 20 mg/L were considered positive for microalbuminuria (group I) and those with albumin levels less than 20mg/L were considered negative for microalbuminuria (group II) [12].

**Coronary angiography and grading of coronary collateral filling:**

Selective coronary angiography was performed in multiple orthogonal projections using the Judkins technique after administration of 5000IU intravenous bolus of heparin. Coronary artery stenoses were estimated visually by 2 independent observers who were blinded to the identities and clinical information of the patients. Single-vessel disease was defined as ≥75% diameter stenosis in only 1 coronary artery. Two- and 3-vessel diseases were defined according to the same criteria. Collateral vessels were graded according to the Rentrop classification: 0= no filling of any collateral vessels, 1= filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2= partial filling of the epicardial artery by collateral vessels, and 3= complete filling of the epicardial artery by collateral vessels. The collateral score was based on the injection that best opacified the collateralized vessel [13]. Written informed consents were obtained from all patients.

**Statistical analysis:**

Statistical analysis was performed with SPSS version (17.0). The differences between the continuous variables are expressed as mean ± SD. Comparisons between continuous variables were carried out with the unpaired Student’s t-test, whereas the chi-square test was performed for the comparison of the proportions of each categorical variable between the patients with and without microalbuminuria. p≤0.05 was considered statistically significant.

**Results**

Table (1) describes the clinical baseline characteristics of the study patients. The two groups were matched in terms of baseline clinical characteristics. Mean age and distribution of risk factors for coronary disease were not significantly different between groups. The majority of patients were males in both groups.

**Table 1:** Comparison of baseline clinical variables for study patients.

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>MA (n=48)</th>
<th>NA (n=52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±9.97</td>
<td>54±9.32</td>
<td>NS</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>45 (94%)</td>
<td>46 (88%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>20.8±4.14</td>
<td>19.1±2.71</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>36 (75%)</td>
<td>36 (69%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidaemia n (%)</td>
<td>8 (17%)</td>
<td>8 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>EF %</td>
<td>50±0.059</td>
<td>52±0.072</td>
<td>NS</td>
</tr>
<tr>
<td>STEMI n (%)</td>
<td>20 (42%)</td>
<td>16 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>NSTEMI n (%)</td>
<td>12 (25%)</td>
<td>16 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina n (%)</td>
<td>16 (33%)</td>
<td>20 (38%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The mean number of diseased vessels was higher in microalbuminuria group (1.9 vs 1.7, p≤0.05). One vessel disease occurred more frequently in the normalalbuminuria group (54% vs 33%, p 0.007). In contrast, the two and three vessel disease occurred more frequently in the microalbuminuria group (67% vs 46%, p 0.005) (Table 2).

**Table 2:** Comparison of angiographic findings between microalbuminuria and normoalbuminuria patients.

<table>
<thead>
<tr>
<th>Coronary artery disease n (%)</th>
<th>MA (n=48)</th>
<th>NA (n=52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>One vessel disease</td>
<td>16 (33%)</td>
<td>28 (54%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Two vessel disease</td>
<td>20 (42%)</td>
<td>12 (23%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Three vessel disease</td>
<td>12 (25%)</td>
<td>12 (23%)</td>
<td>0.013</td>
</tr>
<tr>
<td>2 &amp; 3 vessel disease</td>
<td>32 (67%)</td>
<td>24 (46%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Rentrop score:

| ≥1                             | 32 (67%) | 20 (38%) | 0.006 |
| 0                              | 16 (33%) | 32 (62%) | 0.007 |
Coronary collaterals were present in 48 (48%) patients; 24 patients had grade 1 collaterals, 12 had grade 2 collaterals, and 12 had grade 3 collaterals (Fig. 1).

Microalbuminuria is a predictor of the development of ischemic heart disease, independent of other established atherosclerotic risk factors. Microalbuminuria may represent an early marker of diffuse vascular endothelial dysfunction in patients with and without diabetes mellitus [8]. The prognostic significance of microalbuminuria in patients with myocardial infarction in unselected general patients has been observed earlier [14]. Randomized placebo-controlled trials such as The Heart Outcomes Prevention Evaluation Study have revealed that treatment of persons with baseline cardiovascular disease or persons with important absolute risk of cardiovascular disease, based on a constellation of risk factors including microalbuminuria offers significant primary and secondary prevention against cardiovascular disease [15]. Albuminuria, even within the normal range, is an independent predictor of cardiovascular and all-cause mortality in patients with stable coronary artery disease [16].

The underlying mechanism of the association between microalbuminuria and cardiovascular disease risk is unclear. A pathophysiologic link between micro-albuminuria and atherosclerosis may be mediated through an increased generalized trans-vascular leakage of albumin. It is hypothesized that the systemic trans-vascular leakiness may also include lipoproteins, thus allowing for increased lipid penetration into the vessel walls. The leakiness might be because of hemodynamic factors or structural or functional perturbations of the endothelium or intracellular matrix beneath [9]. As there is no definite mechanism directly linking atherothrombotic disease to the urinary albumin loss, endothelial dysfunction has been suggested to be the pathophysiological process that causes both increased renal albumin loss and coronary artery disease endothelial dysfunction, which occurs early in the atherosclerotic process [17].

Coronary collaterals may help in the protection of myocardium in patients with coronary artery disease, as they limit myocardial ischemia during coronary occlusion [18]. It is now widely accepted that myocardial ischemia somehow triggers collateral growth [19,20]. A biochemical signal produced by ischemic myocardium may trigger the events leading to DNA synthesis and to mitosis in collateral vessels [21]. During collateral development, the collaterals actively grow, as is evidenced by mitotic activity in both endothelial and smooth muscle cells [22]. The endothelium leads the process of growth adaptation; smooth muscle follows [23].

Discussion

Our data indicated that CCVs development is poorer in non-diabetic, non-hypertensive patients with microalbuminuria than patients with normoalbuminuria. To our knowledge, there are no data on the influence of microalbuminuria on collateral development in patients with ACS.
The Relation between Microalbuminuria & Coronary

In a canine model of myocardial ischemia, intracoronary infusion of vascular endothelial growth factor into the ischemic territory has been shown to accelerate native collateral development [24].

Because the function of the endothelium is important in collateral development and there is dysfunction of endothelium in association with the presence of microalbuminuria, our finding that the prevalence of collateral circulation in patients with microalbuminuria is much lower than those without microalbuminuria may be explained by the effect of endothelial dysfunction and systemic vascular disease on patients with microalbuminuria in acute coronary syndrome.

Conclusion
To our knowledge this study is the first in microalbuminuria patients with ACS that shows the relation between microalbuminuria and CCVs development. It shows that collateral vessels development is poorer in patients with microalbuminuria than in patients with normoalbuminuria.

Study limitations:
In the interpretation of our findings, three limitations must be considered. First, regular physical exercise encourages the development of coronary collateralization. In our study, there are no data about physical activity of the patients. Second, coronary collateral vessels could not have been developed in early period in patients with ACS. Third, angiographically visible collaterals represent only a fraction of the total collateral vessels because collaterals are angiographically demonstrable only when they reach 100 µm. Therefore, the collaterals visualized by angiography may not accurately quantify collateral circulation. But the effect of this problem on collateral score must be same in the 2 groups and thus should not change the interpretation of our results.

References


Correlation between VEGF and the Severity of Non ST Elevation Acute Coronary Syndrome

AHMED BATTAH, MD; EMAD OMAR, MD; TAREK EL GOHARY, MD; AHMED MOWAFIE, MD; SHEREEN EL-GENGEHY, MD; MOHAMED HAMDY, MSch; HOSSAM MOWAFI, MD

Background: VEGF is a key regulator of angiogenesis. It is thought to be implicated in the pathogenesis of atherosclerotic plaque neovascularization and thus promotes its infiltration by inflammatory cells with subsequent destabilization.

Aim: To investigate the level of the vascular endothelial growth factor in patients with acute coronary syndrome and whether it is correlated with the severity of the disease and the short in-hospital prognosis.

Methods: The study was conducted on 78 patients with an average age 54.7±9 yrs. Patients were classified into: Group 1: included 31 patients with unstable angina. Group 2: included 26 patients who presented with non ST segment elevation infarction. Both groups were subdivided according to the prior statin use into: Group 1A: included 16 statin treated patients. Group 2A: included 13 statin treated patients. Group 1B: included 15 non statin treated patients. Group 2B: included 13 non statin treated patients. A group of 21 patients with normal coronary angiogram was used as a study control. All patients were subjected to ECG, echocardiography, routine laboratory investigations, also measurement of the serum VEGF by quantitative enzyme linked immunosorbant assay. Extent and severity of CAD was graded using a modified Gensini score. During hospitalization, the major cardiovascular complications were assessed.

Results: The serum level of VEGF was significantly higher in 1B and 2B groups relative to control patients, while 1A and 2A groups had significantly lower serum level of VEGF than controls. The serum VEGF level did not show any significant difference between unstable angina patients and NSTEMI patients either in previously statin treated or non treated patients. Also, there was no significant correlation between the serum level of VEGF and the extent and severity of CAD. Recurrent ischemic attacks were significantly higher in patients with higher serum VEGF level compared with those with low serum VEGF level. Regarding CHF, it occurred more in patients with higher serum VEGF level compared with patients with low serum VEGF level. However, there was no significant correlation between arrhythmias or development of cardiogenic shock and the serum level of VEGF.

Conclusion: VEGF serum level is higher in non statin treated patients presenting with acute coronary syndrome and it may predict an adverse in-hospital prognosis but there was no correlation between VEGF serum level and angiographically defined disease severity and extent.

Key Words: Vascular endothelial growth factor – Non STEMI.
**Aim of the study:**

This study aims to investigate the VEGF serum level in patients presented with non ST elevation acute coronary syndrome and to determine whether this level is higher than in the control group and to determine whether this level is positively correlated to the severity of the disease and the short in-hospital prognosis or not.

**Methodology**

The study was conducted on 78 patients, 57 of them were admitted to the critical care department, El-Kasr El-Aini teaching hospitals, Cairo University, from July 2006 to December 2007 with non ST elevation acute coronary syndrome. The recruited patients were divided into three groups. Group 1 included 31 patients with the diagnosis of unstable angina, defined as the presence of typical angina at rest or on minimal exertion associated with acute and transient ST-T segment ECG changes but with normal cardiac enzymes, including troponin levels. Group 2 included 26 non ST segment elevation infarction patients. The clinical diagnosis of NSTEMI was based on the occurrence of typical rise of troponin and/or rapid rise and gradual fall of CK and CK-MB with at least one of the following: ischemic symptoms or ECG changes indicative of ischemia (ST segment elevation <1 mm or depression). According to the finding that statin treatment decreases the level of VEGF [6] both groups were subdivided into two subgroups according to whether they received statin therapy or not (1A and 2A were on statins, while 1B and 2B were free of any statins). The third group was the control group which included 21 patients without any known myocardial disease were referred to the cath lab for chest pain evaluation and their results revealed normal coronaries.

All patients were subjected to the following: full history taking, routine general and systemic examination, 12-lead ECG, routine laboratory investigations including cardiac biomarkers and Lipid profile, Echocardiography to calculate dimensions and evaluate global and regional left ventricular function were obtained, measurement of VEGF plasma concentrations, and venous blood sample were collected from the patients.

Concentrations of VEGF were measured by quantitative ELISA. Coronary angiograms were undertaken by the percutaneous transfemoral approach and all images were recorded digitally. Coronary angiograms were scored visually into a severity score (0-3) which defined the number of vessels with a luminal stenosis ≥50% (for right, left anterior descending, and circumflex arteries or its main branch e.g., 1st diagonal branch of left anterior descending or obtuse marginal of left circumflex). The severity and extent of CAD was graded using a modified Gensini score. The most severe stenosis in each of the three coronaries and in the left main was graded from 0 to 6 (0, no stenosis; 1, 1-29% stenosis; 2, 30-49% stenosis; 3, 50-69% stenosis; 4, 70-89% stenosis; 5, 90-99%; 6, 100% occlusion) and summed to yield a score of 0-24. During hospitalization, the 5 major cardiovascular complications assessed were the following: 1) recurring myocardial ischemia, translated by the reappearance of angina or acute myocardial infarction. 2) heart failure (HF) defined by signs and symptoms of pulmonary congestion, requiring the use of specific therapy, such as diuretics, vasodilators, or inotropic support. 3) cardiogenic shock defined as systolic blood pressure <90 mm Hg for more than 30 minutes, requiring the use of vasopressors or the development of metabolic acidosis. Oligoare, cold clam skin, clouding memory. 4) arrhythmias requiring pharmacological treatment, electrical cardioversion or use of pacemaker and 5) death.

**Results**

This study was conducted on 78 patients (53 males and 25 females). Their age ranged between 35 and 77 years with a mean age of 54.7±9 yrs. Of these patients, 57 were admitted to critical care department of the Cairo university with non ST elevation acute coronary syndrome and were divided into 2 groups: Group 1: included 31 patients presented by unstable angina and Group 2: included 26 patients presented by non ST segment elevation infarction. Patients in group 1 and 2 were furtherly divided according to the prior statin use into: Group 1A: included 16 statin treated patients in group 1. Group 2A: included 13 statin treated patients in group 2. Group 1B: included 15 non statin treated patients in group 1. Group 2B: included 13 non statin treated patients in group 2. Twenty one patients without any known myocardial disease were referred to the cath. Lab for chest pain evaluation and their results revealed normal coronaries, served as a control group (Group 3).

All recruited patients in the different groups were comparable with respect to age, sex, encountered risk factors of ischemic heart disease, admission ECG findings, results of routine labs, LV systolic function determined by echocardiographic indices.
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Comparing patients in groups 1A & 2A with control group, the latter had a higher serum level of VEGF compared with patients in group 1A & 2A (74.6 ±53.3 vs 60.9 ±53.3 & 43.2 ±47.5 pg/L respectively, p value: 0.009).

On the other hand when patients in group 1B & 2B compared with the control group regarding their serum level of VEGF, patients in group 1B & 2B have a higher serum level of VEGF than patients in control group (357.5±142.8 & 257.0±146.7 vs 74.6±53.3 pg/L respectively, p value <0.001). These findings denote that patients who presented with either unstable angina or NSTEMI & were not previously treated with statin had a higher serum level of VEGF compared with patients in control group. However, when patients in group 1A & 1B were compared with patients in group 2A & 2B respectively. There was no significant difference in these groups (60.9±53.3 & 357.5±142.8 vs 43.2±47.5 & 257.0±146.7, pg/L, p value: 0.914 & 0.065, respectively) so, VEGF could not be used as a marker for myocardial injury.

Correlation between VEGF level & rate of occurrence of cardiac adverse events during hospital admission: When the 5 major adverse cardiovascular events in ischemic patients were assessed, it was found that these complications occurred in higher frequencies in group 2 (i.e. in patients who had higher serum level VEGF) relative to group 1 (i.e. in patients who had lower serum level VEGF).

![Figure 1](image1.png)

**Figure 1:** A comparison between group 1A and 2A with respect to their serum VEGF.

![Figure 2](image2.png)

**Figure 2:** A comparison between group 1B and 2B with respect to their serum VEGF.

### Table 1: Patient demographic data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gp 1a N = 16</th>
<th>Gp 1b N = 15</th>
<th>Gp 2a N = 13</th>
<th>Gp 2b N = 13</th>
<th>Gp 3 N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age SD</td>
<td>60.5±9.5</td>
<td>55.3±7.7</td>
<td>55.9±6.7</td>
<td>54.8±11</td>
<td>49.2±6.4</td>
</tr>
<tr>
<td>Number of male (%)</td>
<td>9 (29%)</td>
<td>11 (35.4%)</td>
<td>9 (34.6%)</td>
<td>8 (30.7%)</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>9 (56%)</td>
<td>7 (46.6%)</td>
<td>6 (46%)</td>
<td>3 (23%)</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (87.5%)</td>
<td>10 (66.6%)</td>
<td>9 (69.2%)</td>
<td>7 (53.8%)</td>
<td>11 (52.4%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13 (81.2%)</td>
<td>8 (53.3%)</td>
<td>10 (76.9%)</td>
<td>6 (46.1%)</td>
<td>7 (33.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (31.2%)</td>
<td>7 (46.6%)</td>
<td>9 (69.2%)</td>
<td>6 (46.1%)</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>4 (25%)</td>
<td>3 (20%)</td>
<td>3 (23%)</td>
<td>2 (15.3%)</td>
<td>8 (38.1%)</td>
</tr>
</tbody>
</table>

### Table 2: Comparison between different studied groups as regards the level of VEGF.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>60.9</td>
<td>53.3</td>
</tr>
<tr>
<td>1B</td>
<td>357.5</td>
<td>142.8</td>
</tr>
<tr>
<td>2A</td>
<td>43.2</td>
<td>47.5</td>
</tr>
<tr>
<td>2B</td>
<td>257.0</td>
<td>146.7</td>
</tr>
<tr>
<td>3</td>
<td>74.6</td>
<td>53.3</td>
</tr>
</tbody>
</table>

Comparing patients in groups 1A & 2A with control group, the latter had a higher serum level of VEGF compared with patients in group 1A & 2A (74.6±53.3 vs 60.9±53.3 & 43.2±47.5 pg/L respectively, p value: 0.009).
Correlation between VEGF & the Severity of Non ST Elevation Acute Coronary Syndrome

When each of the 5 adverse cardiac complications was assessed separately, it was found that the recurrence of ischemic episodes was the most frequent complication & it occurred in 21 patients (36.8%) of the studied patients. Arrhythmia came in the 2nd category as it occurred in 19 patients (33.3%) of the studied patients. Heart failure & cardiogenic shock were the least encountered complications as they occurred in 12 & 4 patients (21.1% & 7%) respectively. None of the studied patients died during the hospital admission & till they underwent coronary angiogram.

Patients on both groups 1 and 2 collectively were stratified according to their VEGF level into the following 3 groups: VEGF 1: Who had VEGF level <100 pg/L, VEGF 2: Who had VEGF level >100 pg/L & less than or equal 200 pg/L, VEGF 3: Who had VEGF level >200 pg/L. Then Patients in these 3 groups were compared to each other as regards the incidence of different adverse cardiac events. It was found that the incidence of recurrent anginal episodes was significantly higher in VEGF 3 group. Nonetheless there was a trend toward increasing of heart failure incidence in patients with high serum VEGF level (12.0 vs 15.4 vs 36.8% in patients with low, moderate and high VEGF level respectively, p value: 0.052). On the other hand, there were no significant correlation between the serum VEGF level and arrhythmias or cardiogenic shock.

![Figure 3: The percentages of the patients who had any of 5 adverse cardiovascular events among the different studied groups.](image)

![Table 3: The number & percentage of each of adverse cardiac events in relation to the level of VEGF.](table)

![Angiographic findings in relation to the serum level of VEGF among the patients in groups 1 & 2: Again patients in both groups 1 & 2 collectively were stratified into 3 groups according to the serum level of VEGF as following; VEGF 1 group: included patients in both groups who had VEGF level <100 pg/L. This group was 25 patients (43.9%) of the whole patients in both groups. VEGF 2 group: had VEGF level >100 pg/L & <200 pg/L. This group was 13 patients (22.8%) of the whole patients in groups. VEGF 3 group: had VEGF level >200 pg/L. This group were 19 patients (33.3%) of the patients in both groups. The 3 groups were compared to each other as regards the severity and the extent of the coronary artery disease was assessed angiographicaly, using modified Gensini score, severity score or presence of fresh thrombus which was strictly defined as a filling defect or hazainess near the lesion visible on at least 2 orthogonal views.](diagram)
Discussion

Growing interest has been focused on the VEGF because it is thought to be implicated not only in the pathogenesis of atherosclerosis but also in atheromotic plaque neovascularization and thus promotes its infiltration by inflammatory cells. These events, through a complex mechanism, may trigger plaque destabilization [7]. Celletti et al have shown that injection of recombinant VEGF enhanced atherosclerosis in hypercholesterolemic mice and rabbits, thereby supporting the possible role of VEGF in plaque progression, so it is expected that there is a relationship between manifestation of complicated atherosclerotic coronary artery disease and the serum level of VEGF [8].

This study aimed at investigating the potential alteration of the serum VEGF level in patients presenting with non ST elevation acute coronary syndrome and to determine whether this level was higher than in the control group and to determine whether this level was positively correlated to the severity of the disease and the short in-hospital prognosis or not. The study was conducted on 78 patients, who were admitted to critical care department, faculty of medicine, Cairo university from July 2006 to December 2007. 57 of these patients were admitted with non ST elevation acute coronary syndrome and were divided into 2 groups. Group 1 included 29 patients who presented with unstable angina, the other 28 patients represented group 2 who presented by non ST segment elevation infarct.

This study showed that the serum level of VEGF was significantly higher in patients presented with either unstable angina or NSTEMI & were not previously treated with statin in comparison to control patients (357.5±142.8 & 257.0±146.7 vs 74.6±53.3 pg/L respectively, p value <0.001). This finding was in agreement with the study conducted by N A Chung, et al in 2003 who studied the plasma concentrations of von Willebrand factor (a marker of endothelial damage/dysfunction), vascular endothelial growth factor (associated with angiogenesis), soluble VEGF receptor Flt-1, and tissue factor (a key component of coagulation) in 111 patients attending for coronary angiography, and he found that all of these indices were raised in the patients compared with 34 healthy controls except sFlt-1, which was lower in the patients [4]. Kaeng W. Lee, et al in 2004. reported the same findings in their study, they demonstrated the increased level of plasma VEGF in patients presented with acute coronary syndrome compared to patients with stable angina and healthy controls (in acute MI, the VEGF ranged between 83 pg/L and 217 pg/L with mean 126 pg/L, in unstable angina ranged between 48 pg/L and 118 pg/L with mean 86 pg/L, in stable angina ranged between 28 pg/L and 67 pg/L with mean 46 pg/L and in control group ranged between 21 pg/L and 30 pg/L with mean 27 pg/ml, these data were significantly different between groups, p<0.001) [9]. Results published by M. Slevin, et al in 2000, Andrew J Makin, et al in 2003 and Nouran Elghandour, et al in 2006 also reported elevated VEGF level in patients presented with either cerebrovascular stroke or peripheral vascular disease [10,11,12]. In M. Slevin, et al study they serially (at days 0, 1, 3, 7, and 14) measured the serum levels of VEGF in 29 patients with acute ischemic stroke and 26 age-matched healthy subjects were used as controls. In their study they found that the mean concentration of VEGF in the serum of patients with stroke was significantly higher than that of the controls at all time points (days 0, 1, 3, 7, and 14; p<0.05). Moreover comparison of the subgroups of stroke patients revealed the highest expression of VEGF in the patients with large infaracts compared with moderate infarcts, whereas patients with small infarcts had the lowest expression [10]. Andrew J Makin, et al & Nouran Elghandour, et al measured the plasma levels of VEGF and its soluble receptor sFlt-1 in patients with proven PAD (ankle brachial pressure index <0.8) and compared them with healthy controls. They found that patients suffering from proven PAD have higher plasma levels of TF and VEGF compared with controls. These findings imply that VEGF increased in any of atherothrombotic disease [11,12]. In contrast to our result H F Alber, et al in 2005 reported that coronary artery disease patients and controls had similar VEGF level [13]. This discrepancy may be related different patient populations as patients with recent acute coronary syndrome were excluded from their study, but were selectively included in our study. Our result also showed that the previously statin treated patients either in unstable angina or in NSTEMI groups had lower serum level of VEGF than controls (60.9±53.3 & 43.2±47.5 vs 74.6±53.3 pg/L respectively, p value:.009). If we consider the possible proatherogenic effect of VEGF to human atherosclerosis, the reduction of VEGF by statin could represent an atheroprotective property of this type of treatment. In accordance with out data, Blann et al recently demonstrated that lipid-lowering therapy with fluvastatin or fenofibrate.
Correlation between VEGF & the Severity of Non ST Elevation Acute Coronary Syndrome

decreased the VEGF plasma levels in hypercholes-
terolemic patients with or without peripheral or
carotid atherosclerosis [8]. In 2002, Hannes Franz
Alber, et al reported that atorvastatin may lower
the plasma level of VEGF in CAD patients, when
they studied 14 male patients with angiographically
confirmed CAD (defined as >30% lumen stenosis
in at least one major coronary artery branch) and
with hypercholesterolemia requiring lipid-lowering
therapy, after two months of atorvastatin therapy.
VEGF plasma concentration was significantly
decreased [6]. H F Alber, et al in 2005 confirmed
their previous results regarding the effect of statin
treatment on the level of VEGF when they studied
the effect of atorvastatin on the VEGF level in
CAD patients [13]. In 2006, Yasushi Kadoma, et al
published that atorvastatin treatment induced an
increase in sFlt-1 levels and a reciprocal decrease
in free VEGF and free PlGF levels at 6 months
after MI compared with placebo treatment.
Nonethe-
less, the increase in sFlt-1 levels and the decrease in
VEGF and PlGF levels were correlated with improve-
ment of left ventricular ejection fraction
during the follow-up period [14]. In contrast, Vasa
et al have shown that atorvastatin therapy (40 mg
for four weeks did not change VEGF levels in
the serum of patients with stable CAD. Potential
explanations for the latter study compared to ours
and the other mentioned study maybe related to
short duration of statin treatment (4 weeks) in their
study [15]. The present study revealed that the
serum VEGF level did not differ between unstable
angina patients and NSTEMI patients either in
previously statin treated patients or in non previ-
ously statin treated patients (60.9±53.3 & 357.5±
142.8 vs 43.2±47.5 & 257.0±146.7, pg/L, p value:
0.914 & 0.065) respectively. In contrast to these
results, Kaeng W. Lee, reported that the VEGF
level is higher in patients with acute MI than with
unstable angina. This discrepancy is possibly related
to the type of patients included in their study, only
27 of 82 patients had NSTEMI while the remainder
had STEMI, such type of patients were excluded
from our study [9].

In the present study, when patients in both
groups I & II were stratified into 3 groups accord-
ing to the serum level of VEGF, although there was a
trend toward increase of number of coronary vessels
affected in high VEGF level groups (1.92±0.76 vs
2.15±0.89 vs 2.21±1.03 in low, moderate and high
VEGF groups respectively, p value: NS), there was
no significant correlation between the serum level
of VEGF and the coronary artery disease severity
that assessed angiographically using modified
gensini score (9.16±4.81 vs 10.31±4.27 vs 9.79±
5.02 in low, moderate and high VEGF groups
respectively, p value: NS). This lack of correlation
between the serum level of VEGF and coronary
artery disease severity is possibly related to the
more generalised nature of thrombogenesis,
angiogenesis, and endothelial disturbance, rather
than that occurring in specific vascular beds.
Nonethe-
less, when the serum level of VEGF was corre-
lated with the presence of fresh thrombus that
detected during coronary angiogram, it was found
that there was no significant correlation between
these two variables (16% vs 0.0% vs 5.3% of
patients had visible fresh thrombus in low, moderate
and high VEGF groups respectively, p value: 0.204)
In accordance to these data, N A Chung, et al
reported similar results. In their study they found
that no significant correlations were found between
the coronary atheroma score or number of coronary
vessels with significant stenoses [4]. In contrast to
our data, Christopher Heeschen, et al reported that
there was trend toward a more severe atheroscle-
rotic coronary disease in patients with higher level
of VEGF as they found that TIMI flow ≤1 was
documented for 10.3% in patients with high VEGF
levels compared with 7.6% for patients with low
VEGF levels (p=0.15), and thrombus was visible
in 7.8% of patients with high VEGF levels com-
pared with 5.9% for patients with low VEGF levels
(p=0.28) [16]. In addition Fleisch and colleagues
found a trend toward higher concentrations of
intracoronary VEGF with more extensive coronary
artery disease, as assessed by the number of dis-
edased coronary arteries (stenosis >50%) on coronary
angiography [17]. In 2004, Nakajima K, et al ex-
amined the plasma level of VEGF concentration
in 73 patients who underwent coronary angiography
and 70 apparently healthy control subjects. Accord-
ing to the number of the three major coronary
vessels with significant (> or = 75%) stenosis, they
divided the patients into two groups: the mild
stenosis group (0- and single-vessel disease, n =
36) and the severe stenosis group (double- and
triple-vessel disease, n = 37). They found that
VEGF value of the severe stenosis group was
significantly higher than that of the mild stenosis
(p<0.05) and control groups (p<0.05). Furthermore,
there was a significant positive trend in the VEGF
value according to the number of vessels with
significant stenosis (p=0.016) [18].

Cardiac adverse events in relation to the serum
level of VEGF As mentioned before, patients in
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groups 1 and 2 were stratified into 3 groups according to the serum level of VEGF. It was found that the incidence of cardiac adverse events including recurrence of myocardial ischemia events, arrhythmia, development of heart failure or cardiogenic shock were higher in patients with higher VEGF level compared with patients with low VEGF level. Recurrent ischemic attacks were significantly higher in patients with higher serum VEGF level compared with patients with low serum VEGF level (12.0 vs 38.5 vs 68.4% in patients with low, moderate and high VEGF respectively, \( p \) value: \(<0.001\)). Regarding development of heart failure, it occurred more in patients with higher serum VEGF level compared with patients with low serum VEGF level (12.0 vs 15.4 vs 36.8% in patients with low, moderate and high VEGF respectively, \( p \) value: 0.052). On the other hand, there was no significant correlation between arrhythmias or development of cardiogenic shock and the serum level of VEGF. These results were in agreement with Christopher Heeschen, et al, who published that VEGF was significantly and independently associated with the patients’ outcome (death and non fatal MI) [16].

References


Correlation of Apolipoprotein A-1 and Lipoprotein (a) with the Severity of Coronary Atherosclerosis in Patients with Angiographically Proven Coronary Artery Disease and Usual Care Statin Therapy

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Background: There is conflicting evidence as regard to the performance of apolipoproteins and lipoprotein (a) (Lp (a)) versus the traditional lipid parameters for predicting the severity of coronary artery disease in high risk patients for coronary heart disease (CHD).

Objectives: To examine the performance of Apo-A1 and Lp (a) in high risk patients for CHD and assess their relationship to the severity of coronary artery disease (CAD) in patients receiving usual-care statin therapy.

Methods: 380 consecutive subjects referred for coronary angiography were screened to select those with minimum two risk factor for CAD and currently receiving statin therapy for at least 2 months prior to selection. Patients with acute coronary syndrome, renal, hepatic or thyroid disease or using steroid therapy were excluded. From 90 patients included for study analysis, positive coronary angiography (CA) (n=60) were compared to those with negative CA (n=30). CA was quantitatively analyzed and a point scoring system (PSS) was used for severity assessment of CAD. Serum total cholesterol (TC), Triglyceride (TG), (HDL-C), LDL-C, in addition to Apo- AI and Lp (a).

Results: TC, TG, LDL-C and Lp (a) were significantly increased while HDL-C and Apo A1 were significantly decreased (p<0.001) in high PSS compared with low PSS subpopulation. From all these lipid parameters only Apo-A1 was negatively correlated (r=-0.27, p<0.05) and Lp (a) was positively correlated (r=0.63, p<0.001) to CAD score. Using receiver operating characteristic curve (ROC) curve, ≥40 mg/dl for Lp (a) and ≤135 mg/dl for Apo A1, as a cutoff point, can differentiate patients with severe CAD (high PSS) with 73%, 77% sensitivity and 57%, 57% specificity and 69% predictive accuracy respectively.

Conclusion: Apo-A1 and Lp (a) remain the key parameters related to angiographic severity of coronary disease in high risk patients receiving usual care statin therapy.

Key Words: Apolipoprotein A-1 – lipoprotein (a) – Coronary artery disease – Usual care statin therapy.

Introduction

Epidemiological studies have shown that long-term morbidity and mortality in coronary artery disease (CAD), is directly related to circulating lipoprotein levels, in particular LDL-cholesterol (LDL) [1]. However, there is increasing evidence that the measurement of apolipoprotein B (apo-B), the moiety of LDL, and apolipoprotein A-I (apo-A1), the protein component of HDL may add valuable information in the clinical assessment of susceptibility to CAD [2-3]. Apolipoproteins are a complex family of polypeptides with several important functions regarding the structure integrity of lipoproteins, receptor interaction and transcellular lipid transport [4]. Preliminary analyses of individuals referred for angiography, who had no major risk factors associated with CAD, indicated that apo-A1 was significantly lower in patients with positive angiograms [5]. In addition apoA-1 was found to be related to the severity of

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Correlation of Apolipoprotein A-I & Lipoprotein CAD. Lp (a) is another peculiar lipoprotein that was shown to be significantly related to the mortality in patients with CAD [6,7]. Elevated plasma Lp (a) levels may represent an independent risk factor for atherothrombotic complications but the relation between Lp (a) plasma levels and the extent of CAD has been discussed controversially [8]. It has a close structural homology with plasminogen and other coagulation zymogene proteases, and so may have both pro-thrombotic and pro-atherogenic potential [9-10]. In addition, Lp (a) is not significantly affected by lipid lowering agents including statins. Individuals referred for coronary angiography with major risk factors and usual care statin therapy may need more detailed evaluation of plasma lipoproteins. This group represents the patients seen in usual clinical practice and parameters rather than total cholesterol (TC), LDL-C, HDL-C and triglycerides (TG) may be more beneficial in risk stratification in such circumstances.

Aim of the work:

The purpose of this study was to clarify whether Lp (a) and apo A-I offer additional information to the traditional lipid parameters in a relatively high-risk individuals for CAD who are receiving usual care statin therapy and their relation, if any, to the severity of coronary atherosclerosis.

Methods

Study population:

The study enrolled 380 consecutive patients referred for elective coronary angiography were screened to select those with minimum two risk factor for CAD and currently receiving usual care statin therapy for at least 2 months (as prescribed by their primary care physician) prior to recruitment. Patients with the following criteria were excluded from the study: patients with ACS, recent use of heparin within 72 hours or steroids and patients with clinical or laboratory evidence of thyroid, hepatic, renal disease or prior coronary intervention or bypass surgery. 90 patients reached our inclusion criteria and subjected to the study analysis.

Patient’s baseline clinical characteristics were evaluated according to a pre-determined questionnaire. Clinical profiles included age, sex, smoking history (ever versus never), hypertension, diabetes mellitus (DM), previous history of CAD and family history (FHx.) of CAD. Smoking was classified as ever smoker and never smoker. An ever-smoker was defined as a patient who had smoked cigarettes regularly at least 1 cigarette/day within 2 years before study inclusion. A never-smoker was defined as a patient without smoking a cigarette in his or her life. Patients were diagnosed as hypertensive if told by a physician that they had hypertension or if they were using antihypertensive medication or if either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg was detected at least twice during admission. DM was diagnosed as a fasting blood glucose ≥126 mg/dl at least two times in admission or if they were treated with hypoglycemic agents or insulin. FHx. of CAD was positive if at least one of the parents, siblings or children had manifestations of cardiovascular disease (i.e. chest pain or sudden cardiac death) before the age of 55 in males and 65 in females. Body mass index (BMI) was calculated using the following formula: weight (kg)/height^2 (m^2) [11].

Dyslipidemia is diagnosed if plasma lipid analysis shows one or more of the following: total cholesterol (TC) ≥230 mg/dl, low density lipoprotein (LDL-C) ≥120 mg/dl, high density lipoprotein (HDL-C) <40 mg/dl and triglyceride (TG) ≥400 mg/dl [12].

The study complies with the Declaration of Helsinki, and the locally appointed ethics committee has approved the research protocol. Informed consent has been obtained from the included subjects.

Scoring of coronary angiography:

Diagnostic coronary angiography (CA) was carried out in all patients using Judkins technique Quantitative analysis of coronary arteries was performed with the computer-assisted Coronary Angiography Analysis System (Pie Data Medical). End-diastolic frames from each arteriogram were selected for analysis. The angiographic catheter was used as a scaling device, and this together with the pincushion-distortion correction allowed the diameters to be recorded as absolute values (expressed in millimeters) [13]. The percentage diameter stenosis (DS) was assessed in different projections and the highest value of each lesion, was chosen.
Scoring of coronary atherosclerosis was performed using the scoring system described by Readon et al [14]. Briefly the percentage by which each lesion in coronary circulation narrowed the artery was assessed relative to the maximal narrowing diameter of the artery in all projections. The extent and severity of coronary atherosclerosis was assessed and assigning points to each lesion: less than 50% DS, 1 point; 50-74%, 2 points; 75-90%, 3 points and total occlusion, 4 points. The point for each lesion was summed and a score for severity of CAD was obtained.

For the purpose of data analysis Patients with positive CA were assigned, according to total coronary Point Score System (PSS), into group I with low PSS (≤6 points) and group II (more severe CAD) with high PSS (≥7 points). Patients with negative CA were used as a control group.

**Laboratory investigations:**

In addition to routine laboratory work-up including TC, TG, LDL-C and HDL-C, the selected patients were subjected to laboratory analysis of apo-A₁ and Lp (a). A 12-hour’s fasting adequate venous blood sample was collected and serum was separated. 0.5 ml of the serum of each selected patient was stored at -80°C for estimation of Lp (a) and apo-A₁. For analysis of TC, TG, LDL and HDL, biomatrix lab reagents and product-kits (Marcy 1 etoile/69260 charbonnierers les bains, France) were used. Quantitative determination of Lp (a) was performed using INNOTEST enzyme immunoassay (ELISA).

**Statistical analysis:**

The collected data was tabulated and analyzed by SPSS statistical package version II on IBM compatible computer. Quantitative data were expressed as mean value ± SD and analyzed with student t-test for comparison of normally distributed values, and Mann Whitney U test for abnormally distributed ones. Chi-square test was used for analysis of qualitative data. Spearman correlation coefficient test was used to detect the association between 2 quantitative variables. Overall accuracy was calculated by the formula: (true +ve cases + true -ve cases)/ total number of patients. Logistic regression was used when appropriate to detect the relation between dependent and independent variables. A value of p<0.05 (test of significance at 5% level) was considered statistically significant. ROC (receiver operating characteristic) curve was used to determine the cut off points for LP (a), and apo-A₁ to differentiate those with from those without angiographic CAD.

**Results**

**Patient’s characteristics and risk profile in all studied population:**

Among the 380 patients, referred for elective coronary angiography, 90 patients were included for study analysis. 60 patients had positive CA had and 30 patients with negative CA. Demographic data, risk factors and lipid profile are shown in Table (1). Patients with positive CA exhibited a significantly higher prevalence of all risk factors (p<0.001). Also the classic lipid variables TC, TG, LDL-C and HDL-C were significantly higher in positive CA compared with negative CA group. Furthermore, Lp (a) was significantly higher (p<0.001) and Apo A₁ was significantly lower (p<0.001) in patients with positive CA.

**Comparison of plasma lipids and lipoproteins in positive CA group:**

Patients with angiographically documented CAD were classified according to PSS into two groups. Table (2) shows comparison of risk factors and lipid variables in subpopulation according to their point scoring system (PSS). 35 patients had low PSS (group I) and 25 patients had high PSS (group II), they were compared to control group. Patients with high PSS showed significant prevalence of diabetes mellitus and dyslipidemia (p<0.001). Also patients with high PSS had higher BMI compared with those with low PSS (p<0.01). In group II serum concentration of TC, TG, LDL-C and Lp (a) were significantly higher (p<0.001) whereas HDL-C and Apo A₁ were significantly lower (p<0.001) in comparison to group I with less severe CAD.

**Relation of Lp (a) and Apo A₁ to atherosclerotic score:**

In the overall high risk population on usual day statin therapy (n=90) a multivariate logistic regression analysis was used to evaluate the classic lipid variables (TC, TG, LDL-C, HDL-C) in addition to Lp (a) and Apo A₁ and identify useful predictors of the presence of CAD. All these lipid parameters
were significantly associated with positive CA (Table 3).

However, when patients with positive CA (group I) were taken separately to examine the relation of various lipid parameters to the severity of CAD and after adjustment for the conventional risk factors, \( \text{Lp (a)} \) and BMI showed strong positive correlation to atherosclerotic score \( (r=0.63, p<0.001, r=37, p<0.01) \). Also Apo \( A_1 \) was negatively correlated to the severity of CAD as estimated by PSS \( (r=-0.27, p<0.05) \). In contrast other classic lipid parameters (TC, TG, LDL and HDL) did not show significant relationship to atherosclerotic score (Table 4).

**Lp (a) and Apo \( A_1 \) in prediction of positive coronary angiography in high risk population:**

Receiver Operating Characteristic (ROC) curve was used to clarify the best cut off value to discriminate patients with positive coronary angiography in all high risk studied population. We utilized >40 mg/dl for \( \text{Lp (a)} \) and <135 mg/dl for apo-\( A_1 \) as cut off points to differentiate between patients with positive CA from those with negative CA. \( \text{Lp (a)} >40 \text{ mg/dl} \) showed 73\% sensitivity, 57\% specificity, and 68\% accuracy while \( \text{Apo-A}_1 <135 \text{ mg/dl} \) showed 77\% sensitivity, 59\% specificity and 69\% predictive accuracy (Table 5).

---

**Figure 1:** Comparison of Apo \( A_1 \) and \( \text{Lp (a)} \) between studied population.

**Figure 2:** Relationship between Apo \( A_1 \) and atherosclerotic score.

**Figure 3:** Relationship between \( \text{Lp (a)} \) and atherosclerotic score.

**ROC curve for \( \text{Lp (a)} \)**

Diagonal segments are produced by ties.
Table 1: Demographic and risk factor profile in all studied population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive CA (n=60)</th>
<th>Negative CA (n=30)</th>
<th>t test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.2±6.3</td>
<td>46.0±7.8</td>
<td>0.13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3±5.9</td>
<td>27.9±3.8</td>
<td>0.74</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>34 (56.6%)</td>
<td>18 (60%)</td>
<td>0.09</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>26 (43.4%)</td>
<td>12 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (61.6%)</td>
<td>8 (26.6%)</td>
<td>9.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (55%)</td>
<td>5 (16.6%)</td>
<td>12.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FHx</td>
<td>32 (53.3%)</td>
<td>6 (20%)</td>
<td>9.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (45%)</td>
<td>5 (16.6%)</td>
<td>7.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>40 (66.6%)</td>
<td>7 (23.3%)</td>
<td>15.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>199.5±45.2</td>
<td>171.7±22.2</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>180.5±49.7</td>
<td>154.6±28.1</td>
<td>2.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>141.0±32.3</td>
<td>122.5±10.6</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>45.5±28.1</td>
<td>50.6±6.8</td>
<td>3.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lp (a) (mg/dL)</td>
<td>40.2±27.3</td>
<td>22.5±15.4</td>
<td>5.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>118.2±33.2</td>
<td>139.9±29.4</td>
<td>3.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FHx : Family history.
TC : Total cholesterol.
TG : Triglyceride.
LDL : Low density lipoprotein.
HDL : High density lipoprotein.
Lp (a) : Lipoprotein (a).

Table 2: Comparison of general characteristics and lipid parameters in relation to the severity of CAD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (n=35)</th>
<th>Group II (n=25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>47.2±4.5</td>
<td>48.5±3.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.2±3.9</td>
<td>28.0±3.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (46.7%)</td>
<td>11 (44%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (34.3%)</td>
<td>9 (36%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (17.1%)</td>
<td>10 (40%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (31.4%)</td>
<td>12 (48%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FHx</td>
<td>9 (25.7%)</td>
<td>6 (24%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>176.8±46.6</td>
<td>217.3±58.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>175.6±47.5</td>
<td>212.4±69.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>135.8±31.2</td>
<td>163.6±42.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>46.6±8.7</td>
<td>39.7±4.6</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>123.9±29.9</td>
<td>97.0±36.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp (a) (mg/dL)</td>
<td>26.7±12.3</td>
<td>59.0±25.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TC : Total cholesterol.
TG : Triglyceride.
LDL : Low density lipoprotein.
HDL : High density lipoprotein.
Lp (a) : Lipoprotein (a).

Table 3: Logistic regression analysis of lipid parameters, for prediction of positive coronary angiography in high risk patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>Risk Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>0.96</td>
<td>0.93-0.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>0.98</td>
<td>0.96-0.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>0.95</td>
<td>0.93-0.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>1.13</td>
<td>1.05-1.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp (a) (mg/dL)</td>
<td>0.94</td>
<td>0.91-0.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TC : Total cholesterol.
TG : Triglyceride.
LDL : Low density lipoprotein.
HDL : High density lipoprotein.
Lp (a) : Lipoprotein (a).

Table 4: Univariate analysis of plasma lipids, lipoproteins, BMI and age versus CAD pint scoring.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>0.22</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>0.12</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>0.18</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>-0.22</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Lp (a) (mg/dL)</td>
<td>0.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apo A1 (mg/dL)</td>
<td>-0.27</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Apo A1 : Apolipoprotein A1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>-0.27</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.20</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>F BG (mg/dL)</td>
<td>0.37</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

TC : Total cholesterol.
TG : Triglyceride.
LDL : Low density lipoprotein.
HDL : High density lipoprotein.
Lp (a) : Lipoprotein (a).
BMI : Body mass index.
FBG : Fasting blood glucose.
Correlation of Apolipoprotein A-1 & Lipoprotein

Discussion

Several randomized controlled trials have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce LDL-C and confer significant improvements in cardiovascular morbidity and mortality [15-18]. The majority of patients with multiple risk factors and/or objective evidence necessitating coronary angiography are usually receiving statin therapy. The usual lipid profile parameters screened in such patients, including TC, TG, LDL and HDL, are altered with statin therapy and may not correlate with the extent and severity of the atherosclerosis process.

In this study, from 380 patients referred for elective coronary angiography and screened for study enrollment, only 90 (~ 27%) patients with one or more risk factor for CAD were established usual care statin therapy for 2 months or more. This is in agreement with Fonarow et al [19] and Ko et al [20] who reported that despite beneficial effects of statins extend to patients regardless of age, sex, or baseline cholesterol levels and statin prescribing has increased dramatically over the past decade, [21] patient selection remains suboptimal.

The present study confirmed associations of total cholesterol, triglyceride LDL-C and HDL-C with increased risk of CAD in high risk patients. Baseline data showed that the patients with angiographically proven CAD were more obese with higher incidence of smoking, diabetes and hypertension compared to the group with negative coronary angiography. According to quantitative angiography and the point scoring system, patients with severe atherosclerotic changes (high PSS) showed a significant elevation of Lp (a) in addition to other classic lipid parameters (TC, TG, LDL-C). Also they demonstrated lower serum concentration of Apo A1 in addition to lower HDL-C level. These findings also provided support for the protective role of Apo A1 and the harmful role of LP (a) in the expression of coronary atherosclerosis.

The present study showed a strong association between Apo A1 and the Lp (a) and the severity of coronary disease in high risk patients despite their use of statin therapy. In contrast, a significant relationship between the classic lipid parameters (TC, TG, LDL-C and HDL-C) and the severity of CAD were not found in those patients category. Although the usually screened lipid particles (TC, TG, LDL and HDL) seemed to be significant discriminator between positive and negative CAD in high risk patients receiving statin therapy, they lost their power to recognize severely diseased from mildly atherosclerotic changes while apo-A1 and Lp (a) were significantly correlated with the severity of CAD.

Similar findings were reported on low risk subjects by Francis et al [6]. They selected 54 subjects (29 with and 25 without angiographic CAD) and no significant risk factors out of one thousand and seventy five consecutive patients. Multivariate analysis revealed that, after adjusting for age and gender, serum apo-A1 level was the only variable predictive of CAD [5]. This effect was independent of HDL cholesterol level.

Our results point to an important role for apo-A1 and Lp (a) in the atherogenic process. The cutoff value between patients with positive CA and controls was <135 mg/dl for Apo A1 and >40 mg/dl for Lp (a) with high predictive accuracy. In one case-control study of 184 patients with angiographic coronary disease and 191 age- and sex-matched control individuals, HDL and apo-A1 were significantly lower in patients with CAD versus control (39 vs. 43 mg/dl and 117 vs. 137mg/dl) respectively (p<0.001) [6].

Moreover, Rasouli et al [22] demonstrated that Lp (a) was among seven significant and indepen-
dent determinants of CAD including apo B/apo A ratio and they are superior to any of the cholesterol ratios.

The present study afford defense for the role of apolipoproteins and lipoproteins over and above the usual lipid measurements in prediction of CAD. To date it remains controversial issue. Some early case–control studies found apo A-I and apoB to be better predictors of CAD than the usual lipids [23,24]. Furthermore this idea was supported by several later cohort studies [25,26]. However, other prospective studies did not confirm these findings [27,28]. Recently, results from one of the largest studies to investigate these factors, the Apolipoprotein-related Mortality Risk (AMORIS) study were published demonstrating that the concentrations of apoB and apoA-I, as well as their ratio, improved prediction of CHD risk [29].

Additionally, elevated plasma Lp (a) levels may represent an independent risk factor for atherothrombotic complications but the relation between Lp (a) levels and the extent of CAD has been discussed controversially. Little is known about potential atherothrombogenic mechanisms of Lp (a). In a case control study of the relation between plasma Lp (a) and the severity of angiographically defined CAD, Lp (a) levels were significantly higher in patients (14.8mg/dl) than in a control group of voluntary blood donors (9.7mg/dl, p < 0.0001) suggesting that elevated plasma Lp(a) may be an independent risk factor for CAD [8]. In the current study both patients and controls were receiving usual care statin therapy. Plasma Lp (a) was significantly higher in patients with angiographic CAD compared to the control group. In addition Lp (a), was significantly correlated with the severity of CAD (r=0.63, p<0.001).

Limitation of study:

Some limitations of our study merit emphasis. First, we determined exposure to statins based upon prescribing by primary care physician, and we cannot establish whether all patients actually receive the optimal dosage. Also long-term adherence to statin therapy has been shown to be suboptimal. However, statin adherence was determined by previous research and among patients least likely to receive they could still lead to an appreciable protection and death reduction. Second we assumed that the relative risk is uniform across the whole high-risk patients. Thus, our estimates of the altered serum concentration of plasma lipids, lipoproteins and apolipoproteins are, if anything, conservative. A third limitation relates to our small sample size of studied population. However, this is because the strict inclusion criteria to only high risk patients without prior evident heart attack and receiving usual care statin therapy. Patient included in randomized controlled trials are frequently healthier than patients in the general population to whom the therapy will eventually be applied. However, as above, it has been demonstrated that apo A1 and Lp (a) still related to atherosclerotic score.

Conclusions

The study shows the relationship between plasma levels of different lipid parameters and the angiographically determined CAD. It demonstrated that in average to high risk patients receiving usual care statin therapy, apo-A1 and Lp (a) plasma levels were significantly correlated with the quantitatively determined CAD severity, compared to other usually screened lipid particles as TC, TG, LDL and HDL. Improvements in the prescribing of statins to high risk patients should be directed toward lipoproteins and apolipoproteins concentrations which are presently the more likely to be related to atherosclerotic process.

References


Correlation of Apolipoprotein A-I & Lipoprotein


The Role of Oral N-Acetylcysteine in Prevention of Contrast Nephropathy After Coronary Angiography

HANAN ZAGHLA, MD; HAZEM EL-AKABAWY, MD; EL-SHAZLY ABD EL-KHALEK, MD; AHMAD MOSA, MD; HASSAN EFFAT, MD

Background: Renal failure induced by radiographic contrast agents is a known complication of coronary angiography, especially among patients with chronic renal failure. Treatment with N-acetylcysteine (NAC) has been shown to have a protective effect but the mechanisms are unknown. We examined the hypothesis that NAC protected against contrast-induced renal impairment through effects on nitric oxide metabolism and oxidative stress.

Purpose: The study purpose was to evaluate the effects of NAC treatment on renal function and to determine the contributions of alterations in nitric oxide metabolism and oxidative stress as possible effects of NAC in patients with mild to moderate chronic renal failure undergoing coronary angiography. And the possible pathophysiologic mechanisms of contrast media volume effect on contrast nephropathy through alteration of nitric oxide and oxidative stress.

Methods: A total of 60 patients were prospectively enrolled with a serum creatinine concentration above 1.4mg/dl who were candidates for elective coronary angiography. Patients were assigned to receive either NAC (40 patients who received NAC 600mg/8 hours diluted in 100cc of water to be given orally 24 hours with intravenous 0.45% saline hydration at a rate of 1mL/kg/hour before coronary angiography and for 48 hours after the procedure) (NAC group). And 10 patients (control group) was not given NAC, But both groups were treated with intravenous 0.45% saline hydration at a rate of 1mL/kg/hour for 24 hours before and 48 hours after coronary angiography. Blood samples for urea and serum creatinine were drawn on admission, 24 hours and 96 hours after coronary angiography. Urine was collected for 24 hours before angiography, during the first 24 hours following angiography, and 96 hours after angiography. Urinary creatinine was measured and creatinine clearance was calculated accompanied by analysis of nitric oxide metabolites and urinary Malonaldehyde (MDA). We studied the effects of NAC treatment on renal function and to determine the contributions of alterations in nitric oxide metabolism and oxidative stress in patients with mild to moderate chronic renal failure undergoing coronary angiography.

Results: In our study we have shown that treatment with NAC before and after coronary angiography had a protective effect against contrast media-induced nephrotoxicity in patients with mild chronic renal failure. This effect was seen at both short (24 hours) and relative long term (96 hours), and was additive to the protective effect of saline hydration and the usage of a nonionic low osmolar contrast agent. Our study provides insight into the possible mechanisms of renoprotection by NAC. Renal vasoconstriction, possibly mediated by alterations in nitric oxide and a direct toxic effect of contrast media agents have been implicated in the pathogenesis of contrast media–induced nephrotoxicity.

Conclusion: Our result suggests that NAC can be a renoprotective substance against CN with the possible mechanisms is increased production of nitric oxide and decreased oxidative stress.

Key Words: N-acetylcysteine (NAC) – Renal failure – Contrast nephropathy (CN).

Introduction

Contrast nephropathy (CN) remains a common cause of acute renal failure in patients undergoing radiocontrast study [1]. It is the third leading cause of hospital-acquired acute renal failure (ARF) after hypotension and surgery [2]. CN is associated with both short- and long-term morbidity and mortality [3], with estimates of in-hospital mortality rates are as high as 34% in patients who develop ARF compared with 7% in those who do not [4]. There is continued controversy about the pathogenesis of this entity despite the better understanding of its risk factors.
The Role of Oral N-Acetylcysteine in Prevention of Contrast Nephropathy

Many different definitions of CN appear in the literature. In many studies, CN is defined as an increase in serum creatinine level by more than 25% of the baseline value or by more than 0.5mg/dL, which appears within the first 48 hours after radiocontrast administration [5]. Depending on the definition of CN and the presence of co-morbidities, the incidence of this complication varies markedly. Clinically, CN is diagnosed when an abrupt deterioration of renal function upon radio-contrast exposure in the absence of other causes of renal failure such as atheromatous embolic disease, ischemia and other nephro-toxins. Typically, CN presents as an asymptomatic, non-oliguric rise in serum creatinine 24 to 48 hours after contrast exposure, peaks within three to five days and typically resolves with a return to baseline serum creatinine by seven to ten days [6].

**Aim of the work:**

The aim of our study was to evaluate the effects of NAC treatment on renal function and to determine the contributions of alterations in nitric oxide metabolism and oxidative stress as possible effects of NAC in patients with mild to moderate chronic renal failure undergoing coronary angiography. And the possible pathophysiologic mechanisms of contrast media volume effect on contrast nephropathy through alteration of nitric oxide and oxidative stress.

**Patients and Methods**

**Patients:**

The study protocol was approved by the local Ethics Committee and each patient gave written informed consent. We prospectively enrolled 60 consecutive patients with a serum creatinine concentration above 1.4mg/dl who were candidates for elective coronary angiography. Serum creatinine was measured at least twice during the month preceding the angiography, with more than 1-week interval between the measurements. Patients who had less than 45mol/L difference were included in our study.

Patients with acute renal failure, acute myocardial infarction, uncompensated congestive heart failure, hemodynamic instability and known sensitivity to contrast media were excluded.

**Study protocol:**

Patients were assigned to receive either NAC [40 patients who received NAC 600mg/8 hours diluted in 100cc of water to be given orally 24 hours with intravenous 0.45% saline hydration at a rate of 1mL/kg/hour before coronary angiography and for 48 hours after the procedure] (NAC group). And 20 patients (control group) was not given NAC, but both groups were treated with intravenous 0.45% saline hydration at a rate of 1mL/kg/hour for 12 hours before and 12 hours after coronary angiography.

Coronary angiography was performed using nonionic, low osmolar iodine, all patients were hospitalized 1 day before and at least 24 hours following angiography. Blood samples for urea and serum creatinine were drawn on admission, 24 hours after coronary angiography and after 96 hours when patients returned to a follow-up visit. Urine was collected for 24 hours before angiography, during the first 24 hours following angiography and 96 hours after angiography.

**Laboratory analysis:**

Urinary creatinine was measured and creatinine clearance was calculated. Two 10mL aliquots from each urine collection were separated and stored at −70°C until analyzed for nitric oxide metabolites and urinary Malonaldehyde (MDA).

**The statistical paragraph in material and methods:**

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used in stead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant.

**Results**

**Demographic data:**

Demographic characteristics of all patients studied as shown in the next tables.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Control group</th>
<th>NAC group</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>4 (20.0%)</td>
<td>10 (25.0%)</td>
<td>14 (23.3%)</td>
<td>0.571</td>
</tr>
<tr>
<td>M</td>
<td>16 (80.0%)</td>
<td>30 (75.0%)</td>
<td>46 (76.7%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>
The mean age of the studied patients in NAC group was 56.7±7.15 years old while the mean age of the studied patients in the control group was 54.4±9.489 years old. There was no statistically significant difference between both groups (p value: 0.06).

**Weight distribution:**
The mean weight of the studied patients in NAC group was 78.63±9.96 kilograms while the mean weight of the studied patients in control group was 84.7±3.212 kilograms.

**Contrast volume:**
The mean contrast volume which was received by the studied patients in NAC group was 235±49.239mL while the mean contrast volume, which was received by the studied patients in control group was 235±66.8mL. There was no statistically significant difference between both groups (p value: 0.015).

**Laporatory results among studied groups:**

1- **Baseline creatinine in both groups:**
The mean baseline creatinine in NAC group was 1.505±0.114mg/dL, while the mean baseline creatinine in control group was 1.6±0.298mg/dL. There was no statistically significant difference between both group (p value: 0.948).

2- **Serum creatinine 24 hrs and 96 hours after coronary angiography in both groups:**
The mean serum creatinine 24 hours and 96 hour after coronary angiography in studied patients of NAC groups were 1.45±1.357 and 1.4±0.175mg/dL respectively while the mean serum creatinine 24 hrs and 96 hours after coronary angiography in studied patients in control group were 1.8±0.442mg/dL and 1.94±0.6059mg/dL respectively and there was statistically significant difference between both group 24 hours and 96 hours serum creatinine (p value: 0.0448 and 0.037 respectively) with significant increase in 24 hours and 96 hours serum creatinine in control group.

3- **Baseline creatinine clearance in both groups:**
The mean baseline creatinine clearance in NAC group was 54.48±13.52mL/minutes. While the mean baseline creatinine clearance in control group was 55.27±13.67mL/minutes and there was no statistically significant difference between both groups in baseline creatinine clearance (p value: 0.88).

4- **Creatinine clearance, 24 and 96 hours after coronary angiography in both groups:**
The mean creatinine clearance 24 hours and 96 hours after coronary angiography in studied patients in NAC group were 56.27±15.275mL/min and 55.05±14.277mL/min respectively while the mean creatinine clearance 24 hours and 96 hours after coronary angiography in studied patients in control group were 50.99±16.285mL/min and 50.13±19.28mL/min respectively and there was statistically significant difference in both groups 24 hours and 96 hour creatinine clearance (p value: 0.045 and 0.043 respectively).

5- **Baseline urinary nitric oxide products (NOx):**
The mean baseline urinary nitric oxide products (NOX) in studied patients in NAC group was 5.39±1.99umol/mg creatinine while the mean baseline urinary nitric oxide products (NOx) in studied patients in control group was 5.71±2.497umol/mg creatinine. There was no statistically significant difference between two groups in baseline urinary nitric oxide products (p value: 0.088).

6- **Urinary nitric oxide products (NOx) 24 and 96 hours after coronary angiography in both groups:**
The mean urinary nitric oxide products 24 hours and 96 hours after coronary angiography in studied patients in NAC group were 11.66±5.28umol/mg creatinine and 13.4±5.38umol/mg creatinine respectively while in control group were 5.81±3.31umol/mg creatinine and 5.98±2.74umol/mg creatinine respectively and our study showed statistically significantly increase in urinary nitric oxide products in NAC group 24 hours and 96 hours after coronary angiography (p value: 0.001 and 0.000 respectively).

7- **Baseline urinary MDA:**
The mean baseline urinary MDA in NAC group was 2.9±1.85nmol/ml while the mean baseline urinary MDA in control group was 3.39±1.703nmol/mL. There was no statistically significant difference between two groups in baseline urinary MDA (p value: 0.350).

8- **24 hours & 96 hours urinary MDA:**
The mean urinary MDA 24 hours and 96 hours after coronary angiography in studied patients in NAC group were 7.31±5.94nmol/mL and 7.80±5.656nmol/mL respectively and the study showed significant
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reduction in urinary MDA 24 hours and 96 hours after coronary angiography in NAC group (p value: 0.000 and 0.05 respectively).

Discussion

As the mean baseline creatinine clearance in NAC group was 54.48±13.52mL/minutes and the mean creatinine clearance 24 hours and 96 hours after coronary angiography in studied patients in NAC group was 56.27±15.275mL/min and 55.05±14.277mL/min respectively, the absence of significant improvement in our patients of NAC group may be due to the fact that all our patients were diabetics, while other studies included both diabetics and non diabetics. In comparison to control group as the mean baseline creatinine clearance was 55.27±13.67mL/minutes and the mean creatinine clearance 24 hours and 96 hours after coronary angiography in studied patients in control group were 50.99±16.285mL/min and 50.13±19.28mL/min respectively and there was statistically significant difference in both groups 24 hours and 96 hour creatinine clearance (p value: 0.045 and 0.043 respectively).

From the preceding result we found that, treatment with NAC before and after coronary angiography had a protective effect against contrast media–induced nephrotoxicity in patients with mild chronic renal failure. This effect was seen at both short (24 hours) and relative long term (96 hours) and was additive to the protective effect of saline hydration and the usage of a nonionic low osmolar contrast agent.

Using creatinine clearance we were able to detect significant, although subtle, changes in renal function following angiography even though the overall rate of clinically significant deterioration in renal function (increase in baseline serum creatinine >25%) in our study was one patient from control group and none of the patients needed renal replacement therapy. This rate is lower than which reported by Tepel et al, who reported that the incidence of contrast nephropathy in patients with renal impairment who received only hydration was (12%) from 50 patients in control group, while in the group who received NAC and hydration was only 2% [7]. Also, Tepel et al, reported that creatinine clearance values increased significantly in the group who received NAC where patients who received hydration only presented no changes.

Although the general trend in mean creatinine clearance is similar, no beneficial effect was reported by Durham et al, where the mean volume of contrast media was 81mL and only two doses of NAC treatment were given [8] and there was also no beneficial effect by NAC detected in a study done by Sandhu C et al (2006) who found that oral NAC had no effect on prevention of CN in patients with moderate to severe renal impairment undergoing coronary angiography (S. creatinine from 1.69 to 4.57mg/dl) [9].

In our study, Angiography resulted in non statistically significant increase in urinary NOx in the control group, with change from mean baseline NO 5.718±2.497μmol/mg creatinine before angiography to 5.81±3.31μmol/mg creatinine and 5.98±2.74μmol/mg creatinine, 24 hours and 96 hours after angiography respectively. The non significant increase in urinary NOx coincided with the decrease in renal function from the mean baseline creatinine clearance 55.27±13.67mL/min. before angiography to 50.99±16.285mL/min and 50.13±19.28mL/min. 24 hours and 96 hours after angiography respectively and this significant correlation between changes in NOx and decrease in creatinine clearance may indicate that nitric oxide had a causative role of a decrease in renal function.

In the other hand, there was significant increase in the NAC-treated group as the mean baseline urinary nitric oxide products (NOX) was 5.39±1.99μmol/mg creatinine before angiography and the mean urinary nitric oxide products 24 hours and 96 hours after coronary angiography was 11.66±5.28μmol/mg creatinine and 13.42±5.38μmol/mg creatinine respectively (p value: 0.001 and 0.000 respectively).

These data implies that NAC treatment resulted in an increase in nitric oxide production and protection against the contrast media–induced reduction in nitric oxide production. In support of the suggestion that nitric oxide production was increased is the in vitro observation that NAC can induce endothelial nitric oxide synthase expression [10].

NAC is a thiol-containing antioxidant. Animal studies showed that NAC treatment had a protective effect in models involving increased oxidative stress such as reperfusion injury and contrast media–induced nephrotoxicity [11]. We used urinary excretion of MDA, as a measure of oxidative stress, to determine if the potential antioxidant effects of NAC explained its ability to protect against contrast-induced impairment of renal function.

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We measured MDA as a marker of lipid peroxidation and we found that, it was significantly higher in urine from baseline 3.39±1.703nmol/mL to 7.31±5.94nmol/mL and 7.80±5.656nmol/mL 24 hours and 96 hours after coronary angiography respectively in control group, while it was lower in NAC group from baseline 2.9±1.85nmol/ml to 2.53±1.54nmol/ml and 2.73±1.98nmol/mL, 24 hours and 96 hour after coronary angiography respectively in comparison to control group (p value: 0.000 and 0.05 respectively).

The opposite result was reported by Shai et al, who reported that, neither contrast media exposure nor NAC treatment had any effect on urinary isoprostanes, indicating that in humans increased oxidative stress may not play an important role in contrast media nephrotoxicity and that antioxidant mechanisms are unlikely to explain the renoprotective effects of NAC [12].

The mean contrast volume which was received by the studied patients in NAC group was 235±49.239mL, while the mean contrast volume which was received by the studied patients in control group was 235±66.8mL and there was no statistically significant difference between both groups (p value: 0.015).

As in our study there was no statistically significant effect of contrast volume in studied patients in NAC group on 24 hours and 96 hours urinary MDA (p value: 0.06 and 0.08 respectively) while in control group there was statistically significant increase in 24 hours and 96 hours urinary MDA as a marker of oxidative stress post coronary angiography (p value: 0.04 and 0.049 respectively). So we found a significant correlation between contrast media volume and alteration of urinary MDA in control group which increased post coronary angiography and the possible role of NAC as renoprotective against CN due to increased contrast media volume and the possible effect of increased contrast volume is mainly by increased oxidative stress more than alteration of level of nitric oxide.

We also studied the Effect of age on urinary MDA 24 hours and 96 hours after coronary angiography in both groups, there was no statistically significant effect of age in NAC group on urinary MDA 24 hours and 96 hours after coronary angiography (p value 0.857 and 0.516 respectively) and the same statistical non significant results in control group (p value: 0.198 and 0.063 respectively). The non significant correlation of urinary NO and urinary MDA with age in our study may be explained by the narrow spectrum of age among the selected patients.

We studied the effect of baseline serum creatinine and baseline creatinine clearance post coronary angiography in both groups and we found that there was no statistically significant increase in 24 hours and 96 hours serum creatinine in NAC group post coronary angiography (p value: 0.36 and 0.133 respectively) and the same results also were found in creatinine clearance (p value: 0.477 and 0.411 respectively) while, there was statistically significant increase in 24 hours and 96 hours creatinine in control group with increased post coronary angiography creatinine in relation to baseline creatinine (p value: 0.02 and 0.01 respectively) and the same statistically significant decrease in 24 hours and 96 hours creatinine clearance (p value: 0.00 and 0.001 respectively).

There was no statistically significant effect of baseline creatinine on 24 hours and 96 hours nitric oxide post coronary angiography in NAC group (p value: 0.953 and 0.789 respectively) and the same result was found in control group. (p value: 0.45 and 0.37 respectively). We also studied the Effect of baseline creatinine on urinary MDA in both groups and we found that there was no statistically significant effect of baseline creatinine on 24 hours and 96 hours urinary MDA post coronary angiography in NAC group (p value: 0.322 and 0.372 respectively) while there was statistically significant increase in urinary MDA in relation to increase baseline creatinine in control group (p value: 0.047 and 0.02 respectively). From this result we proved that increased baseline creatinine before angiography is a risk factor for contrast nephropathy by increased oxidative stress and NAC can protect against contrast nephropathy through decreased oxidative radicals.

**Conclusion**

Our result suggests that NAC can be a renoprotective substance against CN with the possible mechanisms is increased production of nitric oxide and decreased oxidative stress.

**References**

The Role of Oral N-Acetylcysteine in Prevention of Contrast Nephropathy


Short Term Neurological Outcomes of Carotid Artery Stenting: a Multidisciplinary Team Experience

HANY AWADALLA, MD, FSCAI*; HOSNI M HAMZA, MD, FRCR**; HASSAN SALAMA, MD, PhD***

Background: Carotid artery stenting is an alternative method to surgical endarterectomy for treatment of carotid artery stenosis. Nonetheless, in Egypt the procedure is perceived as a nidus for conflicts between multiple specialties, namely interventional neuroradiology, interventional cardiology, neurology and vascular surgery.

Aim: To report the results of a multidisciplinary approach to percutaneous treatment of carotid occlusive disease. The multidisciplinary team is comprised of an interventional cardiologist, an interventional neuroradiologist and a neurologist.

Methods: Sixty consecutive patients underwent a total of sixty six carotid interventions under the care of the multidisciplinary team. Independent neurological assessment was performed both before and after carotid stenting. Procedures were performed at Ain Shams University Hospitals, cardiology and neuroradiology units. All procedures were attempted using distal protection devices to guard against distal embolization. Stents were routinely used in all sixty six interventions.

Results: Rate of neurological events was assessed independently in the early (<30 days) post interventional period. Twenty patients (33.3%) had asymptomatic carotid occlusive disease; in this group there were no strokes reported in the early post interventional period. Forty patients had symptomatic carotid occlusive disease, in the form either transient ischemic attack (TIA), ipsilateral stroke, or amaurosis fugax; in this group, TIA was reported in three patients (7.5%) and an ipsilateral stroke was reported in two patients (5%) in the early post interventional period (p=0.005). Cardiovascular mortality was not observed in any patient in the current registry.

Conclusion: Carotid artery stenting with distal protection devices yields acceptable short term results with respect to neurological events. Asymptomatic patients have significantly less periprocedural strokes than symptomatic patients. Independent neurological assessment is crucial to the accurate reporting of adverse events following the procedure.

Key Words: Carotid artery stenting – Neurological outcomes.
and stenting arms. Statistically, however, non-inferiority of stenting could not be proven [11]. EVA-3S investigators demonstrated that symptomatic patients showed a higher neurological event rate in the stent arm [12]. EVA-3S had significant methodological flaws, allowing also inexperienced interventionalists to participate [12].

Patients and Methods

The current study enrolled sixty consecutive patients, who underwent sixty six consecutive carotid interventions between October 2005 and May 2008. Patients were enrolled into the study when the degree of carotid stenosis met the criteria of guidelines for carotid surgery, i.e. carotid stenosis of ≥50% in symptomatic patients; carotid stenosis ≥70% in asymptomatic patients [13].

Stenoses were assessed pre-procedure by duplex ultrasound assessment. Other imaging modalities were used had the duplex been inconclusive. Patients enrolled in the current registry did not necessarily need to have a contraindication to carotid endarterectomy. A careful history was elicited in search for cardiovascular risk factors, other co-morbidities and potential contraindications to the stenting procedure. An oral (occasionally written) informed consent was obtained in all patients. Exclusion criteria to carotid stenting were refusal to undergo angioplasty, pregnancy, contraindications to the use of dual antiplatelet therapy with aspirin and a thienopyridine ADP antagonist for at least 4 weeks and contraindication against the use of contrast agents.

Preprocedural neurological assessment: Independent neurological assessment was done before carotid stenting. During the intervention, neurological monitoring was performed clinically. The severity of strokes was graded according to a modified Rankin scale: minor stroke is Rankin grades 0-2, grade 2 denoting slight impairment with inability to perform all activities previously possible, while the patient is able to live his life without external help. Major stroke is defined by grades 3 (needs some help, but can walk alone) to 5 (severe disabling stroke). Transient ischemic attacks were defined as temporary deficit completely reversible within 24h.

Procedural details: Pre-treatment with acetyl salicylic acid (100mg/d) and clopidogrel (75mg/d) for ≥3 days prior to intervention and at least 4 weeks thereafter was mandatory in all patients. Procedures were performed by the first two authors. Both authors had performed at least twenty carotid stenting procedures (each) prior to the enrollment of patients in this registry, both inside and outside Egypt. The use of distal protection device was attempted in all cases and was not deferred unless there was failure to deliver and properly seat the distal protection device to a distance of at least 30mm beyond the target lesion. The use of stents was attempted in all cases.

Post procedural neurological assessment: Independent neurological assessment was done 30 days after carotid stenting. All sixty patients were available for follow-up neurological assessment, which was performed by the third author.

Statistical analysis: All demographic, clinical and technical data were collected using the "Data Collection Form" and entered into a computerized database. Data obtained from all patients were statistically analyzed. Continuous variables were compared using analysis of variance (ANOVA) for repeated measures. The Fischer-exact chi square test with was used for comparison of categorical variables. p-value <0.05 was considered statistically significant. All data were expressed as mean ± standard deviation (mean ± SD) or number (%) as appropriate.

Results

Sixty patients with sixty six carotid stenotic lesions were enrolled. Forty (75%) were males, twenty (25%) were females. The mean age ± SD of the study cohort was 66±8 years (range 45-82 years). Carotid stenosis by duplex ultrasound was 75±10%. Twenty patients had asymptomatic carotid stenosis that was discovered accidentally, either during the course of a preoperative assessment prior to CABG (n=8), or during a routine medical check-up procedure (n=12). Forty patients had one or more neurological symptom(s) before the procedure in the form of: Ipsilateral non-disabling stroke (n=12), ipsilateral major stroke (n=8), TIA (n=18), amaurosis fugax (n=5). Co-morbidities were frequently encountered, with arterial hypertension and coronary artery disease (either by history or documented by coronary angiography) being the two most common co-morbidities. Table (1) summarizes the co-morbidities encountered in the current study.

Six patients had bilateral carotid stenosis and lesions were tackled on two separate interventional settings. All sixty six procedures were performed via the right transfemoral approach. Accessing the carotid artery was achieved using a long 95 centi-
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meter sheath in sixty procedures (90.9%). In the other six procedures (9.1%), accessing the carotid artery was achieved using a coronary 8-French guiding catheter.

Distal protection devices used were Cordis’ Angioguard™ (48/66, 72.7%), Boston Scientific’s EZ™ filter (14/66, 21.2%), or EV3’s Spider™ (2/66, 3%). In two procedures, there was failure of adequate seating of the guidewire of the distal protection device owing to tortuosity of the internal carotid artery. In these two cases, distal protection was abandoned and the stenting procedure was performed using a standard 0.014 inch guide wire. Post stent deployment balloon dilatation, known to be associated with the highest likelihood of distal embolization was also discarded. One patient developed a TIA following this unprotected stenting approach; the other patient had an uneventful postprocedural course.

Predilatation was done in six procedures (9.1%). In all other procedures, direct stenting was performed. Stent delivery was successful in all sixty six procedures. The mean stent length was 48±9mm; the mean stent diameter was 8±0.6mm. The following stents were used: Cordis Smart, (n=20), Cordis Precise (n=28), Boston Scientific’s Sentinol (n=14) and EV3’s Protégé (n=4).

Post dilatation was done in 90.9% (n=60) of procedures. As mentioned earlier, post dilatation was discarded in two procedures in which there was inability to properly “park” a distal protection device at least 30 millimeters distal to the lesion. In the other four occasions, post dilatation was discarded because of minimal indentation within the stent. The mean balloon diameter was 5.1±0.8mm.

Procedural success (defined as adequate seating of a distal protection device distal to the stenosis, stent deployment in the target lesion, ± post stent deployment balloon dilatation and finally retrieval of the distal protection device) was achieved in 97% of attempted procedures (n=64). Procedural details are summarized in Table (2).

**Neurological outcomes in the 30-day post procedural interval:**

Independent neurological assessment was carried out in all patients. In the asymptomatic group (prior to carotid intervention), no neurological events were reported in the 30 days post-procedural interval. In patients who were symptomatic prior to carotid intervention, TIA occurred in three patients (3/40; 7.5%) and an ipsilateral major stroke occurred in two of the three patients (2/40; 5%) following the occurrence of the TIA, despite hospitalization and initiation of anticoagulation.
Case 2: Tight stenosis of the left internal carotid artery (RAO).

Case 2: After stent deployment.

Case 2: Final angiographic result (LAO).

Case 3: Tight stenosis of the right internal carotid artery (LAO).

Case 3: AngioGuard Filter secured in the distal internal carotid artery.

Case 3: Final angiographic result (LAO).

Table 1: Common Co-morbidities.

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>75</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>45</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td>8.3</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>25</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>30</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>70</td>
</tr>
<tr>
<td>Tobacco</td>
<td>20</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>3.3</td>
</tr>
</tbody>
</table>
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The current study confirms the safety of carotid artery stenting as an alternative to carotid endarterectomy. Since the clinical introduction of carotid stenting, registry data, observational studies, but only few randomized trials assessing the clinical outcome have been published [1,10-17]. In the randomized CAVATAS trial [1], the combined endpoint of any death and stroke at 30 days occurred in 10.0% of patients treated percutaneously, Vs. 9.9% treated surgically. In this study, 96% of patients were symptomatic prior to intervention; the percutaneous intervention was performed without embolic protection, stents were used in 26% of patients [1]. The randomized SAPPHIRE trial, generally using stents and emboli-protection-devices, included both symptomatic (29.9%) and asymptomatic surgical high-risk patients [10]. The 30-day endpoint of stroke, myocardial infarction or death was 4.8% in the PCI arm and 9.8% of patients undergoing surgery. There was, however, no difference in the neurological event rate in both treatment groups [10]. In the SPACE trial [11], including only symptomatic patients, angioplasty was performed without protection in 73% of the cases. The 30-day results showed no difference in ipsilateral stroke or death in patients treated surgically (6.34%) or percutaneously (6.84%). In contrast, the EVA-3S study [12] in symptomatic patients showed a significantly lower 30-day stroke and death rate in surgically treated patients (3.9% Vs. 9.6% in the stent arm). In this study, the surgical results are exceptionally good. However, the minimum requirements for interventionalists to participate in this study (previous performance of 12 carotid interventions or five carotid interventions plus 30 other supraaortic stenting procedures) are very much different from joint interdisciplinary recommendations, e.g., from Italy, requiring at least 75 carotid stenting procedures (50 thereof as primary operator) and 150 supraaortic vessel engagements to achieve basic competence and technical skill for carotid stenting [16]. Thus, investigator experience may have influenced the overall results of the stent arm by incorporating the individual learning curve in EVA-3S given the well-known relation between operator volume and outcome [7].

A non-randomized retrospective single center analysis [18] in asymptomatic patients showed similar outcomes after carotid stenting for high-risk patients (stroke 1.1%, additional death 1.1% at 30 days) and endarterectomy for standard-risk patients (stroke 2.1%, additional stroke plus death 0.7%).

An overview of published registry data and observational studies showed that the combined endpoint of any death and stroke in hospital or at 30 days, respectively, was within a range of 2.8-6.9% [9,16]; there was, however, a considerable incompleteness of neurological assessment in some of these studies. When comparing asymptomatic to symptomatic patients, a higher event rate was found in symptomatic patients (3.8-5.8% Vs. 3.2-3.8%) [9].

The use of distal protection devices in this study was the "standard" procedure, given the increasing popularity of such procedure and the fact that many would consider not using this tool despite being available as a shortcoming on the behalf of the operator. It is of note however that despite the data from several large trials, series and registries of carotid artery stenting-reflecting the experience with distal protection in thousands of patients—routine use of cerebral protection has not been confirmed by level 1 evidence [19]. A recent small scale randomized study [20] demonstrated that the use of filters during carotid artery stenting provided no demonstrable reduction of microemboli, in contrary to expected. Authors pointed out that

### Discussion

#### Table 2: Summary of procedural details.

<table>
<thead>
<tr>
<th>Procedural Detail</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal Protection Attempted</td>
<td>100</td>
</tr>
<tr>
<td>Distal Protection Device Parked</td>
<td>97</td>
</tr>
<tr>
<td>Failure to Park DP Device</td>
<td>3</td>
</tr>
<tr>
<td>Predilatation</td>
<td>9.1</td>
</tr>
<tr>
<td>Post Dilatation</td>
<td>90.9</td>
</tr>
<tr>
<td>Attempt to Deliver a Stent</td>
<td>100</td>
</tr>
<tr>
<td>Successful Stent Delivery</td>
<td>100</td>
</tr>
</tbody>
</table>

**DP devices used:**
- Cordis: 72.7%
- Boston scientific: 21.2%
- ev3: 3%

**Stents:**
- Cordis smart: 30.3%
- Cordis precise: 42.4%
- Boston sentinol: 21.2%
- ev3 protégé: 6.1%

Mean Stent Length: 48±9 mm
Mean Stent Diameter: 8±0.6 mm
Post Dilatation Attempted: 90.9%
Post Dilatation Performed: 90.9%
Post Stent Deployment Balloon Diameter: 5.1±0.8 mm
“Routine use of cerebral protection filters should undergo a more critical assessment before mandatory universal adoption”.

This registry is distinct in the completeness of the neurological outcome data both pre and post-procedural. The risk of any stroke at 30 days was zero % in asymptomatic and 5.0% in symptomatic patients in this small registry. These results are comparable to the reported neurologic event rates both of randomized studies and registry data for carotid stenting [1, 10-17] and also meet the established criteria for surgical interventions [13]. Some may contemplate that the current registry patients could have undertaken a carotid endarterectomy; given it is the "benchmark" for tackling carotid occlusive disease. In Egypt however, there has been no randomized data comparing carotid stenting, without or with distal protection to endarterectomy and there are not any national guidelines that rule which patient may undergo carotid stenting. In this "unregulated" environment, the decision is usually left to patient’s choice and operator discretion. The center for Medicare and Medicaid services (CMS) in the US has restricted reimbursement for CAS to patients who are high risk for carotid endarterectomy. FDA currently recommends that CAS should be in the context of randomized trials. Results of the Carotid Revascularization Endarterectomy vs. Stenting (CREST) are being anxiously waited for in the interventional community.

The current study underscores the importance of a multidisciplinary approach to treating patients with carotid disease. The decision to proceed to some form of carotid revascularization was the neurologist’s and the performance of the procedures was conducted in such a way that patients did benefit from the cumulative, rather than the individual experience of the first two authors. This may in part explain the low complication rates reported in the asymptomatic group. Operator experience lowers complication rates in carotid stenting [7] as in other procedures. The net effect is a better service delivered to the patient.

**Limitation:**

The current study is limited by the small sample size and the lack of long term neurological outcomes data. These shortcomings will need to be addressed in a larger more thorough study in the future.

**References**


Platelet Aggregation Response to 150-Mg Maintenance Dose of Clopidogrel Compared to the Conventional Dose of 75 Mg for Patients Scheduled for Elective PCI. One Month Follow-Up Study

AHMED MOWAFY, MD, FSCAI; HESHAM EYSSA, MD

Aim: Our prospective in this study to test whether increase in the clopidogrel maintenance dose results in increased platelet inhibition that may be reflected in decreasing major adverse cardiac effects after PCI.

Methods and Results: Thirty one patients after pretreatment with 600 mg loading dose of plavix and after successful elective PCI were included in this trial. They were allocated to receive one of two clopidogrel daily maintenance doses, (75 or 150 mg) for 30 days in a non randomized manner. Platelet function was evaluated 30 days after the intervention with the impact R device which measures the surface coverage (SC%) and average particle size (AS Um²) as reflection of platelet adhesion and aggregation. SC% after 30 days was 2.4±0.52 AS: 23.9±3.5 in pts treated with 150 mg/day whereas it was 3.6±0.88, AS: 33.8±4.2 in pts treated with 75 mg/day with p value of SC = 0.02, AS = 0.7.

Conclusion: Administration of a 150 mg maintenance dose of Clopidogrel results in more inhibition of platelet aggregation than administration of currently recommended 75 mg maintenance dose.

Key Words: PCI – Platelet aggregation – Clopidogrel.

Introduction

Dual antiplatelet therapy consisting of aspirin and clopidogrel is currently the therapy of choice to prevent thrombosis after percutaneous coronary intervention (PCI) [1,2]. Clopidogrel is a prodrug that needs to be metabolized to an active metabolite. The active metabolite covalently binds to and irreversibly blocks the P2Y12 platelet ADP receptor [3]. The effect of clopidogrel on platelet function is most commonly assessed by measuring ADP-induced platelet aggregation with optical aggregometry. This method was also used in initial studies on single- and repeated-dose pharmacodynamics [4-6]. In these dose-finding studies, the antiaggregatory effects of daily maintenance doses ranging from 10 to 150 mg were studied [5,6]. Although, in one study, a trend towards increased inhibition of ADP-induced aggregation with a 150 mg daily maintenance dose was observed when compared with daily doses ranging from 50 to 100 mg, it was assumed that a plateau response is reached with administration of 75 mg once daily [5]. Moreover, with administration of 75 mg once daily, the same degree of inhibition of platelet aggregation was achieved as with ticlopidine 250 mg twice daily, which was the target level of inhibition. On the basis of these results, the currently recommended maintenance dose of clopidogrel (75 mg/day) was chosen for the phase III Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.

Despite clopidogrel's proven efficacy in reducing thrombotic events, acute or sub acute stent thrombosis is still a significant clinical problem that occurs in 1-2% of patients treated. A considerable interindividual variability in response to clopidogrel has been observed after administration of loading doses of clopidogrel and in patients chronically treated with the recommended maintenance dose [8-13]. In a significant proportion of patients (10-30%), no or little inhibition of platelet aggregation are achieved with the currently used dosing regimens [8-11]. Some data suggest that

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Platelet Aggregation Response to 150-Mg Maintenance Dose

these patients are at an increased risk of stent thrombosis [8,11,14–16].

Pre-treatment with clopidogrel-loading dose is recommended in patients undergoing PCI [2]. Recently, it was shown that administration of a 600 mg dose of clopidogrel in patients already chronically treated with a maintenance dose of 75 mg/day results in a significant additional inhibition of ADP-induced platelet aggregation and surface expression of glycoprotein (GP) IIb/IIIa and P-selectin after stimulation with ADP [17]. These results also suggest that the antiplatelet effect achieved with the currently recommended maintenance dose can be augmented. In fact, administration of a 150 mg daily maintenance dose is now broadly discussed and occasionally used in clinical practice, although there is still a lack of functional data proving its efficacy. More intense inhibition of platelet aggregation associated with an increased daily maintenance dose may result in fewer ischaemic events after PCI, particularly in high-risk patients [3,18].

The main hypothesis was that an increase in the clopidogrel daily maintenance dose from 75 to 150 mg results in a more intense inhibition of ADP-induced platelet aggregation.

Patients and Methods

Patients on chronic aspirin therapy, who are scheduled for PCI after administration of a 600 mg loading dose of clopidogrel, were eligible for this trial. Patients who underwent primary PCI due to acute myocardial infarction or those who were haemodynamically unstable were excluded from the trial. Other exclusion criteria included stroke within 3 months, malignancies, active bleeding and bleeding diatheses, oral anticoagulation therapy, recent treatment with a GP IIb/IIIa antagonist, low platelet count, serum creatinine > 2 mg/dL, and/or liver disease resulting in bilirubin > 2 mg/dL. Patients were divided into two groups; group 1 was given conventional clopidogrel maintenance dose 75 mg, whereas group 2 received the high maintenance dose 150 mg.

Patients in both groups received the first clopidogrel maintenance dose within 12 h of PCI. A 30-day follow-up visit was arranged to assess the antiplatelet effect of the two different clopidogrel maintenance doses and clinical status. At the 30-day (outpatient) follow-up visit, blood samples were obtained for platelet-function testing.

Platelet aggregation was measured using the Diamed Impact R device:

Requires 130 ul citrated whole blood, it functions in an automated, semi automated procedure that usually takes around 5-7 min time. This device creates the required physiological conditions for platelet aggregation and adhesion; whole blood, thrombogenic surface and flow. Upon exposure of blood to the polystyrene surface of the test cartridge, the plasma proteins adhere and create a thrombogenic surface. Arterial shear rate (1800 s⁻¹) is formed by rotation of the core (720 rpm) for 2 min. Platelet adhesion and aggregation on the polystyrene is evaluated using an image analysis system. The results are expressed as the percentage of Surface Coverage (%SC) by platelet aggregates and the average particle size (AS, um²). Their normal reference range is surface coverage (SC%): 7.0-15% and for average size (AS) 25-70 um². Both SC and AS reflects platelet adhesion and aggregation.

Results

Base line characteristics of the patients in the two groups are presented in Table (1). Demographic data of both groups were almost the same with non significant p value. During 30 days follow-up after PCI, no MACE occurred in both groups. Platelet function was assessed 30 days after PCI in all patients. All patients in both groups were totally compliant to their medication & doses. Platelet function was assessed by measuring the surface coverage percentage (SC%) and average particle size (AS in Um²) as reflection of platelet adhesion and aggregation.

<table>
<thead>
<tr>
<th></th>
<th>150 mg/day</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Deviation</th>
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<tr>
<td>Age</td>
<td>51.88</td>
<td>7.805</td>
<td>53.07</td>
<td>7.950</td>
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<tr>
<td>Platelet count</td>
<td>180.81</td>
<td>17.611</td>
<td>179.87</td>
<td>16.707</td>
</tr>
<tr>
<td>EF%</td>
<td>58.94</td>
<td>4.878</td>
<td>58.73</td>
<td>5.599</td>
</tr>
<tr>
<td>HTN</td>
<td>13 (81.2%)</td>
<td>11 (73.3%)</td>
<td>9 (56.2%)</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>9 (56.2%)</td>
<td>7 (46.7%)</td>
<td>10 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (68.8%)</td>
<td>10 (66.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (56.2%)</td>
<td>7 (46.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (1): Demographic data in both groups.
The results of platelet function - testing 30 days after PCI are shown in Fig. (1). Surface Coverage (SC%) as reflection of platelet aggregation 30 days after PCI was significantly lower in group treated with 150 mg/day, (SC: 2.4±0.52) than in the group treated with 75 mg/day (SC 3.6±0.88) with p value of SC = 0.02. However, AS did not differ significantly in both groups 23.9±3.5 in group treated with 150 mg versus 33.8±4.2 in the conventional dose group with p value of 0.7.

Although and increase in bleeding complications associated with high maintenance dose of clopidogrel was a potential concern, yet no major bleeding occurred in both groups. Only three patients in the high maintenance dose had complained from minimal gum bleeding not necessitating stopping the drug.

Discussion

The main message of our study was to demonstrate that doubling of the conventional maintenance dose of clopidogrel may be an option to improve platelet inhibition that might lead to decrease thrombotic complications after PCI. This study shows that administration of 150 mg daily maintenance dose of clopidogrel results in more intense inhibition of platelet function when compared with administration of the currently recommended daily maintenance dose of 75 mg. This result was obtained by measuring the Surface Coverage (SC%) and Average particle Size in Um² (AS) as an indicator for platelet adhesion and aggregation. Previous studies have used the Verify Now P2Y12 device assay to demonstrate the same objective [21]. A large variability in platelet aggregation data was also observed in the group of patients treated with the high daily maintenance dose.

In previous studies, the 150 mg daily maintenance dose has been used in healthy male adults in one of the dose-finding researches [5]. In that study, subjects received 25 (n = 6), 50 (n = 6), 100 (n = 5), or 150 mg (n = 6) clopidogrel once daily. The treatment period was 16 days. A direct comparison with the antiplatelet effect of ticlopidine (250 mg twice daily) was missing. A dose-dependent inhibition of ADP-induced platelet aggregation was observed. ADP-induced platelet aggregation on day 16 before dosing was 79, 55, 37, 39 and 27% for treatment with daily doses of 25, 50, 100 and 150 mg, respectively [5]. In two other dose-finding studies that incorporated a comparison with the antiplatelet effects of ticlopidine (250 mg twice daily), one in healthy volunteers and one in patients with documented atherosclerotic disease, a similar degree of platelet-function inhibition was observed with 75 and 100 mg of clopidogrel daily [5,6]. Therefore, it was assumed that a plateau response is reached with administration of 75 mg once daily, and this dose was chosen for the subsequent phase-III trial (CAPRIE) [5]. Since the initial dose-finding studies, the subsequently recommended daily dose of clopidogrel has not been questioned only until recently [3,18].

Clopidogrel and its predecessor thienopyridine, ticlopidine in combination with aspirin, are very effective in preventing thrombosis after PCI [1,22]. Intensified perinterventional antiplatelet therapy provides additional benefit [23]. Clopidogrel pre-treatment with a 600 mg loading dose is more effective in suppressing ADP-induced platelet aggregation than a 300 mg loading dose [18,24,25]. An increase in the loading dose from 600 to 900 mg does not result in an additional significant increase in platelet-function inhibition because of limited intestinal absorption of single doses exceeding 600 mg [25]. In addition to pre-treatment with 600 mg of clopidogrel, the administration of abciximab results in a further reduction of adverse events after PCI in patients who present with an acute coronary syndrome (ACS) and elevated troponin levels [26]. In contrast to the data on different clopidogrel-loading doses in patients treated with PCI, no comparable data exist so far on different clopidogrel maintenance doses [11].

One of the largest prospective studies on the influence of platelet-function inhibition on the rate of adverse clinical events after PCI was discussing
the clopidogrel dose and platelet response [15]. In that study, ADP-induced platelet aggregation was assessed in 802 consecutive patients with stable coronary disease before clopidogrel loading with 600 mg and immediately before PCI. Patients were stratified in quartiles of platelet-function inhibition at the time of the intervention (level of ADP-induced platelet aggregation) and the primary endpoint was the 30-day composite of death, myocardial infarction, and target lesion revascularization (MACE), which occurred in 15 patients [15]. Thirty-day MACE differed significantly \( p = 0.03 \) between quartiles of platelet aggregation. Patients above the median of platelet aggregation carried a 6.5-fold risk of 30-day MACE [15].

The intensified clopidogrel effect of the high oral maintenance dose used in this trial has the potential to further reduce the incidence of ischemic events after PCI. Whether the whole spectrum of patients undergoing PCI or only certain subgroups (e.g., patients with an ACS, who are known to have high baseline platelet reactivity) [9] would benefit from the daily dose of 150 mg of clopidogrel and the duration of such a regimen needs to be tested in specifically designed clinical trials. Recently, it was shown that the 150 mg daily maintenance dose is also more effective than the 75 mg daily maintenance dose in diabetic patients with a suboptimal response to clopidogrel [27].

The TRIION - TIMI 38 study has shown that Prasugrel, a new thienopyridine, when compared to clopidogrel in the conventional maintenance dose, was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with increased risk of major bleeding. This arouses again the need for another drug or may be another dose of clopidogrel that may overcome modest antiplatelet effect, with substantial inter patient variability and delayed onset of action [29, 30].

In our study patients who had high clopidogrel maintenance dose had higher platelet inhibition more than the patients on conventional regimen (150 mg Vs 75 mg respectively). It was not related for any short term events and patients in both groups did not experience adverse events in the one month follow-up period.

An increase in bleeding complications associated with the high maintenance dose is a potential concern. Analyses of bleeding events in the recently completed Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial suggest, however, that patients with a high atherothrombotic risk are exposed to a lower risk of severe bleeding in response to the combined therapy with clopidogrel in addition to aspirin than patients with a low atherothrombotic risk [28]. Since it is likely that the high 150 mg daily maintenance dose will only be applied in high-risk patients, the incidence of bleeding complications with the high maintenance dose may remain acceptable.

In our study patients in both groups did not experience any major bleeding events necessitating stopping of the medication.

Few limitations for this study need to be mentioned. First, baseline values of platelet function (before clopidogrel treatment) were not available. Therefore, we were not able to calculate the actual reduction of aggregation in response to clopidogrel treatment and provide the number of non- and/or poor responders. Secondly, the exclusion of patients with an ACS from this study prevents us from drawing conclusions on the effect of the 150 mg daily maintenance dose in this high-risk subset of patients. Last but not least, this is a small number of patients that compared the effects of different clopidogrel maintenance doses on parameters of platelet function. It is far too small to comment on the safety of the higher maintenance dose. The possible clinical benefits of this regimen require confirmation in adequately powered randomized trials.

In conclusion, administration of a 150 mg daily oral maintenance dose of clopidogrel results in a more intense inhibition of platelet aggregation than administration of the currently recommended 75 mg daily maintenance dose.

**Recommendation:**

Therefore, we recommend a larger, randomized, double blinded study to assess platelet function before and after clopidogrel administration in the standard conventional dose and higher doses.

**References**


2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D,
Ahmed Mowafy & Hesham Eyssa


Effect of Left Ventricular Geometry on the Immediate Outcomes Following Multi Track Balloon Mitral Valvuloplasty

AYMAN SADEK, MD

For over a decade balloon mitral valvuloplasty was the treatment of choice for severe mitral stenosis and replaced surgical commissurotomy in many selected cases. In spite of this, balloon mitral valvuloplasty has many disadvantages. Such disadvantage might may related to the effect of left ventricular geometry which was proven that it is changed in patient with rheumatic mitral stenosis.

The Aim of this Study: Was to evaluate the effect of different left ventricular geometrical parameters on early results of balloon mitral valvuloplasty using Multi-Track balloon system in patients with rheumatic mitral stenosis.

Subjects and Methods: The study included (50 subjects): Group I: 10 persons normal subjects as a control group and group II: 40 patients with symptomatic rheumatic mitral stenosis undergoing Balloon Mitral Valvuloplasty using multi track system. The patients were subjected to (transthoracic and transesaphogeal echocardiography) before and after valvuloplasty. Several echocardiographic parameters were measured in order to study the left ventricular geometry. The baseline criteria for all patients in the two groups were comparable with no significant statistical difference between them. Left ventricular geometry in patients with MS showed that long axis of the left ventricle was shorter than in normal subjects (7.2±0.7cm VS 7.9±0.5cm with p<0.001) Greater short axis/long axis diameter ratio at every level with the most pronounced in the apical (D3 / L 0.49±0.09 VS 0.40±0.05 p<0.001). LV spherical index was markedly increased in group II (0.57±0.09 VS 0.40±0.05 p<0.001). Following valvuloplasty the patient in group II were subdivided into 2 groups according the results optimum and non optimum. Successful dilatation was achieved in 75% of patient. The left ventricular long axis was found to be the only LV geometrical parameter which affected the early results of BMV as the shorter LV long axis was associated with the more incidence of non-optimal results. By ROC analysis, we reached a cut-off point regarding longitudinal axis of the LV=5.09cm to ensure an optimum result (100% PPV and 76% NPV) using the multi track system.

Conclusion: Balloon valvuloplasty using the multi track system is an effective treatment for rheumatic mitral stenosis however the altered LV geometry especially the longitudinal axis may affect the early outcomes.

Key Words: Multi track balloon – Mitral valvuloplasty.

Introduction

Rheumatic Mitral stenosis (MS) is a continuous, progressive, lifelong disease, usually consists of a slow, stable course in the early years and progressive acceleration later in life. In developed countries, there is a long latent period of 20 to 40 years from occurrence of rheumatic fever to onset of symptoms [1]. Isolated MS affection occurs in 40% of the cases. While 50% of the cases have combined mitral stenosis and regurgitation [2]. Critical mitral stenosis occurs when the opening is reduced to 1cm², at this stage, elevated left atrial pressure (LAP) is required to maintain a normal cardiac output [3]. This increase in left atrial pressure will lead to pulmonary hypertension, tricuspid and pulmonary incompetence and eventual right heart failure. Moreover, progressive dilatation of the left atrium will predispose to two major complications, 1st mural thrombus formation with subsequent embolization in 20% of the cases and atrial fibrillation [4].

The left ventricular geometry was found to be changed in patient with rheumatic mitral stenosis. The patients with mitral stenosis had shorter long axis diameter and greater short axis/long axis
diameter ratios at every level with the most pro-
nounce change in the apical segment of the cavity
[5].

Treatment of mitral stenosis include medical
therapy, percutaneous balloon mitral valvuloplasty
(PBMV) and surgical therapy. Balloon mitral val-
vuloplasty is an effective method for treating rheu-
matic mitral valve stenosis, producing good short-
and long-term results that are comparable to sur-
gical valvotomy [6].

Inoue et al (1984) were the first to perform
percutaneous mitral commissurotomy in 1982. The
good result obtained by the technique had led to
its increasing worldwide use [7,8].

The Multi-Track system is a recent variant of
the double balloon technique and aims to make
the procedure easier through the use of two balloons
and only single guide wire Although the Multi-
Track system is a simple procedure with less costly
catheters; however, these catheters have different
sizes but single length which may not favor differ-
ent left ventricular geometrical patterns [9].

Aim of the work:
The aim of this work is to studying the effect
of left ventricular geometry on early outcome in
patient with mitral stenosis undergoing balloon
mitral valvuloplasty using Multi-Track balloon
system.

Patients and Methods
Candidates included in this study were chosen
randomly from patients who presented to the car-
diology department, Ain Shams university and
specialized hospitals in the period from May 2006
to March 2007 with symptomatic rheumatic mitral
stenosis.

Candidates were divided into 2 groups:
• Group I: Included on 10 normal healthy individual
as a control group.
• Group II: Included on 40 patients with symptomatic
mitral stenosis undergoing balloon mitral
valvulo-plasty using multi track system.

Patient inclusion criteria:
1- Rheumatic M.S with MVA ≤1.5cm².
2- MV score <10 according to Wilkins score.
3- Absence or mild degree of mitral regurgitation.
4- Absence or mild degree of other valvular dis-
eases.

5- Absence of left atrial thrombus by trans-
oesophageal echocardiography.

Patient exclusion criteria:
1- Associated mitral regurgitation more than grade
II.
2- Associated aortic valve disease that need surgical
correction.
3- Acute rheumatic activity or infective endocarditis.
4- History of recent thrombo-embolic event <2
months.
5- Left atrial thrombus on T.E.E performed within
24 hours before the procedure.

Pre-Procedural assessment:
All patients were subjected to the following:
History taking and clinical examination, ECG,
Laboratory investigations, Echocardiographic stud-
ies:

Trans-thoracic echo cardio graphic study:
All patients were studied with M. mode, two
dimensional and color Doppler echocardiography
before the procedure and 1 day after the procedure.
With particular emphasis on:
• Mitral valve area was calculated by direct mea-
urement in short axis parasternal view (plannim-
etry) and by continuous Doppler using pressure
half time formula.
• Echo study of other valvular lesions.
• The morphological features of the mitral valve
leaflet and sub valvular apparatus were assessed
according to the scoring system described by
Willkins.
• Left ventricular geometry.

Description of left ventricular geometry:
The minor axis diameter (D-1) in the parasternal
long axis view was measured at the level of the
tips of the leaflets of the mitral valve. Minor axis
diameters (D-2, D-3) in the apical four-chamber
view are drawn perpendicular to the long axis,
dividing the left ventricular cavity into three equal
segments.
• Left ventricular long axis diameter was measured
at end of left ventricular diastole from mid mitral
annuls to left ventricular apex.
• Short axis diameters were taken at 3 levels at end of left ventricular diastole:
  ° D1 (basal line) was taken in long axis parasternal view.
  ° D2 (mid cavity line) was taken in apical four chambers view.
  ° D3 (apical line) was taken in apical four chambers view [10].

Figure 1: Schematic diagram of cross-sectional echocardiographic parasternal long axis (L) is represented by a line drawn from the endocardium of the apex of the left ventricle to the midpoint of an imaginary lion joining the anterior and posterior attach-ments of the mitral leaflets.

Measurement of Left ventricular geometry included the following parameters:

1- Short axis/long axis ratio were calculated [10].
2- Left ventricular spherical index was calculated from EDV / [(LAD^3 x π) / 6] [11].
3- Left ventricular relative wall thickness (LV hypertrophy index from M. mode echo study h/r = [(PDTd + IVSTd) / 2] / (EDD / 2) with normal range; 0.33-0.41 [12].
4- Left ventricular mass index: [13]
   Measurement of LVMi by M. mode echocardiography.
   LVMi = (1.05 x [(EDD + PWTd + IVSTd^3 – EDD^3] – 13.6) / BSA (g/m²)

Normal LVM index:
• Males: 76±13gm/m².
• Females: 66±11gm/m².

• EDV: End-diastolic volume, ml.
• LAD: Long axis, cm.
• BSA: Body surface area (m²).
• EDD: LV end-diastolic diameter (cm).
• ESD: LV end-systolic diameter (cm).
• IVSTd: Interventricular diastolic thickness (cm).
• PWTd: LV postero-lateral diastolic wall thickness (cm).
• PWTs: LV postero-lateral systolic wall thickness (cm).
• SAP: Systolic arterial pressure (mmHg).

Percutaneous balloon mitral valvuloplasty procedures:

• BMV was performed with Multi Track balloon, the size of balloons used was left to the choice of the experienced operators taking in consideration mitral valve annulus measured by trans-esophageal echo.
• Hemodynamic assessment was done immediately before and after the procedure, left and right heart catheterization with determination of intra cardiac and intra vascular pressures were performed. The transmitral pressures gradient were measured.

Post procedural assessment:

Immediately after percutaneous balloon valvotomy patients were subdivided as follows:

Optimum results:

Procedural success was defined as MVA >1.5cm² or increase by 40% from original area with absence of major complications (cardiac tamponade, cerebral embolism, severe mitral regurgitation need urgent surgery and death) with mitral regurgitation less than grade II).

Non-optimum results:

This included submaximal valve dilatation, incomplete procedure or presence of major complications (severe MR needs surgery, left ventricular perforation, embolic events and death).

A detailed echocardiographic and Doppler assessment following valvuloplasty was done measuring: Trans-mitral pressure gradient, MVA, MR, and pulmonary artery pressure.
Statistical analysis:
Data were tabulated and statistically analyzed to evaluate the difference between the groups under study as regards the various parameters. Results are expressed as mean±SD. The statistical significance of differences between groups was assessed by an analysis of variance (ANOVA) and t-test. The correlations were evaluated by Pearson’s test. Results are significant if \( p<0.05 \), highly significant if \( p<0.01 \), non significant if \( p>0.05 \).

Results

Demographic data:
As shown in Table (1), there was no significant statistical difference between both studied groups; as regarding the age, sex, weight, height, heart rate, systolic and diastolic blood pressure.

Table 1: Baseline demographic data of both control group and patient group.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Group I</th>
<th>Group II</th>
<th>( t )-test</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs):</td>
<td>Range</td>
<td>16.00-34.00</td>
<td>19.00-46.00</td>
<td>-1.273 ( \times ) 10(^{-4} )</td>
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<tr>
<td></td>
<td>Mean±SD</td>
<td>25.40±5.54</td>
<td>28.40±6.90</td>
<td>0.209</td>
</tr>
<tr>
<td>Height (cm):</td>
<td>Range</td>
<td>161.00-191.00</td>
<td>155.00-182.00</td>
<td>0.457 ( \times ) 10(^{-2} )</td>
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<tr>
<td></td>
<td>Mean±SD</td>
<td>173.70±29.24</td>
<td>170.25±5.96</td>
<td>0.152</td>
</tr>
<tr>
<td>Weight (kg):</td>
<td>Range</td>
<td>62.00-88.00</td>
<td>54.60-87.00</td>
<td>2.616 ( \times ) 10(^{-3} )</td>
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<tr>
<td></td>
<td>Mean±SD</td>
<td>76.90±8.23</td>
<td>69.17±8.40</td>
<td>0.062</td>
</tr>
<tr>
<td>HR (Beat/min):</td>
<td>Range</td>
<td>68.00-88.00</td>
<td>62.00-91.00</td>
<td>-0.891 ( \times ) 10(^{-1} )</td>
</tr>
<tr>
<td></td>
<td>Mean±SD</td>
<td>75.60±6.65</td>
<td>77.73±6.76</td>
<td>0.377</td>
</tr>
<tr>
<td>BPs (mmHg):</td>
<td>Range</td>
<td>100.00-130.00</td>
<td>110.00-130.00</td>
<td>-1.206 ( \times ) 10(^{-2} )</td>
</tr>
<tr>
<td></td>
<td>Mean±SD</td>
<td>115.10±28.44</td>
<td>118.25±7.12</td>
<td>0.234</td>
</tr>
<tr>
<td>BPd (mmHg):</td>
<td>Range</td>
<td>60.00-90.00</td>
<td>54.00-85.00</td>
<td>4.24 ( \times ) 10(^{-1} )</td>
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<tr>
<td></td>
<td>Mean±SD</td>
<td>77.00±8.23</td>
<td>73.50±6.62</td>
<td>0.161</td>
</tr>
</tbody>
</table>

As shown in Table (2) and figure, there is no significant statistical difference between both studied groups as regarding to M-Mode echocardiographic data including (LVEDD, LVESD, PWT, IVS, FS and EF%).

Table 2: M-mode echocardiographic parameters in both studied groups.

<table>
<thead>
<tr>
<th>Trans thoracic ECHO cardio graphic data</th>
<th>Group I n=10</th>
<th>Group II n=40</th>
<th>( t )-test</th>
<th>( p )-value</th>
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</thead>
<tbody>
<tr>
<td>LVEDD:</td>
<td>Range 3.90-5.20</td>
<td>3.80-5.90</td>
<td>-0.305</td>
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<tr>
<td></td>
<td>Mean±SD 4.73±0.45</td>
<td>4.78±0.50</td>
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<tr>
<td>LVESD:</td>
<td>Range 3.10-3.50</td>
<td>2.50-4.50</td>
<td>-0.489</td>
<td>0.627</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 3.26±0.14</td>
<td>3.33±0.44</td>
<td></td>
<td></td>
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<tr>
<td>PWT:</td>
<td>Range 0.80-1.10</td>
<td>0.70-1.20</td>
<td>1.055</td>
<td>0.275</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 0.95±0.13</td>
<td>0.90±0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVS:</td>
<td>Range 0.80-1.10</td>
<td>0.70-1.20</td>
<td>0.805</td>
<td>0.425</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 0.94±0.10</td>
<td>0.91±0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FS:</td>
<td>Range 31.00-40.00</td>
<td>21.00-40.00</td>
<td>1.206</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 34.30±2.50</td>
<td>32.80±3.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF%:</td>
<td>Range 64.00-71.00</td>
<td>43.00-78.00</td>
<td>1.654</td>
<td>0.105</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 67.30±5.89</td>
<td>64.15±5.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table (3) and figure, there is no significant statistical difference between both studied groups as regarding to M-Mode echocardiographic data including (LVEDD, LVESD, PWT, IVS, FS and EF%).

Table 3: Dimensional descriptors of left ventricular geometry in both patient and control groups.

<table>
<thead>
<tr>
<th>Left ventricular geometry</th>
<th>Control</th>
<th>Patients</th>
<th>( t )-test</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L:</td>
<td>Range 6.90-8.40</td>
<td>4.70-8.10</td>
<td>4.771</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 7.75±0.48</td>
<td>6.46±0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1:</td>
<td>Range 4.20-5.40</td>
<td>3.06-5.60</td>
<td>3.588</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 4.74±0.39</td>
<td>4.16±0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2:</td>
<td>Range 3.90-4.50</td>
<td>2.70-4.20</td>
<td>4.915</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 4.16±0.22</td>
<td>3.53±0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3:</td>
<td>Range 2.40-3.10</td>
<td>2.10-4.00</td>
<td>-3.068</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Mean±SD 2.68±0.21</td>
<td>3.09±0.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As shown in Table (3):

- Left ventricular long axis is shorter in patients with rheumatic MS than in normal subjects (6.46±0.82 cm vs 7.75±0.48 cm) with significant statistical difference (p<0.000).
- Minor short axis (width axis) of left ventricle in patients with rheumatic MS were shorter in every segment than normal persons.
- Basal short axis (D₁) (4.16±0.47 cm vs 4.74±0.39 cm, p<0.000).
- Mid short axis (D₂) (3.53±0.39 cm vs 4.16±0.22 cm, p<0.000).
- Apical segment (D₃) (3.09±0.41 cm vs 2.68±0.21 cm, p<0.004).
- There was significant statistical difference in between patient group and normal persons in every level of minor short axis.

Table 4: Measurement of left ventricular geometry in both patients and normal control group.

<table>
<thead>
<tr>
<th>Left ventricular geometry</th>
<th>Control</th>
<th>Patients</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁/L:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.54-0.66</td>
<td>0.54-0.81</td>
<td>-2.234</td>
<td>0.437</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.61±0.04</td>
<td>0.65±0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₂/L:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.49-0.61</td>
<td>0.46-0.68</td>
<td>-0.704</td>
<td>0.485</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.54±0.04</td>
<td>0.55±0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₃/L:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.30-0.41</td>
<td>0.42-0.64</td>
<td>-9.032</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.35±0.03</td>
<td>0.48±0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table (4), the breadth to length (D/L) ratio in every segment of the left ventricle has no significant statistical difference except in apical segment only (p<0.000).

Table 5: Mean and standard deviation of left ventricular spherical index in both studied groups.

<table>
<thead>
<tr>
<th>Left ventricular geometry (spherical index)</th>
<th>Control</th>
<th>Patients</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVsph:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.35-0.45</td>
<td>0.44-0.66</td>
<td>-6.811</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.40±0.03</td>
<td>0.56±0.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table (5) and Fig. (2), there was highly significant statistical difference between the patient group and normal group regarding spherical index (0.56±0.07 vs 0.40±0.03, p<0.001).

Table 6: Mean and standard deviation of left ventricular mass index and left ventricular relative wall thickness in both studied groups.

<table>
<thead>
<tr>
<th>Left ventricular geometry</th>
<th>Control</th>
<th>Patients</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVmass index:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>64.00-104.00</td>
<td>61.00-117.00</td>
<td>-0.515</td>
<td>0.609</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>88.50±13.54</td>
<td>91.58±17.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVrwt:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.38-0.43</td>
<td>0.32-0.48</td>
<td>2.298</td>
<td>0.126</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.41±0.02</td>
<td>0.38±0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table (6), there was no significant statistical difference between both studied groups as regarding to LV MI and LV relative wall thickness.

Table 7: Baseline hemodynamic characteristics of all patient in group II.

<table>
<thead>
<tr>
<th>Pre-dilatation data</th>
<th>MVA (cm²)</th>
<th>Mean mitral pressure (mmHg)</th>
<th>Mean PASP (mmHg)</th>
<th>Mean gradient across mitral valve by catheterization (mmHg)</th>
<th>Mean left atrial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.050±0.147</td>
<td>12.050±0.194</td>
<td>41.500±0.135</td>
<td>15.100±0.147</td>
<td>22±</td>
<td></td>
</tr>
<tr>
<td>3.502</td>
<td>19.946</td>
<td>3.640</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8: Immediate results of BMV.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Optimum</th>
<th>Non-optimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Techni.</td>
<td>No. of</td>
<td>patients</td>
</tr>
<tr>
<td>Multi-trak</td>
<td>40</td>
<td>30 (75%)</td>
</tr>
</tbody>
</table>

Pre dilatation assessment:

As shown in Table (8), the immediate results of BMV in group II: Optimum results were reached in 30 cases, non-optimum results were seen in 10 patients as follows: Four cases developed intra-procedural tamponade with no need for surgical interference except in one case that necessitated operative transfer and died in operating theatre, 4 cases developed severe mitral regurgitation which planned for elective mitral valve replacement, 2 cases the MVA failed to reach the desirable area.

Mean and standard deviation of comparative results of both pre- and post-dilatation in patients underwent BMV using Multi-Track balloon system (Group II) showed that Mitral valve area (MVA) increased from (1.05±0.147cm²) to reach (1.789±0.373cm²), (p<0.001) with significant statistical difference. Mean Mitral pressure, across the mitral valve decrease from (12.05±3.5) before dilatation to (4.447±2.315mmHg) after dilatation with significant statistical difference (p<0.001). Mean pulmonary artery systolic pressure drop from (41.5±19.94mmHg) to (32.105±1.546mmHg) post dilatation with significant statistical difference (p<0.001). Gradient across mitral valve by left heart catheterization drop from (15.1±3.64mmHg) to (3.526±2.19mmHg) with significant statistical difference (p<0.001).

Relation of left ventricular geometry and immediate results of BMV:

As shown in Table (9): There was no statistical significance between optimum and non optimum group regarding D1, D2 and D3 however Left ventricular long axis (L) was (6.63±0.74cm) Vs (5.95±0.86cm) in non-optimum results (p=0.021).

Table 9: Mean and standard deviation of measurement of left ventricular geometry and immediate results after BMV using multi-track system.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Optimum</th>
<th>Non-optimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>t-test</td>
</tr>
<tr>
<td>L</td>
<td>5.95±0.86</td>
<td>6.63±0.74</td>
</tr>
<tr>
<td>D1/L</td>
<td>4.00±0.57</td>
<td>4.22±0.43</td>
</tr>
<tr>
<td>D2/L</td>
<td>3.38±0.39</td>
<td>3.58±0.38</td>
</tr>
<tr>
<td>D3/L</td>
<td>2.87±0.38</td>
<td>3.17±0.40</td>
</tr>
</tbody>
</table>

Relation of measurements of left ventricular geometry and immediate results:

As shown in Table (10), there were no significant statistical difference between optimum and non optimum group regarding breadth to length ratio at every level and left ventricular spherical index. The same was observed also in the left ventricular mass index and left ventricular relative wall thickness 0.38±0.03 versus 0.38±0.03 (p=0.896).

Table 10: Correlation between left ventricular long axis and post-BMV mitral valve area.

<table>
<thead>
<tr>
<th>Metric</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left (L) ventricular long axis</td>
<td>0.333</td>
<td>0.038*</td>
</tr>
</tbody>
</table>

Correlation between post-dilatation mitral valve area and left ventricular long axis (L):

As shown in Table (11) there was a positive correlation between left ventricular long axis and post-valvuoloplasty mitral valve area (p=0.038).

Table 11: Correlation between left ventricular long axis and post-BMV mitral valve area.

<table>
<thead>
<tr>
<th>Metric</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left (L) ventricular long axis</td>
<td>0.198</td>
<td>0.001</td>
</tr>
<tr>
<td>Post-Dilatation gradient by left heart catheterization</td>
<td>0.221</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Correlations between left ventricular long axis and immediate post-dilatation gradient by left heart catheterization:

As shown in Table (12), there was a negative correlation between left ventricular long axis and immediate post-dilatation gradient across mitral valve by left heart catheterization, with significant statistical value ($p<0.001$).

Table 13: Cut off point in Mutli-Track group.

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sens.</th>
<th>Spec.</th>
<th>+PV</th>
<th>-PV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=5.09</td>
<td>42.9</td>
<td>100.0</td>
<td>100.0</td>
<td>76.5</td>
<td>0.703</td>
</tr>
</tbody>
</table>

ROC in multi-track group:

As shown in Table (13), the cut off point of LV longitudinal long axis for Multi-Track system was 5.09cm with specificity 100% and sensitivity 42.9%.

Discussion

Rheumatic fever and rheumatic heart disease still form a major health problem in developing countries including. Rheumatic fever is considered as the predominant cause of mitral stenosis [14]. Rheumatic inflammation of the left ventricular myocardium is common in patients with mitral stenosis [15]. This process often leads to anatomical distortion of the left ventricle and mitral apparatus [16].

However, this process is usually related to subvalvular fibrosis along with the involvement of posterobasal segment. The status of intrinsic contractility is controversial and so abnormal intrinsic contractility in mitral stenosis should lead to architectural remodeling even in absence of segmental asynchrony [5].

Collagen matrix is responsible for maintaining the alignment of cardiac muscle fibres. This provides tensile strength to the muscle to resist deformation. Ultrastructural changes of a myopathic process involving the collagen matrix have been shown in the left ventricular myocardium of the patients with mitral stenosis [15].

An increase in chamber size without alteration in shape is possibly an adaptive response to variations in work load. A change ventricular shape without an increase in ventricular size as shown in the patients with mitral stenosis is morphological evidence of a myopathic process. Altered left ventricular geometry may be related to the severity of the pathological changes and hence may precede or follow the onset of left ventricular systolic dysfunction depending on the role played by the loading factors. So, the left ventricular shape in the patients with rheumatic mitral stenosis is less ellipsoidal due to architectural remodeling along with increased wall stress. In the normal ellipsoidal ventricle, the position of the papillary muscle permits their contractions to exert a vertical force on the charade tendinae [10].

This significantly contributes to the left ventricular long axis dynamics towards ejection performance and maintenance of the mitral valve orifice competence.

In a more spherically shaped ventricle, the papillary muscles undergo lateral migration and hence may be responsible for the occurrence of mitral regurgitation following mitral commissurotomy besides the adverse effects on the long axis dynamics [5]. The introduction of percutaneous trans-septal mitral commissurotomy modified once again the therapeutic strategy for mitral stenosis and decreased the need for surgery. The early and late results of balloon valvuloplasty were comparable to surgical techniques but without the risks and complications of general anesthesia and extracorporeal circulation pump [17]. The double balloon system was introduced for the first time in 1986 [18]. The Multi-Track system is a recent variant of the double balloon techniques and was introduced by Bonhoeffer 1995, as a valid alternative to the existing procedure for treatment of mitral stenosis that simplifies the procedure and reduce the cost of mitral dilatation [17].

Left ventricular geometry:

In the present study, our observations suggested that the left ventricular cavity shape in patients with rheumatic MS tends to approach a spherical shape or less ellipsoidal and this process is most marked in the apical segments so the ventricular apical area tends to be thinner than the rest of the left ventricular myocardial wall. This was seen in our measurement of LV geometry as:

- Long axis was shorter in patients with MS than normal subjects.
- Minor short axis were shorter in patients with MS than normal subjects at 3 levels (D1, D2 and D3).
• The short axis/long axis diameter ratio were shorter and statistically significant at the level of the apical segment.

• The left ventricular end diastolic spherical index increased in patients with rheumatic MS. Left ventricular mass index and relative wall thickness (hypertrophy index) were not significantly altered neither in group 1 nor group 2.

Yoshida et al (1981) studied the cross sectional left ventricular geometry of abnormal left ventricular configuration and contraction in patients with rheumatic MS. The study included on 40 patients, abnormal configuration and asynergy were observed in 23 patients (56%), the left ventricular shape diverted from circular to half moon or pear like configuration.

The same results obtained by Mohan et al. when studied cross sectional echocardiography in 20 patients with rheumatic MS and 20 normal subjects, they found that the Long axis of the left ventricular was shorter in patients with rheumatic MS than in normal subjects (7.2±0.7cm VS 7.9±0.5cm with p<0.001. Greater short axis/long axis diameter ratio at every level with the most pronounced in the apical (D3/L 0.49±0.09 VS 0.40±0.05 p<0.001. LV spherical index was markedly increased (0.57±0.09 VS 0.40±0.05 p<0.001 [5].

Such changes in the configuration of the LV might be attributed to the progression of the disease resulting from calcification, fibrosis and thinning of the myocardium [10].

**Immediate results of BMV:**

Mitral valve area (MVA): In the present study, showed that the MVA significantly increased from (1.047±0.15cm²) to (1.789±0.373cm²) with high significant statistical difference between pre- and post-dilatation MVA (p<0.001).

El Sayed et al, published a comparative study between various methods of percutaneous mitral commissurotomy metallic valvotome, Inoue balloon and double balloon, each group comprised 50 patients. Their results were improvement in the MVA by similar degree in double balloon and metallic valvotome (2.1±0.5cm², 2.0±1.2cm² respectively) and greater than Inoue group (1.87±0.4cm²), they concluded that in contrast to Inoue balloon technique, metallic valvotome and double balloon produced an excellent and comparable early improvement of MVA associated with minimal complications [20].

Cribier et al (published the immediate results of balloon mitral valvuloplasty by Inoue balloon and double balloon. The results obtained that MVA reach less than 2cm² in the majority of the cases, but double balloon ranging (1.93±0.34cm²), while in Inoue balloon group (1.84±0.412cm²) [21].

**Relation of different left ventricular geometrical parameters and Immediate results of BMV using Multi Track balloon system and double balloon system:**

Paul et al, described the criteria of successful BMV as increase of MVA more than 1.5cm² or 40% increase of MVA from pre dilatation area with absence of major complication (left ventricular perforation, cardiac tamponade, severe mitral regurgitation and death [22].

In our present study, we concluded that the left ventricular long axis significantly affected the early results of BMV in group II. LV long axis was shorter in non optimum group (5.95±0.86cm), while in optimum group it was (6.63±0.74cm) with significant statistical difference p<0.021.

On the other hand, minor short axis, left ventricular spherical index, left ventricular mass index and LV hypertrophy index had no relation to the immediate results of BMV.

In addition by ROC analysis we reached a cut off point for LV longitudinal axis=5.09cm in Multi-Track group to achieve optimum results a value that reached 100% positive predictive value and 76.5% negative predictive value.

As far as we know, we did not reach similar researches in the literature studying the effect of the LV geometry and its impact on the success of balloon mitral valvuloplasty as to compare them with our results.

**Conclusion**

The study concluded that:

• Left ventricular geometry is changed in patients with rheumatic MS, these changes appear mainly in:
  • Short long axis length.
  • Short minor short axises.
  • Increased left ventricular spherical index.
Ayman Sadek

- Percutaneous mitral valvuloplasty using Multi-Track improved MVA and significantly reduced transmirtal pressure gradient, mean left atrial pressure.
- Only left ventricular long axis affected the immediate results of BMV as the shorter long axis the more incidence of non optimum results.

Limitations:
- Small number of patients included in the study.
- Other variable might have affected the non optimum results as operator’s experience.
- Other type of balloon valvuloplasty might be have been used (e.g Inoue) and compare its results to multi track.
- Other comparative studies are necessary.

Recommendations:
- Left ventricular long axis should be taken in consideration when choosing the proper system used in dilatation process especially when the length of the axis is less than 5.1.

References
Premature Atherosclerosis in Female Patients with Systemic Lupus Erythematosus

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**Purpose:** To evaluate the prevalence of carotid atherosclerosis in premenopausal women with SLE and to verify if endothelial function is impaired in pre-menopausal women with SLE.

**Methods:** 60 women with SLE (1997 revised criteria) and 28 healthy women were studied. Demographic and risk factor data were collected. In patients, disease activity was also assessed. Endothelial function was assessed by flow-mediated dilation (FMD) in the brachial artery in response to reactive hyperemia. Carotid intima-media thickness (IMT) and the presence of carotid plaques were also assessed in SLE patients.

**Results:** IMT of the right and left common carotid arteries as well as the mean IMT were significantly higher in the patients group than in the control group ($p<0.01$). Furthermore, SLE patients had 11.57-fold risk of developing premature atherosclerosis than age and sex matched healthy controls. FMD percentage and the dilatation ratio were significantly lower in patients group than controls ($p<0.001$). IMT is significantly increased in the active disease patient than those without active disease while there is no significant difference between both groups as regards the flow mediated dilatation or the dilatation ratio.

**Conclusion:** Patients with SLE have endothelial dysfunction that remained significant even after adjustment for other classic coronary heart disease (CHD) risk factors. Within SLE patients, endothelial dysfunction correlates negatively with IMT, another marker of early atherosclerosis. Furthermore, IMT is significantly increased with the activity of the disease that clarifies the importance of prompt treatment of the activity in prevention of the vascular complication. Understanding the mechanism(s) of endothelial dysfunction in SLE may suggest novel strategies for CHD prevention in this context.

**Key Words:** Atherosclerosis – Female – Systemic lupus erythematosus.

**Introduction**

Systemic lupus erythematosus (SLE) is a chronic inflammatory, autoimmune disease that affects mainly young women, a group usually free of atherosclerosis [1]. Accelerated atherosclerosis is a recognized leading cause of morbidity and mortality in SLE [2] and therefore the identification of SLE patients at risk for cardiovascular events is important. Traditional atherosclerotic risk factors including hypertension, obesity, diabetes mellitus, smoking, hyperlipidemia and sedentary lifestyle, do appear to explain the increased risks for SLE patients [4]. However, there is consensus that, even after these factors are controlled for, the diagnosis of SLE remains the strongest risk factor for cardiovascular disease [5].

Endothelial dysfunction is another key event in atherogenesis appearing long before the formation of a structural atherosclerotic lesion [6]. Carotid ultrasonography has been found to be a reliable non-invasive method of detecting carotid atherosclerosis, which correlates strongly with the presence of coronary artery disease [8]. Enhanced carotid IMT is an established marker for atherosclerosis [9]. Thus, early detection of atherosclerosis may provide an opportunity for early therapeutic intervention [8].

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Address for Correspondence: Dr. Mohamed Abd El-Kader, Department of Cardiology, Minia University.
Patients and Methods

The study included 60 premenopausal women with SLE compared to 28 age and sex matched healthy controls. All patients were satisfying the updated revised criteria for the classification of SLE [10]. Each SLE patient underwent a complete history review and physical examination according to a standard protocol. Demographic and risk factor data were collected from both patients and controls. In patients, disease activity and treatment-related parameters were also assessed. SLE disease activity was measured by Systemic Lupus Activity Measurement (SLAM) [11]. History of drugs was also included and cumulative prednisolone equivalent dose was recorded on a separate sheet.

The traditional risk factors assessed were the presence or absence of a family history of premature myocardial infarction (before 55 years of age in first-degree male relatives or before 65 years in female relatives), smoking status, the presence or absence of hypertension (as defined by a blood pressure of at least 140/90mm Hg or the use of antihypertensive medications), the presence or absence of diabetes mellitus (as defined by fasting blood glucose >126mg/dl) and hyperlipidaemia.

Ultrasonographic studies:

Carotid arteries of both patients and controls were evaluated using the high-resolution B-mode ultrasound equipment Medison 9900 multibeam 30 UL (Korea) equipped with a linear probe (5-12MHz) with the use of a standardized protocol [3]. This evaluation aims to determine the intima media thickness (IMT) and to detect carotid plaques and the presence or absence of accompanying stenosis. The mean IMT were assessed (the mean of both right and left side) was assessed. Plaques were defined as focal widening relative to adjacent segments, with protrusion into the lumen of calcified or non-calcified material [12].

Endothelial function:

To assess endothelial function non-invasively with B-mode ultrasound, conduit vessel endothelium-dependent vasodilatation was induced by reactive hyperemia, while endothelium-independent vasodilatation was induced by administration of sublingual nitroglycerine (glyceryl trinitrate, GTN). Measurements were made of changes in the diameter of the brachial artery using color duplex Doppler ultrasound. The ultrasound examination was performed in a quiet room at a temperature between 21°C and 22°C. Subjects rested in a supine position for 15 minutes before examination. A B-mode scan was obtained of the right brachial artery in longitudinal section. A resting measurement was taken, and a pneumatic cuff was then inflated to a pressure of 200mm Hg for 4 minutes. The diameter of the artery was recorded again 45-60 second after cuff deflation. A period of 15 minutes was allowed for recovery before testing for endothelium–independent relaxation. A repeat baseline measurement of the diameter was made before a 400-µg dose of sublingual GTN spray was administered. The brachial artery diameter was again measured 3-4 minutes after the GTN was given [13]. A single investigator performed all imaging and analysis, blinded to the subjects disease. Echocardiography, performed with the use of standard techniques [14].

Statistical analysis:

Data were analyzed by the Statistical Package for the Social Sciences (SPSS, version 11.0 under windows) [15]. Two-tailed tests were used throughout and statistical significance was set at conventional 0.05 levels.

Results

Table (1) demonstrates a comparison between SLE patients and controls regarding the clinical characteristics.

The incidence of risk factors was demonstrated in Fig. (1).
The overall prevalence of atherosclerosis in the studied patients and controls was shown in Table (2).

Table (3) shows the ultrasonographic findings of carotid arteries of the patients and the controls. IMT was found to be positively correlated with age, hypertension, FBS, waist-hip ratio, cumulative corticosteroids, total cholesterol, triglyceride, LDL and TNF, alpha and significantly negatively correlated with flow mediated dilatation, physical activity index and HDL (Table 4).

In stepwise regression analysis with the mean IMT as the dependent variable; only triglycerides, age and SLAM remained after elimination of non-significant variables, Table (5).

The flow mediated dilatation percentage was significantly lower in patients group than controls \((p<0.001)\). Furthermore, the dilatation ratio was significantly lower in patients than controls \((p=0.03)\) (Table 6).

There is significant increase in IMT in the active disease patient than those without active disease while there is no significant difference between both groups as regards the flow mediated dilatation or the dilatation ratio (Table 7). Furthermore, Table (8) shows that there was a significant correlation between Slam score and mean IMT.

### Table 1: Clinical characteristics of patients and control population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient (n=60)</th>
<th>Control (n=28)</th>
<th>(t)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>25.7±8.58</td>
<td>24.8±9.46</td>
<td>0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>123.5±12.63</td>
<td>116.7±10.90</td>
<td>2.79</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>83.5±9.79</td>
<td>78.2±7.72</td>
<td>2.92</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.6±5.87</td>
<td>28.2±5.45</td>
<td>-1.15</td>
<td>0.25</td>
</tr>
<tr>
<td>Waist: Hip ratio</td>
<td>0.85±0.05</td>
<td>0.84±0.04</td>
<td>0.80</td>
<td>0.43</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>29.8±3.54</td>
<td>34.3±3.62</td>
<td>-5.55</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

### Table 2: Prevalence of premature atherosclerosis in patients and controls.

<table>
<thead>
<tr>
<th>Premature atherosclerosis:</th>
<th>Patients (n=60)</th>
<th>Controls (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency %</td>
<td>Frequency %</td>
<td></td>
</tr>
<tr>
<td>Thickened intima</td>
<td>18 30</td>
<td>1 3.6</td>
</tr>
<tr>
<td>Plaque</td>
<td>2 3.3</td>
<td>0 0</td>
</tr>
</tbody>
</table>

### Table 3: Ultrasonographic duplex findings in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>SLE Patients (n=60)</th>
<th>Controls (n=28)</th>
<th>(t)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT</td>
<td>0.06±0.01</td>
<td>0.05±0.01</td>
<td>4.84</td>
<td>0.001**</td>
</tr>
<tr>
<td>LT IMT</td>
<td>0.06±0.02</td>
<td>0.05±0.01</td>
<td>4.12</td>
<td>0.001*</td>
</tr>
<tr>
<td>RT IMT</td>
<td>0.07±0.02</td>
<td>0.05±0.01</td>
<td>4.95</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

### Table 4: Correlation between IMT and disease variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient ((r))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.61**</td>
<td>0.001</td>
</tr>
<tr>
<td>Plaque</td>
<td>0.28</td>
<td>0.03</td>
</tr>
<tr>
<td>FMD</td>
<td>-0.29*</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.33*</td>
<td>0.01</td>
</tr>
<tr>
<td>FBS</td>
<td>0.30**</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Waist: Hip ratio</td>
<td>0.43**</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>-0.35</td>
<td>0.005</td>
</tr>
<tr>
<td>Cumulative corticosteroids</td>
<td>0.49**</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.59**</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.67**</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.54**</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>0.66*</td>
<td>0.001</td>
</tr>
<tr>
<td>US-CRP</td>
<td>0.11</td>
<td>0.42</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>0.36**</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Premature Atherosclerosis in Female Patients with Systemic Lupus Erythematosus

Discussion

The presence of accelerated atherosclerosis is well documented in our SLE patients when compared to the general population. In the present study, highly carotid IMT was detected in 18 (30%) of SLE patients compared with only 1 (3.6%) of controls. In addition, the mean IMT was significantly higher in SLE patients than our healthy controls (0.06 ± 0.01 versus 0.05 ± 0.01) cm respectively.

This result is in agreement with that of Falashi et al, 2000 who compare the carotid IMT measured by B-mode ultrasound in 26 patients with SLE onset before the age of 16 years and in 26 sex- and age-matched healthy control subjects and concluded that the mean IMT of the SLE patients was significantly higher than that of the control group (0.57 ± 0.05 mm and 0.54 ± 0.03 mm, respectively; p=0.006).

In accordance with our results, a study by Esdaile et al, 2001 who reported that 30% of patients with SLE have atherosclerosis, and also in accordance with a prevalence rate of 28% in a
study of 78 SLE patients [3]. Studies using a control group also confirm that the prevalence of the disease is higher in SLE patients than in the general population. A case-controlled study of 197 patients with SLE and age-matched controls (mean age 44 years) demonstrated that carotid abnormality, as detected by B-Mode Doppler Ultrasound, were significantly more prevalent in SLE patients than in controls (37.1% versus 15.2%; p<0.001) (Roman et al, 2003). Similarly, Asanuma et al (2003) found a higher prevalence of coronary calcification in SLE patients than in a control population (31% versus 9%) with a higher coronary calcification scores in SLE patients than controls (68.9±24.2 versus 8.8±41.8, p<0.001). In our study, the mean IMT was significantly higher in SLE patients than in our healthy controls (0.06±0.01 versus 0.05±0.01) cm respectively. This figure is in accordance with a study by Svenungsson et al (2001) where the common carotid IMT of SLE cases were greater than that of the controls (0.07±0.01 versus 0.06±0.01) cm.

Previous studies have assessed atherosclerosis at different sites within the carotid and it is unclear to what extent the choice of site has influenced the results. Some studies focused on the common carotid IMT (Roman et al, 2003 and El-Magadmi et al, 2004), others on the internal carotid IMT and still others on the average IMT in the common carotid artery, carotid bulb and internal carotid artery [3]. Thickening may progress at different rates in the common carotid and internal carotid arteries and associations with risk factors may differ between these sites. Another important factor is that the cut off point between normal and high IMT was different between studies. In Doria et al (2003) study, normal IMT was defined when complex intima-media is ≤0.09cm. Therefore, IMT values ≥0.09cm were considered indicative of thickened intima. In our study, intima-media thickness is considered abnormal if >0.07cm which is in agreement with Marasini et al (2005) study.

Another factor and owing to our selection of cases, only women were included in our study. Lawlor et al (2004) reported that IMT in men is significantly thicker than that in women when estimated using 7-8MHz frequency ultrasound.

Endothelial dysfunction is believed to represent a widespread phenomenon that occurs at an early stage in the atherogenic process. There is a correlation between endothelial function measured in the brachial and coronary circulations (Anderson et al, 1995). In our study, there is significant decrease in the endothelial function in SLE patients compared to the controls.

This is in agreement with that of the El Magadmi et al, 2004 who concluded that patients with SLE have endothelial dysfunction that remained significant even after adjustment for other classic CHD risk factors. Within SLE patients, endothelial dysfunction correlates negatively with IMT, another marker of early atherosclerosis. This is also in agreement with that of the Lee et al, 2006 who concluded that impaired endothelial function was prevalent in clinically quiescent SLE.

Within SLE patients, IMT showed a negative correlation with FMD (p<0.05). This is in agreement with the study by El-Magadmi et al (2004) who studied 62 women with SLE and 38 healthy women aiming to determine whether endothelial dysfunction occurs in SLE women or not and found also that in SLE patients, endothelial dysfunction correlates negatively with IMT which is considered another marker of early atherosclerosis. Therefore IMT, as an early marker of atherosclerosis, will represent the final common pathway of several other risk factors for the development of atherosclerosis.

At the same time, GTN responses did not differ between our SLE patients and controls (17.1% versus 20.2%) respectively. Our results were similar to that study by El-Magadmi et al (2004) where GTN dilatation in SLE patients was 17.4% versus 22.2% in the controls.

When comparing the subgroup of patient with active disease and those without active disease, the intima-media thickness of the active group is significantly thicker than those without active disease while the flow mediated dilatation or the dilatation ration did not differ and this may indicate that the intima-media thickness is more sensitive parameter in determination of the disease activity than endothelial dysfunction.

This is in agreement with the results of Turner et al, 2005 that concluded that there was no significant relationship between flow-mediated dilation
and markers of disease activity and this may be attributed to corticosteroid administration in the active disease group as steroid administration induced an improvement of vascular reactivity as detected by Tani et al, 2006.

Conclusion

Patients with SLE have endothelial dysfunction that remained significant even after adjustment for other classic coronary heart disease (CHD) risk factors. Within SLE patients, endothelial dysfunction correlates negatively with IMT, another marker of early atherosclerosis. Furthermore, IMT is significantly increased with the activity of the disease that clarifies the importance of prompt treatment of the activity in prevention of the vascular complication. Understanding the mechanism(s) of endothelial dysfunction in SLE may suggest novel strategies for CHD prevention in this context.

References


Carotid Artery Intima-Media Thickness and Echocardiographic Evaluation in Children with Type 1 Diabetes

HANAN M KAMAL, MD; HODA A ATWA, MD*; GEHAD SELMI, MD**

**Background:** Individuals with type 1 diabetes have a two- to fourfold increased risk of developing atherosclerotic diseases. The atherosclerotic process begins in childhood and develops non obviously for many decades before cardiovascular complications. Atherosclerotic vascular lesions involving a combination of fatty degeneration and vessel stiffening of the arterial wall and myocardial involvement impairing diastolic function may be present in adolescents and children with type 1 DM.

**The Aim of this Work:** Is to evaluate cardiac mass, cardiac function and carotid intima-media thickness in children with type 1 diabetes as a predictor of early atherosclerotic changes.

**Methods:** Sixty five children with type 1 diabetes and 30 healthy control age and sex matched children were studied. Blood pressure (BP) measurement was performed. Lipids profile, and glycosylated hemoglobin (HbA1c) were assayed. Carotid artery intima-media thickness (cIMT) was measured using High-resolution ultrasound. Echocardiography was performed to evaluate cardiac mass and function.

**Results:** Carotid IMT was significantly higher in diabetic children than control (0.44±0.08 vs. 0.41±0.02 mm). The mean cIMT was positively correlated with patients age, diabetes duration, BMI, BP, LDL cholesterol and HbA1c. High density lipoprotein cholesterol (HDL) was negatively correlated with cIMT. In a multivariate analysis, duration of diabetes, BMI, lower HDL cholesterol and HbA1c were independent risk factors for increased carotid IMT in diabetic children. No significant difference was found between both groups as regards cardiac mass, systolic and diastolic functions.

**Conclusion:** These data suggest that although there were no alteration in cardiac mass and function in diabetic children in the first few years after diagnosis, type 1 diabetes can be considered a risk factor for increased carotid IMT and may be related to early atherosclerotic vascular changes in those children.

**Key Words:** Type 1 diabetes – Carotid artery intima-media thickness – Cardiac mass – Cardiac functions.
Non invasive methods have confirmed fibrosis as a key feature of the heart in diabetic patients without evident cardiac disease. Increased levels of collagen have been detected in patients with type 1 or type 2 diabetes, as have changes in left ventricular diastolic function [7].

High-resolution ultrasound is a reliable, noninvasive method for detecting early structural and functional atherosclerotic changes in the arterial wall. Increased carotid intima-media thickness (IMT) is a structural marker of early atherosclerosis that correlates with vascular risk factors [8]. The aim of the present study is to determine the presence of increased subclinical atherosclerosis (measured as carotid intima-media thickness) and its related risk factors in children with type 1 diabetes.

**Subject and Methods:**

**Participants:**

The study included 65 children with type 1 diabetes (aged 11.56±4.03 years) and 30 healthy control subjects aged (11.66±3.17). The patients with diabetes were recruited from the outpatient clinic of the Department of Pediatrics, Suez Canal university hospital. The groups were matched for age, sex, and body size. None of the children had hypercholesterolemia. All children had total cholesterol and LDL cholesterol values less than the age- and sex-specific 90th percentile. All study population were normotensive, and had no chronic diseases other than type 1 diabetes. None of the patients with diabetes had evidence of microvascular complications (diabetic retinopathy, neuropathy, or microalbuminuria). None of the control children had chronic diseases or were taking regular medications.

**Ultrasound studies:**

The study was performed using an Acuson XP10 mainframe (Acuson, XP10) and a 7.5-MHz linear array transducer. All ultrasound scans were performed by an experienced vascular operator who was unaware of children’s clinical details. Blood pressure was measured three times from the brachial artery during the ultrasound study using a standard mercury sphygmomanometer.

**Carotid artery studies:** All studies were done following a predetermined, standardized scanning protocol for the right and left carotid arteries, using images of the far wall of the distal common carotid arteries. The place of measurement was anatomically standardized in every study by identifying the proximal part of the carotid bulb and then scanning the common carotid artery [8]. The bulb region was first scanned carefully in many interrogation angles to identify the beginning of the bulb. The scan was focused on the posterior (far) wall, and resolution box function was used to magnify the arterial far wall. Several images of common carotid far wall segment from 10 to 20 mm proximal to the carotid bulb (a far wall segment of 10 mm in width) were acquired. Also, the far wall IMT was taken at the mid segment of each carotid bulb. Images of the common carotid segment were acquired by using two interrogation angles in each case; anterior oblique (30° from midline) and lateral (100° from midline). The measurement of common carotid IMT, using either a mean of the two interrogation angles (anterior oblique and lateral) or a mean of 15 interrogation angles, yielded similar results.

All scans were digitally stored on the ultrasound system internal hard disk for subsequent off-line analysis. Two end-diastolic frames were selected and analyzed for mean IMT and maximum IMT, and the average reading from these two frames was calculated for both right and left carotid arteries.

**Echocardiography:**

Echocardiography was performed in the echocardiography laboratory of Suez Canal University Hospital. M-mode, Two-Dimensional and Doppler echocardiographic measurements were made by independent observers who had no knowledge of the clinical history.

End-diastolic measurements of posterior wall, interventricular septal thickness, end-systolic and end-diastolic measurements of LV diameter, left atrial diameter, ejection fraction (EF) by Simpson’s rule and LV mass measurement by the Penn Convention were measured [9]. Left ventricular mass index (LVMI) was obtained by dividing left ventricular mass by body surface area. The body surface area was calculated by using child nomogram using measurements of weight and height. For assessment of diastolic function, the following pulsed Doppler measurements were obtained: Maximal early transmitral velocity in diastole ($V_E$), maximal late transmitral velocity in diastole ($V_A$) and pulmonary venous flow to determine S wave, D wave and Atrial reversal wave [10].

**Serum lipids and HbA1c measurements:**

Venous blood samples were taken in the morning, after an overnight fast (10-12 h). Serum total
cholesterol, HDL cholesterol, and triglyceride concentrations were measured using standard enzymatic methods with the use of Boehringer Mannheim reagents, with a fully automated analyzer (Hitachi 917; Hitachi, Tokyo, Japan). LDL cholesterol concentration was calculated using Friedewald’s equation [11]. HbA1c was measured by high-performance liquid chromatography. Normal mean HbA1c is 5.4% (range 4.4-6.3).

Statistical methods:

Results are expressed as means ± SD. Comparisons between the groups were conducted by Student’s t test. Univariate associations between the study variables were analyzed by calculating the Pearson’s correlation coefficients. Multivariate analyses were done using linear regression technique. All statistical analyses were performed using SPSS 14.

Results

The two groups were matched for age, sex, and BMI. There were no significant differences between both groups as regards systolic and diastolic blood pressure (Table 1). Duration of DM in diabetic patients was 2.6±1.4 years. The mean HbA1c level in diabetic group was 8.9±1.8%. The diabetic group had significantly higher LDL cholesterol concentration (p=0.016), and higher serum triglycerides level (p=0.045) compared with control subjects (Table 1).

The mean carotid IMT was significantly increased in children with diabetes compared with healthy control subjects (0.44±0.08 vs. 0.41±0.02 mm; p<0.001) (Table 1). The mean bulb IMT was also significantly higher in children with diabetes (0.54±0.07 vs. 0.46±0.02 mm; p<0.001), but no plaque formations were observed in any of the children studied. Mean IMT was 0.43±0.1 vs. 0.40±0.2 mm (p=0.02) in boys with diabetes and control boys respectively, and 0.44±0.08 vs. 0.41±0.03 mm (p<0.001) in girls with diabetes and control girls, respectively. Thus, the difference in IMT between children with diabetes and control subjects was similarly seen in boys and in girls.

As regards the echocardiographic data, interventricular septal thickness (6.36±0.51 vs. 6.38±0.54 mm), LV posterior wall thickness (6.18±0.40 vs. 6.17±0.40 mm), and LV mass index (70.16±2.68 vs. 70.32±2.75 g/m²) were similar in patients and controls. Similarly the LV ejection fraction at rest was similar in patients and controls (70.43±1.74 vs. 70.56±1.78%). All study population has normal diastolic functions (Table 1).

The correlations between risk factors and carotid IMT are shown in (Table 2), separately for children with diabetes and control subjects. In children with diabetes, carotid IMT correlated significantly with age, diabetes duration, BMI, BP, HbA1c, HDL cholesterol and LDL cholesterol (Fig. 2). In control subjects, mean carotid IMT correlated with LDL cholesterol only.

In a multivariate regression model for children with diabetes, including age, sex, BMI, HbA1c, LDL cholesterol, HDL cholesterol triglycerides, and systolic blood pressure as independent variables, and carotid IMT as dependent variable r² 0.66. The significant predictor of carotid IMT were the duration of DM (t=5.73, p<0.000), HbA1c (t=3.81, p=0.000), HDL cholesterol (t=-3.13, p<0.003), and BMI (t=3.3, p<0.002) (Table 3).

Table 1: Clinical, biochemical profile, IMT, and echocardiographic findings of diabetic and control groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diabetic Mean±SD</th>
<th>Control Mean±SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.56±4.03</td>
<td>11.66±3.17</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.85±3.13</td>
<td>20.86±0.93</td>
<td>1.68</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>107.7±13.8</td>
<td>104.5±8.74</td>
<td>1.18</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic Blood pressure (mmHg)</td>
<td>74.92±7.67</td>
<td>74.50±6.47</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>160.54±40.70</td>
<td>134.70±14.52</td>
<td>3.37</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>68.96±25.47</td>
<td>57.43±5.31</td>
<td>2.44</td>
<td>0.016</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>52.47±7.77</td>
<td>48.73±6.47</td>
<td>2.29</td>
<td>0.024</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>51.32±9.07</td>
<td>47.76±4.56</td>
<td>2.02</td>
<td>0.045</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.44±0.083</td>
<td>0.41±0.024</td>
<td>6.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid bulb IMT (mm)</td>
<td>0.54±0.079</td>
<td>0.46±0.020</td>
<td>9.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>6.36±0.51</td>
<td>6.38±0.54</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>6.18±0.40</td>
<td>6.17±0.40</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac mass index</td>
<td>70.16±2.6</td>
<td>70.32±2.75</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>LV Ejection fraction</td>
<td>70.43±1.70</td>
<td>70.56±1.78</td>
<td>0.35</td>
<td>NS</td>
</tr>
</tbody>
</table>
Several previous studies demonstrated that carotid IMT is increased in adults with type 1 diabetes [12,13]. The results of the recent Epidemiology of Diabetes Interventions and Complications study [13], however, were somewhat contradictory, showing increased IMT only in male subjects in the internal carotid arteries but not in the common carotid. Differences in methodology and study population may offer an explanation for the discrepancy. The present study showed that young children with type 1 diabetes have significantly increased carotid artery IMT compared with healthy control children. The same results was reported by Järvisalo et al 2002 [14].

In the present study, all children had normal LDL cholesterol levels. Despite this, LDL cholesterol concentration was significantly related to increased IMT, both in children with diabetes and in control subjects. Our observations thus suggest that serum LDL cholesterol concentration, even within a normal range, is an important determinant of structural arterial changes already in childhood. In line with this, autopsy studies in children have also shown a significant relationship between serum cholesterol concentration and early atherosclerotic lesions [2]. Studies in adults have shown that LDL oxidation is increased in diabetes [15] and may explain some of the enhanced cardiovascular risk in type 1 diabetes [16].

Our results emphasize the importance of early detection and control of vascular risk factors in...
these children. For example, the target level for serum LDL cholesterol concentration may be different in diabetic than in healthy children, because diabetes may render the arterial wall more susceptible to harmful influences of circulating LDL cholesterol [17].

In the present study although all children have normal level of HDL cholesterol there was a negative correlation with carotid IMT. The HDL cholesterol is responsible for the removal of free cholesterol from the blood. Low plasma levels of HDL cholesterol are associated with increased cardiovascular risk. Some studies demonstrated the antiatherogenic properties of HDL, reducing the number of fatty streaks and inducing disease regression in the rabbit experimental model.

In multivariate analysis including diabetic children, HDL cholesterol emerged as an independent correlate for IMT, together with the metabolic control, duration of DM and BMI.

Epidemiologic and clinical evidence has emphasized the role of hyperglycemia in explaining the increased cardiovascular morbidity and mortality in diabetes [18]. Chronic state of hyperglycemia may induce atherogenesis by increasing oxidative stress [19], leading to increased LDL oxidation [20] and decreased nitric oxide bioavailability, including endothelial dysfunction [21]. Diabetic endothelial dysfunction is also expressed by increased vascular permeability related to hyperglycemia-induced ROS production occurring as early as two weeks after the onset of diabetes [22].

In the present study, the HbA1c levels in the children with diabetes were comparable to those reported previously in a population-based sample of children and adolescents [23]. This study showed a relationship between HbA1c and carotid IMT in children with diabetes. Alternatively, hyperglycemia may exert its deleterious effects by leading to glycosylation of LDL, which may increase its atherogenicity [24].

Consistent with previous studies, blood pressure was an independent predictor of IMT in the present study. The relationship between increased IMT and blood pressure suggests that smooth muscle proliferation also plays a role in the early diffuse thickening of the arterial wall [14].

As reported by previous studies also [25] there were no alterations in cardiac mass and functions in diabetic children noticed in this study which can be explained by short duration after diagnosis of diabetes.

The present study shows that young children with type 1 diabetes have significantly increased carotid artery IMT compared with healthy control children. These findings extend to observations of postmortem studies that have indicated a relation between early atherosclerotic vascular lesions and diabetic state [26], by demonstrating in vivo that diabetes predisposes to increased subclinical atherosclerosis at a very early age.

According to these postmortem findings and consistent correlations between lipid risk factors and IMT seen in the present study, it may be suggested that the diffusely increased carotid artery wall thickness in the children with diabetes reflects intimal changes related to early atherogenesis.

We conclude that type 1 diabetes is a risk factor for increased carotid IMT and may be related to early atherosclerotic vascular changes in children with diabetes. These results emphasize the importance of early detection and control of vascular risk factors in young children with diabetes. Ultrasound might be useful in clinical practice as a noninvasive method for monitoring vascular changes.

References
Carotid Artery Intima-Media Thickness & Echocardiographic


Surgical Closure of ASD: Comparative Study between Thoracotomy and Sternotomy Approaches

HANY A EL-DOMIATY, MD; HANAN M KAMAL, MD*; HUSSAM M ATTEF, MD**

**Background:** In recent years, cosmetic sequelae of operations have gained relatively more importance. The median sternotomy is the universal approach for closure of atrial septal defect (ASD). However, a prominent midline scar remains an unsightly and lifelong reminder of an otherwise low-risk and successful procedure.

**Aim of the Work:** To evaluate the efficacy of antrolateral thoracotomy for closure of ASD and comparing its result with that of median sternotomy.

**Material and Methods:** The study included 65 patients submitted for ASD closure after evaluation by transthoracic and transesophageal echocardiography in Suez Canal University hospital. The patients were divided into two groups according to surgical approach. Sternotomy group included 35 patients and thoracotomy group included 30 patients.

**Results:** Both patient groups were comparable as regard age, type of ASD, right ventricular (RV) diameter, RV pressure and the associated lesions. However, thoracotomy group included more female sex (88%) than sternotomy group (36%). Operative time (138±37 minutes in thoracotomy patients versus 118±18 minutes in sternotomy patients, \( p>0.05 \)), cardiopulmonary bypass time (52±34 minutes in thoracotomy patients versus 49±14 in sternotomy patients, \( p>0.05 \)), and cross clamp time (34±26 minutes in thoracotomy patients versus 33±23 minutes in sternotomy patients, \( p>0.05 \)), were comparable between the two patient groups. Operative and postoperative blood loss was more in sternotomy patients than thoracotomy patients but do not reach statistical significant level (1040±220 ml versus 864±582 ml, \( p>0.05 \)). Intensive care unit (ICU) stay was (1.41±0.7 days in sternotomy group, \( p>0.05 \)) and total hospital stay (8.2±5.1 days in sternotomy group versus 6.7±2.4 days in thoracotomy group, \( p<0.05 \)). In hospital pain score was high in sternotomy patients than thoracotomy patients but did not reach statistical significance (3.4±1.1 versus 3.1±1.4). Daily pain score was fluctuating; thoracotomy patients had more degree of pain in the first two postoperative days, while sternotomy patients had more pain from the 3rd postoperative day till the 6th day. Postoperative echocardiographic follow-up showed no evidences of persistent ASD, with insignificant differences between the two groups as regard cardiac dimensions and functions. Cosmetic satisfaction from the skin appearance was appreciated for thoracotomy than sternotomy in both females and males.

**Conclusion:** Antrolateral thoracotomy approach for closure of ASD can be accomplished safely and easily with no added difficulty. It is a valid alternative to sternotomy with improved cosmetic result and without any difference on cardiac structure and functions.

**Key Words:** Atrial septal defect – Thoracotomy – Sternotomy – Closure approach.

**Introduction**

Median sternotomy is the conventional approach for correction of cardiac defects, it is routinely performed with minimal morbidity and mortality at most centers but it is invasive and often yields poor cosmetic results [1,2,3]. This has been the rationale for modified surgical approaches for repair of atrial septal defects, such as a lower ministernotomy, transverse subxiphoid, right parasternal, and right antrolateral thoracotomy. It has also been one of the driving forces behind percutaneous device closure [2,4].

In this study we evaluate our experiences in surgical repair of atrial septal defect through right antrolateral thoracotomy comparing the results with closure through median sternotomy and study its effect on cardiac structure and function.
Material and Methods

This is prospective clinical study conducted in Suez Canal University hospital in Egypt. Sixty five patients were operated for closure of atrial septal defect.

The study included all patients operated for closure of atrial septal defect, as single lesion or associated with mitral valve disease and/or tricuspid valve disease.

Excluded from the study, all patients who had associated pulmonary stenosis, patent ductus arteriosus, complete atrioventricular canal, patients with persistent left superior vena cava, and female patients below 12 years old.

The patients were divided into two groups according to surgical approach. The type of approach was selected according to the patient’s preference after complete discussion of the two alternatives and the possible complications, and getting written consent.

**Sternotomy group:** Included 35 patients approached through median sternotomy incision.

**Thoracotomy group:** Included 30 patients approached through right antrolateral thoracotomy.

All the patients were prepared for surgery with full laboratory assessment, plain chest X ray, echocardiographic assessment, and coronary angiography if age above 40 years.

**Echocardiographic studies:** [5]

**Transthoracic echocardiography:** The patient was examined in parasternal short-axis, apical four chambers, and the subcostal views. Direct visualization of the atrial septum to assess the presence, location, size and type of ASD (secundum, primum or sinus venosus defects ) was done. Identification of the direction and magnitude of the shunt was assessed by color Doppler techniques.

The right chambers were properly estimated by transthoracic echocardiography together with any abnormal paradoxic septal motion which suggests a right chamber volume overload. An estimate of RV pressure was measured via the jet of tricuspid insufficiency.

When an ostium primum atrial septal defect was detected, careful assessment for the presence of associated abnormalities was done, including (1) an inlet ventricular septal defect, (2) a cleft mitral valve, (3) the presence and severity of atrioventricular valve regurgitation, and (4) partial attachment of the septal leaflet of the mitral valve to the interventricular septum. Cleft mitral valve was detected from the parasternal short-axis view by careful scanning at the tips of the mitral leaflets. The cleft will generally be recognized as a gap at approximately the 12 o’clock position.

Mitreral regurgitation is invariably present and often oriented in an eccentric direction.

Left ventricular ejection fraction was measured as an indicator of systolic functions.

**Transesophageal echocardiography:** Was done in some patient for further anatomic definition and to demonstrate if there is a sinus venosus defect.

**Anesthesia:**

The patients were operated under general anesthesia with single lumen endotracheal tube for patients submitted to median sternotomy and double lumen endotracheal tube in patients submitted for thoracotomy, invasive arterial line, and central venous line. The trans-esophageal echocardiography probe was inserted for evaluation of de-airing and assessment of surgical correction. Defibrillator pads are properly placed across the chest wall.

**Surgical technique:**

**Sternotomy group:** The patient positioned supine and a pillow is placed under the shoulder. The patient painted with iodine solution and draped exposing the anterior chest from the lower neck to the level of umbilicus.

Standard medline incision was done with skin incision extended from two finger breadth below the sternal notch to the xyphosternal junction, with skin flap advanced to the sternal notch and to the tip of xyphoid process, medline sternotomy was done utilizing vertical saw. Standard cannulation of aorta and bicaval cannulation was done after heparinization.

**Thoracotomy group:** The patient positioned supine and a pillow is placed under the right scapulae and shoulder to elevate the right chest about 45 degrees. The patient is painted with iodine solution and draped exposing the right anterior and lateral chest wall and both groin areas. The incision was performed over the fourth right intercostal space in male. While, in adult females the skin incision was done around the breast fold with...
elevation of the breast to the level of fourth intercostal space. In young female with ill defined breast fold, the skin incision was done 5 cm below the nipple level to avoid cutting through the breast tissue, then the subcutaneous fat and the mammary gland tissue are dissected from the fascia up to the fourth rib.

The pectoralis major was cut from the sternal edge to the anterior axillary line, and the thorax is entered through the bed of the fourth rib. The pericardium is opened longitudinally anterior to the phrenic nerve. Thymus tissue when large has to be dissected. An adequate exposure is achieved by traction on pericardial stay sutures.

The right side of the aorta is easily visualized, and selected for cannulation after passing tape around the aorta. Both venae cava were cannulated from the right atrium, for venous drainage. Right superior pulmonary vein was cannulated for venting in cases of simultaneous mitral valve replacement.

Normothermic cardiopulmonary bypass was utilized in both patient groups, and after snaring of both vena cava, myocardial protection was achieved with warm blood potassium infused antegradely in the aortic root by the perfusionest. Potassium chloride 30 milliequivalent was infused over three minutes initially and maintenance dose of 10 milliequivalent potassium chloride infused over three minutes every 20 minutes.

Right atrium was opened and explored for the extent of the ASD, and left atrium explored for the orifices of the four pulmonary veins. Then the mitral valve pathology was corrected first through the ASD if large enough or through left atriotomy if ASD is small. The ASD was closed either with direct suture, or with pericardial patch, according to the size and the site.

The pericardial stay-sutures are then removed before gradually inflating the lungs for removal of air from the left atrium through the patch before tying the suture of the patch. The right atrium was closed and both vena cava snares were removed to fill the heart with blood. De-airing of the cardiac chambers was done through the aorta by root vent suction and left atrial vent if inserted.

De-airing was confirmed with trans-esophageal echocardiography. Sinus rhythm was regained either spontaneously or with electrical cardiac shock with internal paddle.

After weaning from cardiopulmonary bypass and careful hemostasis, two pericardial drains was inserted for sternotomy patients. While, in thoracotomy patients, one pericardial and one pleural drain was inserted. The pericardium was closed partially in all patients.

All patients were evaluated in ICU and during their hospital stay. Standard analgesic medications were given to all patients in the two groups (paracetamol one gram every 6 hours), addition of tramadol or pethidine was given according to the degree of pain and patient request. The severity of pain related to the chest wound was assessed daily, using numerical scale from 0 to 10 (The answer was given orally and written on a scale, with 10 being described as an excruciating pain, and 0 as no pain at all).

**Statistical analysis:** Statistical analyses were carried out with the use of SPSS software version 12 (SPSS Inc, Chicago, IL). The data were collected as mean ± standard deviation; student t-test was utilized for comparing quantitative values, chi-square test and fisher exact test for qualitative values, and ANOVA test for repeated measures. p-value considered significant if <0.05, highly significant if <0.01 and non significant if >0.05.

**Results**

The study included 65 patients submitted for ASD closure, the patient were divided into two groups according to surgical approach. Sternotomy group included 35 patients and thoracotomy group included 30 patients.

There was no significant differences between the two groups, as regard patient’s age (18.1±13.9 years in thoracotomy group, versus 16.4±10.1 years for sternotomy group, p>0.05). Thoracotomy group included 88% females, however sternotomy group included 36% females, p<0.05.

There were no significant differences between the two patient groups as regard the type of atrial septal defect or the associated lesions. Within patients of sternotomy group, there were 31 patients (88.6%) with secondum ASD, four patients (11.4%) with premium ASD, two patients (5.7%) had cleft anterior mitral valve leaflet, one patient (2.9%) had rheumatic mitral valve require replacement, and two patients (5.7%) had tricuspid regurgitation required repair. However, in thoracotomy group, there were 28 patients (93.3%) with secondum ASD, two patients (6.7%) with premium ASD, two
patients (6.7%) had cleft anterior mitral valve leaflet, one patient (3.3%) had rheumatic mitral valve require replacement, and two patients (6.7%) had tricuspid regurgitation required repair (Table 1). There were no significant differences also between the two groups as regard the echocardiographic parameters including the RV diameter, the RV pressure and the ejection fraction preoperatively (Table 2).

There was no operative or postoperative mortality in both patient groups. Total operative time was prolonged in thoracotomy group than sternotomy group, but do not reach statistical significant level (138±37 minutes versus 118±18 minutes, p>0.05). Also, no statistical significant differences were detected between the two patient groups as regard both cardiopulmonary bypass time (52±34 minutes in thoracotomy group and 49±14 minutes in sternotomy group, p>0.05) and aortic clamping time (34±26 minutes in thoracotomy group and 33±23 minutes in sternotomy group, p>0.05) (Table 3).

There was no statistical significant difference between the two groups as regard the technique of ASD closure. Direct suture closing of ASD was utilized in 17 patients (48.6%) in sternotomy group, while utilized in 14 patients (46.7%) in thoracotomy group. Pericardial patch closure was utilized in 18 patients (51.4%) in sternotomy group, while utilized in 16 patients (53.3%) in thoracotomy group.

Blood loss both operative and postoperative was more in sternotomy group than thoracotomy group, but not reach statistical significant level (1040±282 ml versus 864±582 ml, p>0.05). Also, the need for blood transfusion was higher in sternotomy group than thoracotomy group, but did not reach statistical significant value (650±350 ml (versus 420±530 ml, p>0.05).

ICU stay was comparable between the two patient groups (1.4±0.7 days versus 1.32±0.4 days, p>0.05). Also, total hospital stay was comparable in both patient groups (8.2±5.1 days in sternotomy group versus 6.7±2.4 days in thoracotomy group, p<0.05) (Table 3).

The total in hospital pain score was high in sternotom group than thoracotomy group, but did not reach statistical significance (3.4±1.1 versus 3.1±1.4, p>0.05) daily postoperative pain score was high in thoracotomy group than sternotomy group during the first two postoperative days (5.2±1.4 versus 3.2±1.1, respectively, p<0.05).

However, from the 3rd postoperative days to the 6th postoperative day thoracotomy group show significant less degree of pain than sternotomy group (2.1±1.2 versus 4.8±1.7, respectively, p<0.05). After the 6th postoperative day, there was no significant differences in the two patient groups (1.1±0.9 versus 1.3±0.8, respectively, p>0.05). The requirement for additional pain control medication was correlated with the degree of pain in the two patient groups.

Postoperative complications were reported in 8 patients (22.9%) in sternotomy group. One patient (2.9%) was explored for bleeding, 6 patients (17.1%) had postoperative atelectasis, one patient (2.9%) had post-pericardiotomy syndrome, and two patients (5.7%) had superficial wound infection.

Postoperative complications were reported in 6 patients (20%) in thoracotomy group. One patient (3.3%) had postoperative bleeding required exploration and ligation of the internal mammary artery. Three patients (10%) had postoperative atelectasis of right lung responded to conservative management, and one patients (3.3%) had superficial wound infection.

Length of skin incision was significantly small in thoracotomy patients than sternotomy patients, 7.5±1.8 cm versus 13.1±2.5 cm respectively, p<0.05.

Postoperative echocardiography follow-up at hospital discharge & 6 months postoperative, show no evidences of persistent postoperative ASD, with insignificant differences between the two groups as regard cardiac dimensions and functions (Table 4).

Patient's satisfaction with the incision was high in thoracotomy group than sternotomy group, especially in female and young male patients.

**Table 1: Preoperative diagnosis in the two patient groups.**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Sternotomy group</th>
<th>Thoracotomy group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>%</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Secondium ASD</td>
<td>31</td>
<td>28</td>
<td>93.3</td>
</tr>
<tr>
<td>Primum ASD</td>
<td>4</td>
<td>11.4</td>
<td>2</td>
</tr>
<tr>
<td>Cleft AMV</td>
<td>2</td>
<td>5.7</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic MV</td>
<td>1</td>
<td>2.9</td>
<td>1</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>2</td>
<td>5.7</td>
<td>2</td>
</tr>
</tbody>
</table>

ASD = Atrial septal defect.  
AMV = Anterior mitral valve leaflet.  
MV = Mitral valve.
In recent years, cosmetic sequelae of operations have gained relatively more importance, even in heart surgery. The median sternotomy is the universal method of exposure for most cardiac procedures [1,4]. However, especially in patients with simple cardiac defects, a prominent midline scar remains an unsightly and lifelong reminder of an otherwise low-risk and successful procedure [2,6].

Several alternative approaches were described for closure of atrial septal defect. Lower medline incision with partial sternotomy [1,7] and right parasternal incision [3], both incision were smaller than medline sternotomy. However, both skin incisions appear in the front of the chest and their cosmetic results were unsatisfactory for most of the patients.

Transxyphoid approach without sternotomy for closure of ASD [8], had good cosmetic results. However, it required cannulation of groin vessels with its own complication, also require excessive retraction of the sternum to gain visualization through small surgical field which may turn the simple procedure into technically difficult one [9].

Bilateral submammary incision with medline sternotomy, utilized by some authors for closure of ASD [9,10] but this incision required extensive dissection to expose the sternum with potential risk of postoperative infection and seroma formation, also late sensory change in the breast was reported.

Right antrolateral thoracotomy was utilized initially for redo mitral valve surgery, to avoid re-sternotomy with its own complications, and now widely used for closure of ASD by several authors [2,4,10-13] as it give good exposure to the intra-thoracic structures, also has better cosmetic result in females as the scar almost invisible in the breast fold.

In this study we reported our result with closure of atrial septal defect through right antrolateral thoracotomy and comparing the result with that of median sternotomy.

To avoid the effect of antrolateral thoracotomy on breast development, which documented by several studies [14,15], we did not perform it in females below 12 years of age without defined breast tissue.

In our study we preferred central cannulation of the heart, in the expenses of enlarging the skin incision to avoid groin incision for femoral cannulation. Thoracotomy incision in our study was 7.5±1.8 cm. Also, Giamberti [13], Bichell [12], and Abdel-Rahman [11], preferred one thoracotomy incision with central cannulation than adding a groin incision for femoral vessels cannulation.

However, Mulder et al 2002 [16] preferred 5 cm skin incision minithoracotomy and groin incision 3 cm for femoral artery and vein cannulation with central SVC cannulation. But they reported

Table 2: Preoperative Echocardiographic data in the two patient groups.

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Sternotomy group</th>
<th>Thoracotomy group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV diameter (mm)</td>
<td>30.20±2.86</td>
<td>30.50±3.18</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RV pressure (mmHg)</td>
<td>42.7±3.72</td>
<td>42.9±5.13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>EF %</td>
<td>64.31±4.24</td>
<td>64.20±4.27</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

RV = Right ventricle. 
EF = Ejection fraction.

Table 3: Operative and postoperative data of the two patient groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sternotomy group</th>
<th>Thoracotomy group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOR time (minute)</td>
<td>118±18</td>
<td>138±37</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CBP time (minute)</td>
<td>49±14</td>
<td>52±34</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AC time (minute)</td>
<td>33±23</td>
<td>34±26</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Skin incision</td>
<td>13±2.5</td>
<td>7.5±1.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>1040±220</td>
<td>864±582</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>1.41±0.7</td>
<td>1.32±0.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>8.2±5.1</td>
<td>6.7±2.4</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

TOR time = Total operative time. 
CBP = Cardiopulmonary bypass. 
AC = Aortic clamp. 
ICU = Intensive care unit.

Table 4: Postoperative echocardiographic data in the two patient groups.

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Sternotomy group</th>
<th>Thoracotomy group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV diameter (mm)</td>
<td>28.94±2.88</td>
<td>28.53±2.72</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RV pressure (mmHg)</td>
<td>40.71±3.72</td>
<td>40.96±5.13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>EF %</td>
<td>67.31±4.23</td>
<td>67.20±4.18</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

RV = Right ventricle. 
EF = Ejection fraction.

Discussion

In our study we preferred central cannulation of the heart, in the expenses of enlarging the skin incision to avoid groin incision for femoral cannulation. Thoracotomy incision in our study was 7.5±1.8 cm. Also, Giamberti [13], Bichell [12], and Abdel-Rahman [11], preferred one thoracotomy incision with central cannulation than adding a groin incision for femoral vessels cannulation.
complications of femoral artery in 2% require patch enlargement of the artery, and iliac vein lesion require stenting in 4% of their patients, also groin wound infections were reported in 6% of their patients. Moreover, the summation of both thoracotomy incision and groin incision was not differ from lone thoracotomy incision.

Tiete [15] and Doll [9] preferred a right sub-mammary mini-incision and considered direct aortic cannulation to be hazardous and femoral arterial cannulation was used instead. However, we found insertion of tape around the aorta with slight traction by assistant during the insertion of aortic cannula is efficient to make insertion of aortic cannula easily performed and we reported no difficulty in insertion of aortic cannula. Also, both Debritz [2] and Giamberti [13] reported no difficulties in insertion of aortic cannula through right anterolateral thoracotomy in their groups of patients.

Helps [11] reported phrenic nerver damage in 31% of their patients after right anterolateral thoracotomy. They define several possible causes for their results included (direct injury, electrocautery used near a nerve, extensive thymus dissection, placement of pericardial stay sutures and traction, internal jugular vein cannulation, and topical cooling).

We did not report any patient with phrenic nerve impairment postoperative, this may be due to avoidance of topical cooling in our patients as we use normothermic cardiopulmonary bypass, also our patients were older age than the previous study. Moreover, many other studies [1,2,12,13] did not report any patient with phrenic nerve injury with the use of hypothermic cardiopulmonary bypass and topical cooling during ASD closure.

Therefore, the anterolateral approach can be used safely by appreciating the course of the nerve, pulling adequately on the pericardial traction sutures, and avoiding topical cooling.

Although data were collected prospectively, a limitation of this study is that patients were not randomized and the decision as to which incision to use was left to the patients. However, due to the relative simplicity of the procedures and all the procedure were operated by the same surgeon, it is unlikely that this factor had an influence on the outcome variables. The lack of randomization is also reflected in the higher number of female patients who select the thoracotomy incision.

In our study, there were no significant differences was reported between the sternotomy and thoracotomy groups, as regard total operative time, cardiopulmonary bypass or aortic clamping time. In agreement with our results both Bichell [12] and Giamberti [13] reported no significant differences between thoracotomy and sternotomy during closure of ASD. However, Tiete [15] and Doll [9] reported significant prolonged total operative time, cardiopulmonary bypass time and aortic clamping time, in thoracotomy patients. This may be due to his selection of thoracotomy and groin incision, which consume more time, also, working through a small thoracotomy field may slow the procedure.

Intra-operative and postoperative blood loss was comparable in both groups. Also most of the published literatures reported no significant differences in blood loss or the need for transfusion between thoracotomy and sternotomy. Actually the simplicity of the procedure with short time on cardiopulmonary bypass minimizes the incidence of blood loss and the requirement for transfusion.

The exposure of intra-cardiac structures, using the anterolateral thoracotomy was good, with no added difficulty if working through thoracotomy than sternotomy. Also, associated procedure of the mitral valve can be easily performed through the ASD or separate left atriotomy without difficulty [1,12,13,16]. In our series, simultaneous procedures like mitral valve repair or replacement were performed through the same skin incision, without additional morbidity. Other procedures like tricuspid valve repair also can be done without adding difficulties.

The cosmetic healing after using both sternotomy and anterolateral thoracotomy was excellent in our series. Wound dehiscence was completely absent and superficial wound infection was infrequent in the two patient groups. The length of skin incision was significantly shorter in thoracotomy patients than sternotomy patients. Also, patient satisfaction by the wound appearance was highly appreciating the thoracotomy incision over sternotomy.

**Conclusion**

Anterolateral thoracotomy approach for closure of ASD can be accomplished safely and easily. It is a valid alternative to sternotomy with small skin incision and improved cosmetic results without any difference on cardiac structure and functions.
References


Introduction

Over the past decades, continuous improvement of the endocardiac mapping techniques resulted in a better understanding of the typical right atrial flutter (AFL) circuit [1-2]. This advance contributed to the improvement in the radiofrequency energy (RF) ablation technique for the treatment of cavo-

cricuspid isthmus (CTI) dependent AFL [3]. Catheter ablation of the CTI using RF is considered now as the first line of therapy in patients with AFL with a higher success rate, lower recurrence rate and better quality of life compared to pharmacologic therapy [4].

Two main approaches namely the electrophysiological (EP) conventional cavotricuspid isthmus (CTI) mapping and the 3-D electroanatomic guided CTI mapping and ablation are widely used by most EP centres nowadays. In this work, we represent a prospective randomized study comparing both techniques in terms of safety and efficacy.
Patients and Methods

Patients:

Thirty-eight patients (pts) with symptomatic recurrent AFL (27 M, mean age 58±13 years), admitted to the EP lab-Critical Care Department-Cairo University were enrolled for RF ablation of AFL. Twenty pts (53%) had structural heart disease and 9 (24%) had associated paroxysmal atrial fibrillation (Table 1).

Table 1: Clinical characteristics of the patients included in the study.

<table>
<thead>
<tr>
<th></th>
<th>All pts (N=38)</th>
<th>Group A (N=19)</th>
<th>Group B (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±13</td>
<td>58±14</td>
<td>59±13</td>
</tr>
<tr>
<td>Sex</td>
<td>27 (71%)</td>
<td>15 (79%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>SHD</td>
<td>1 (58%)</td>
<td>9 (47%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>AF</td>
<td>9 (24%)</td>
<td>6 (32%)</td>
<td>3 (16%)</td>
</tr>
</tbody>
</table>

On admission, all pts. were subjected to full history taking, complete physical examination, standard 12-leads ECG, tranthoracic echocardiography and laboratory investigations including serum potassium, complete blood picture and coagulation profile. All antiarrhythmic drugs were discontinued for 5 half lives before the electrophysiological mapping procedure except for amiodarone.

Programmed electric stimulation (PES) was carried using Nihon Koden stimulator Patients were randomly divided into 2 equal groups: Group A included 19 pts subjected to EP guided CTI mapping and ablation using the 24 pole orbiter mapping catheter and group B included 19 pts subjected to 3-D electroanatomic guided mapping and ablation of the CTI using the Carto XP system.

The femoral vein was then punctured under local anesthesia using the Seldinger’s technique with subsequent insertion of the diagnostic and ablation catheters under fluoroscopic guidance. A conventional computerized EP system was used as bipolar electrogams (bandpass, 30 to 500Hz) were recorded on a multichannel polygraph (LabSystem PRO®, Bard Electrophysiology). For group B pts, the CTI was constructed using an electroanatomic mapping system (CARTO™ XP, Biosense Webster, Johnson & Johnson).

Group A (conventional mapping and ablation):

A 6-F 24-pole mapping catheter (Orbiter, Bard Inc, 2-7-2mm electrode spacing) was used for mapping the CTI. It was introduced into the CS via the femoral vein, then advanced and rotated so that the distal poles were in the CS, the middle poles on the CTI and the proximal poles on the lateral RA wall (Fig. 1). A 7-F deflectable quadripolar mapping/ablation catheter (Cordis-Webster, Johnson and Johnson Inc., 2mm electrode spacing, 8mm tip catheter, or Stinger, Bard 8mm tip catheter) was introduced for ablation of the CTI.

Figure 1: Fluroscopic image in LAO (right side) and RAO view (left side) showing the Orbiter 24 poles mapping catheter with its distal electrodes within the coronary sinus (CS), its mid poles at the CTI and its proximal poles over the right atrial lateral wall. The ablation catheter (RF) is placed over the CTI with its distal tip at the anterior limit of the CTI (inferior border of the Tricuspid annulus) as evident in the RAO view.

Endocardial bipolar electrograms were obtained from both the 24-pole mapping catheter and the quadripolar mapping/ablation catheter. Electrograms recorded were filtered between 30 and 500MHz using the Electrophysiology Bard lab-system Duo at a chart speed of 100mm/sec.
The mapping procedure was started either in AFL rhythm or during CS pacing for patients presenting in sinus rhythm during the EP procedure.

The Orbiter catheter showed a septo-lateral activation wavefront of the CTI and a caudo-cranial activation wavefront of the lateral wall of the RA for patients mapped during clockwise typical AFL or those presenting in sinus rhythm and mapped during CS pacing (Fig. 2). Whereas, it showed a latero-septal activation of the CTI and a cranio-caudal activation of the lateral wall of the RA during counterclockwise typical AFL (Fig. 3). Radiofrequency ablation was carried during CS pacing at 600ms for pts. presenting in sinus rhythm, and after restoring sinus rhythm for those presenting in AFL in order to validate for CTI conduction block.

Figure 2: Electrocardiogram (right side) showing leads I, III and V1 surface ECG leads in the upper 3 panels, endocardial activity from the ablation catheter in the 4th panel, and endocardial atrial activity from the 24 poles of the Orbiter catheter (shown fluoroscopically on the left side) with the pacing spike shown on its distal pole and endocardial atrial electrograms spreading from its septal to lateral poles as shown by the arrow.

Figure 3: On the left side, a 12 lead surface ECG is shown consistent with a typical counterclockwise AFL. On the right side, endocardial atrial electric activity obtained from the Orbiter catheter (shown fluoroscopically in the middle) shows a latero-septal atrial depolarization of a macroreentrant circuit of 280ms, which is consistent with a pericricuspid counterclockwise rotating AFL.
The ablation catheter was then placed at the anterior aspect of the CTI (the inferior border of the Tricuspid annulus), which is confirmed by recording an endocardial atrial and ventricular electrograms with a ratio 1:1. Radiofrequency energy was applied between the distal tip of the ablation catheter and a cutaneous patch electrode placed over the left scapula of the patient with a maximal target temperature of 70ºC and a maximum power of 70 Watt. The first RF point was then applied at the anterior aspect of the CTI. The catheter was then withdrawn over the CTI where RF energy was applied in a stepwise point by point fashion for 60 s each point till the posterior part of the CTI (the junction of the IVC with the right atrium) aiming at creating a complete line of block created by the RF applications in the CTI.

Complete bidirectional conduction block within the CTI was defined by the presence of complete reversal of lateral right atrial activation sequence up to the line of ablation during CS pacing and detection of double potentials throughout the whole length of the ablation line, with an isoelectric line of at least 90 ms (Fig. 4).

If complete block of conduction was not achieved, remapping of the ablation line was performed by the ablation catheter, where RF applications were applied at sites with no wide double potentials till achievement of complete block.

**Group B (Electroanatomic mapping and ablation):**

In cases presenting in AFL, the CTI was mapped during AFL and the window of interest was defined to be 95% of the tachycardia cycle length and...
Ahmed Abdelaal, et al

divided equally into 2 intervals extending before and after the atrial electrical reference potential on the CS catheter. Whereas in cases presenting in sinus rhythm, the CTI was mapped during low septal pacing (CS pacing) and the window of interest was selected to be extending 300ms after the pacing spike of the CS catheter.

The Navistar mapping/ablation catheter was introduced in the RA under fluoroscopic guidance. Then it was placed over the CTI with its tip on the TA, where 3 points were acquired (with an AV ratio <1:1), a central point at the most inferior part of the TA and 2 points at adjacent lateral and septal sites, each approximately 15-20mm apart from the central point. After these points had been acquired, the mapping procedure was continued using the EA mapping system without fluoroscopy. The mapping catheter was then withdrawn, over the CTI till the limit of the IVC, where another 2-3 points were acquired corresponding to the first AV 3 points. The 3 points at the TA were tagged with coloured dots and the 3 points at the IVC were tagged with different colour. This 6-point reconstruction resulted mostly in a rectangular shaped figure that clearly defined the target area for catheter ablation, i.e. the CTI area. If necessary, different mapping points could be acquired while dragging the catheter over the CTI (Fig. 5).

Figure 5: A 12 lead surface ECG consistent with a typical counterclockwise AFL (shown on the left side). Electroanatomical map of the CTI (shown in the middle) using the 6 point approach: 3 orange points tagged as the lower border of the Tricuspid annulus and 3 purple points tagged as the limit of the IVC with the CTI. A colour scale bar on the right side showing a colour coded activation time gradient with red denoting earliest activity and purple as latest activity. The CTI map shows a latero-septal spread of activation as shown by the homogenous colour gradient from red (on the lateral side of CTI) to purple on its septal side. Each of the 3 rectangles (shown on the right side) shows AVF surface ECG lead (white coloured upper panel), endocardial electrical activity from the reference coronary sinus catheter (green coloured middle panel) and local electrical activity from the NaviStar catheter at different points on the CTI (blue coloured lower panel).

Radiofrequency ablation was carried during CS pacing at 600ms for pts. presenting in sinus rhythm. Whereas, it was carried during AFL till sinus rhythm was restored and then the procedure was continued during CS pacing at 600ms.

Radiofrequency energy was applied in a 70 Watt, 70°C power and temperature limited mode. It was then applied in a linear point by point fashion (each for 60 seconds) within the CTI from the TA till the IVC while observing the catheter stability.
Mapping & Ablation of Typical Atrial Flutter

using the CARTO XP® system during each RF energy application. The sites of all RF pulses were annotated & colourly coded on the EA map (Fig. 5).

The "bottom" view (strictly caudal projection) was mainly used to manipulate the ablation catheter because lateral or septal displacement can be judged, as can the distance from the TA and IVC. Additional projections, like the right anterior oblique view, were additionally used if necessary.

After the ablation line was completed anatomically till the IVC, the CTI was remapped during CS pacing (for patients presenting in sinus rhythm or those presenting in AFL after restoration of sinus during RF ablation) to control for double potentials (on the ablation line) and conduction times on either sides of the ablation line (Fig. 6) in order to validate for the presence for complete block or conduction gaps along the CTI.

Complete bidirectional conduction block within the CTI was defined by the presence of Cranio-caudal depolarization of the lateral right atrial wall up to the line of ablation during CS pacing (7) and double potentials (with an isoelectric line >90ms) throughout the whole length of the ablation line (Fig. 7).

Figure 6: Electroanatomic remap of the CTI during pacing from the CS catheter showing block of conduction anteriorly and posteriorly marked by the tagged blue dots of double potentials. A conduction gap is unmasked at the mid CTI as evident by the homogenous septo-lateral spread of activation at this area with recording a sharp atrial electrogram at this point (shown on the right side). Two RF pulses (2 tagged red points) were applied at this point to achieve complete CTI block.

Figure 7: Electroanatomic map of the CTI during coronary sinus pacing denoting complete conduction block along the ablation line as shown by the latero-septal depolarization of the CTI lateral to the ablation line (from light blue to purple) and the recording of double potentials along the ablation line.
Ahmed Abdelaal, et al

If remapping the CTI didn’t reveal complete block of conduction, RF applications were applied at the conduction gaps within the line of ablation as detected by the absence of wide double potentials and the smooth passage of the depolarization wavefronts from septal to lateral CTI throughout these gaps within the ablation line during CS pacing.

Results

This group included 38 pts., with a mean age of 58±13 years. Twenty-seven pts. (71%) were males and 6 (29%) were females. Structural heart disease was present in 20 pts. (53%) and associated episodes of paroxysmal AF was documented in 9 pts. (24%). Twenty-two pts. (58%) presented in sinus rhythm and 16 (42%) in incessant typical counterclockwise AFL by the time of the mapping procedure.

Patients were randomly and equally divided into 2 major groups (the control and case study groups) matched for age, sex and clinical characteristics.

Both groups were compared in terms of primary and secondary end points:

The primary endpoint was defined as the achievement of complete bidirectional CTI block by the end of the procedure.

The secondary endpoints were defined as the incidence of complications (%), total procedure and fluoroscopic exposure times (min), number and duration (min) of RF pulses required to achieve complete CTI block.

The primary endpoint:

The overall success rate was 97% as complete bidirectional CTI block was achieved in all but 1 of the pts. (37/38) with insignificant difference between both groups: 95% (18/19) for group A compared to 100% for group B (p>0.05).

The secondary endpoints:

The overall incidence of complications was 5% (2/38 pts) with no statistically significant difference between both groups (first degree AV block in 1 pt from either groups).

The duration of RF energy applied was insignificantly shorter in group B (9.4±4.7min) compared to group A (12±4.7min). Total procedure time was not different between both groups (104±33min in group A and 104±32min in group B). However, fluoroscopic exposure was significantly lower (p<0.05) using EA mapping (8±6min) compared to conventional mapping (20±12min) (Table 2).

Table 2: Secondary endpoints of both groups of patients.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Conventional mapping (group 1 N=19)</th>
<th>Electroanatomic mapping (group 2 N=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF number</td>
<td>13.6±6</td>
<td>11.6±6.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RF duration (min)</td>
<td>12±4.7</td>
<td>9.4±4.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>104±33</td>
<td>104±32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fluoroscopic exposure (min)</td>
<td>20±12</td>
<td>8±6</td>
<td>0.004</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1/18 (5.5%)</td>
<td>1/19 (5.3%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Discussion

Our study consisted of 38 pts. subjected to RF ablation of the CTI for treatment of typical AFL. Complete bidirectional CTI block was achieved in all but 1 of our pts. (97%) with a 5% complication rate and a mid term (6 month follow-up) recurrence rate of 5% (2/38 pts.). Our overall results were in agreement with most studies conducted on typical AFL ablation [5,6,7] (Table 3).

Table 3: Results of typical atrial flutter ablation.

<table>
<thead>
<tr>
<th>Calkins et al</th>
<th>Schmieder et al</th>
<th>Willems et al</th>
<th>Our study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts.</td>
<td>150</td>
<td>363</td>
<td>80</td>
</tr>
<tr>
<td>Complete CTI</td>
<td>88%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Complications</td>
<td>2.7%</td>
<td>3%</td>
<td>–</td>
</tr>
<tr>
<td>Mean follow-up period (months)</td>
<td>6</td>
<td>16.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Recurrence</td>
<td>13%</td>
<td>9.6%</td>
<td>11%</td>
</tr>
</tbody>
</table>

The results of our study demonstrated that both conventional and EA mapping and ablation strategies are highly and similarly effective for treatment of typical AFL with a success rate of 100% and an insignificant difference regarding RF energy applied. However the fluoroscopic exposure time could be markedly reduced (p=0.004) with the EA mapping system (11.1±6.9) compared to the conventional system (22.9±12.6) without prolongation of the procedure time required to achieve acute success. This was in complete concordance with the Willems et al, that showed that the elec-

|
troanatomic mapping system isn’t superior to conventional technique for ablation of typical atrial flutter apart from its ability to significantly reduce the fluoroscopic exposure time [5] (Table 4).

Table 4: Comparison between conventional and electroanatomical mapping and ablation of typical atrial flutter.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts.</td>
<td>Conventional</td>
<td>Electroanatomic</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.9±8.2</td>
<td>62.4±9.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>SHD</td>
<td>42.5%</td>
<td>50%</td>
</tr>
<tr>
<td>Acute success</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>172.5±47.4</td>
<td>169.3±47.3</td>
</tr>
<tr>
<td>RF number</td>
<td>16.7±6.5</td>
<td>13.2±5.3</td>
</tr>
<tr>
<td>RF duration (sec)*</td>
<td>54.8±4.9</td>
<td>55.6±4.3</td>
</tr>
<tr>
<td>Fluroscopic duration (min)</td>
<td>29.2±9.4</td>
<td>7.7±2.8</td>
</tr>
<tr>
<td>Recurrence</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

SHD: Structural heart disease. Sec: Seconds. *: Mean duration of RF energy per application.

These findings were confirmed by a prospective randomized multicenter center comparing both techniques for typical atrial flutter ablation. It demonstrated a 50% reduction in fluoroscopic exposure using the electroanatomic mapping but at the expense of increased cost of the procedure [8].

Conclusion

The electroanatomic mapping system isn’t superior to the conventional fluoroscopic guided mapping and ablation for treatment of CTI dependent atrial flutter apart from its ability to reduce the fluoroscopic exposure time.

References

Supraventricular Tachycardia with Multiple Pathways. Prevalence and Outcome of Radiofrequency Ablation: A 15 Years Registry

KHALED HUSSEIN, MD

**Background:** Radiofrequency (RF) ablation of supraventricular tachycardia (SVT) depends upon precise diagnosis of the underlying arrhythmogenic substrate [AV nodal or accessory pathway (APs)]. Application of RF current in the apparently appropriate site may not be successful and an occasional mechanism is the presence of more than one pathway.

**Aim of the Study:** Was reporting the results of RF ablation in cases of SVT having more than one mechanism over a period of 15 years (from Jan. 1992 to Jan. 2007).

**Methods and Results:** Thirty sex patients (pts) of total 915 (3.9%) cases having more than one mechanism of SVT (18 M, 18 F; mean age 26±14 yr), referred to EP lab of Critical Care Medicine Department at Cairo University. Associated heart disease was met in 5 pts. The resting ECG was pre-excited in 9 pts. All pts were subjected to detailed EP study and radiofrequency catheter ablation (RFCA) at the same sitting in our institution.

Thirteen pts had 2 types of SVT [atrioventricular nodal reentrant tachycardia (AVNRT) and atrophicventricular reentrant tachycardia (AVRT)], 21 pts had more than one AP. While the remaining two pts had 3 types of SVT (AVNRT+AF+AT). The two types of tachycardia (AVNRT & AVRT) were suspected during the study in 7 pts, while in the remaining 6, the second type of tachycardia was induced after ablation the first one. Successful ablation was achieved in 12 pts without recurrence except one who was successfully ablated in 2nd session. Complications occurred in 2 pts, one with midseptal AP who developed complete heart block and needed permanent pacemaker implantation and the other developed acute lower limb ischemia.

SVT with two APs was suspected during the study in 4 pts. Dual APs were suspected from ECG in one pt (atypical pre-excitation during sinus rhythm which did not conform to a specific location). In the remaining 16 pts, the second AP was diagnosed after the ablation of AVRT utilizing the first AP. Successful ablation was achieved in all pts without complications or recurrence except in 7 pts who experienced recurrence of AVRT (4 pts with right anteroseptal AP). All underwent redo ablation, the procedures were successful and no recurrence reported on follow-up. Regarding the 2 pts with triple tachycardia, they underwent successful ablation trials with no recurrence.

**In Conclusion:** The presence of more than one arrhythmogenic mechanism should always be kept in mind. Meticulous EP diagnosis and careful post ablation analysis would obviously save effort to allow careful diagnosis of the unlikely situations of multiple pathways.

**Key Words:** Supraventricular tachycardia – Radiofrequency ablation – Multiple accessory pathways.

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**Introduction**

Supraventricular tachycardias include all tachyarrhythmia that originate above the bifurcation of the bundle of His or incorporate tissues proximal to the bifurcation of the bundle of His. The two basic mechanisms of supraventricular tachycardias are enhanced impulse formation and abnormalities of conduction leading to reentry [1]. A reentrant SVT can be caused by a reentry circuit in the sinus node or the sinus node and a part of the contiguous atrium (sinus node reentry), in the atrium (atrial tachycardia, atrial flutter and atrial fibrillation), in the AV node-His bundle axis, (AV junctional tachycardia), reentry involving AV node and its approaches (AVNRT) [2,3] and reentry by AV node-His pathway for antegrade AV conduction and an accessory AV pathway for retrograde conduction.

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Supraventricular Tachycardia with Multiple Pathways

(orthodromic AVRT) or the reverse (antidromic AVRT) [4]. Radiofrequency ablation of the reentrant SVT depends upon precise diagnosis of the underlying arrhythmogenic substrate [AV nodal or accessory pathway (APs)] [5,6]. Application of RF energy in the apparently appropriate site may not be successful and an occasional mechanism is the presence of more than one pathway.

AVNRT is commonly associated and induced in pt with AVRT. This is manifested by documentation of dual AV nodal pathways, or VA conduction during AVRT alternates between fast and slow pathway, or the initiation of one form of tachycardia (e.g. AVNRT) after another form (e.g. AVRT) [7,8].

The purpose of our study was to report efficacy of RF catheter ablation in SVT with multiple mechanisms.

Patients and Methods

The study group consisted of 36 patients (pts) having more than one mechanism of SVT (18 M, 18 F; mean age 26±14 ys), out of total 915 cases of SVT (3.9%) referred to EP laboratory of Critical Care Medicine Department at Cairo University from January 1992 to January 2007. Associated heart disease was met in 5 pts. The resting ECG was pre-excited in 9 pts.

Data were mostly obtained retrospectively from patients’ files and the following points were looked for: Age, sex, history analysis, clinical examination, electrocardiogram (ECG) resting and during tachycardia, echocardiography to exclude structural heart disease, indication for electrophysiological study (EPS) and radiofrequency (RF) ablation, informed consent, EP diagnosis, result of RF ablation, detection of intra and post catheter. Complications, detection of recurrence, redo and their results.

Electrophysiological study (EPS) and RF Ablation:

All the patients included in this study underwent detailed EPS to diagnose the type of SVT. All pts were studied in post absorptive sedated state. All anti-arrhythmic drugs were discontinued for at least five half-lives in all patients. Three quadripolar catheters were inserted in high right atrium (HRA), atrioventricular junction (AVJ) and right ventricular (RV) apex together with a multipolar one in the coronary sinus (CS) for recording of left sided activation. Electrical stimulation was delivered through a programmable stimulator (Nihon-Cohden from Japan). Radiofrequency ablation was performed with different generators from several manufacturers including (Radionics 3C from Radionics Inc. Stockert, ep shuttle from Biosense and Attakr from Medtronic) connected to mapping/ablation catheters including (Cordis-Webster from Biosense and Stinger from Bard). Ablation was either power and/or temperature-guided. Catheter ablation of AVNRT was performed with the posterior approach targeting the slow pathway while catheter ablation of AVRT directed to either atrial or ventricular insertion of the AP using retrograde aortic approach according to the location of AP [13,14].

Statistical methods:

Descriptive analysis for quantitative and qualitative data respectively in the form of (mean ± SD and percentage).

Results

I- Patients with SVT of dual types:

The present study comprised 13 patients with dual types of SVT. The presence of two types of tachycardia (AVNRT & AVRT) was suspected during the study in 7 pts, in the remaining 6 pts the presence of the second form was only discovered after ablating the first (Fig. 1A,B). The end results of those pts regarding acute success, failure rate, recurrence and complications were shown in Table (1).

<table>
<thead>
<tr>
<th>Item</th>
<th>SVT with (AVNRT+AVRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13/36 (36.1%)</td>
</tr>
<tr>
<td>Surface ECG</td>
<td>Pre-excited in 3 pts</td>
</tr>
<tr>
<td>SHD</td>
<td>In 5 pts</td>
</tr>
<tr>
<td>Acute success rate</td>
<td>13/13 (100%)</td>
</tr>
<tr>
<td>Failure rate</td>
<td>0%</td>
</tr>
<tr>
<td>Commonest AP present</td>
<td>LLAP in 5 pts, LPSAP in 2 pts, RPSAP in 2 pts, ASAP in 2 pts and Midseptal in 2 pts</td>
</tr>
<tr>
<td>Complications</td>
<td>CHB in 1 pt</td>
</tr>
<tr>
<td>Recurrence</td>
<td>One, ablated successfully in second session</td>
</tr>
</tbody>
</table>

Abbreviations:

No = Number.

SHD = Structural heart disease.

AP = Accessory pathway.

LLAP = Left lateral accessory pathway.

LPSAP = Left posteroseptal accessory pathway.

ASAP = Accessory pathway.

CHB = Complete heart block.
II- Patients with multiple APs:

Out of total 470 cases with AVRT, 21 pts all with normal heart (4.5%) had multiple APs (double APs in 20 & triple APs in one pt). The AP locations were documented in (Table 2).

Table 2: Accessory pathway locations in pts with dual AVRT.

<table>
<thead>
<tr>
<th>Multiple APs</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + LT posteroseptal APs</td>
<td>5/470 (1.1%)</td>
</tr>
<tr>
<td>RT anteroseptal + LL APs</td>
<td>3/470 (0.6%)</td>
</tr>
<tr>
<td>LL + RT posteroseptal APs</td>
<td>2/470 (0.4%)</td>
</tr>
<tr>
<td>RT anteroseptal + LT midseptal APs</td>
<td>2/470 (0.4%)</td>
</tr>
<tr>
<td>RT posteroseptal + RT anteroseptal APs</td>
<td>3/470 (0.6%)</td>
</tr>
<tr>
<td>RT lateral + LT posteroseptal APs</td>
<td>1/470 (0.2%)</td>
</tr>
<tr>
<td>LL + LT posteroseptal APs</td>
<td>2/470 (0.4%)</td>
</tr>
<tr>
<td>LL + Rt lateral APs</td>
<td>1/470 (0.2%)</td>
</tr>
<tr>
<td>LL + LPL APs</td>
<td>1/470 (0.2%)</td>
</tr>
<tr>
<td>RT + LT posteroseptal + LT lateral APs</td>
<td>1/470 (0.2%)</td>
</tr>
</tbody>
</table>

Abbreviations:

- RT = Right.
- LT = Left.
- LL = Left lateral.
- APs = Accessory pathways.
- LPL APs = Left posterolateral accessory pathways.

The end results in the 21 pts having SVT with multiple APs including acute success, failure rate, complications and recurrence were shown in Table (3).

Table 3: The end results in pts with SVT with multiple APs.

<table>
<thead>
<tr>
<th>Item</th>
<th>SVT with multiple APs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>21/36 (58.3%)</td>
</tr>
<tr>
<td>Surface ECG</td>
<td>Pre-excited in 9 pts</td>
</tr>
<tr>
<td>Acute success rate</td>
<td>21/21 (100%)</td>
</tr>
<tr>
<td>Failure rate</td>
<td>0%</td>
</tr>
<tr>
<td>Commonest AP present</td>
<td>RPSAP; LPSAP &amp; LLAP</td>
</tr>
<tr>
<td>Complications</td>
<td>Acute LL ischemia in 1 pts</td>
</tr>
<tr>
<td>Recurrence</td>
<td>6 pts (4 with RASAP)</td>
</tr>
</tbody>
</table>

Abbreviations:

- RPSAP = Right posteroseptal accessory pathway.
- LPSAP = Left posteroseptal accessory pathway.
- RASAP = Right anterior septal accessory pathways.
- ECG = Electrocardiogram.
- LL = Lower limb.

An example of one pt with SVT due to double APs (right posteroseptal and left lateral) who had successful outcome was shown in Fig. (2A-F).

III- Patients with SVT of triple types:

The present study comprised only 2 patients with triple types of SVT. Both had normal resting 12-lead ECG. During the EP study; AVNRT, AFl & AT were induced. The RF catheter ablation was successful in terminating all forms of tachycardias with neither reported complication nor recurrence.

Our final results of the study group (36 pts) including success rate, failure rate, complications and recurrence rate are summarized in Table (4).

Table 4: The final results of our study group (36 pts).

<table>
<thead>
<tr>
<th>Item</th>
<th>Study group (21pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>36/36 (100%)</td>
</tr>
<tr>
<td>Failure rate</td>
<td>0%</td>
</tr>
<tr>
<td>Complications</td>
<td>In 2 pts, CHB in 1 &amp; acute LL ischemia in another pt.</td>
</tr>
<tr>
<td>Recurrence</td>
<td>In 7 pts (19.4%), 6 pts had SVT with multiple APs and the other one had AVNRT+AVRT.</td>
</tr>
</tbody>
</table>

Abbreviations:

- CHB = Complete heart block.
- SVT = Supraventricular tachycardia.
- APs = Accessory pathways.
Supraventricular Tachycardia with Multiple Pathways

Figure 2-A: Baseline pre-excited ECG before ablation (LT lateral location).

Figure 2-B: Induction of AVRT utilizing LL AP for retrograde conduction.

Figure 2-C: Successful RF ablation of the LL AP with AV prolongation.

Figure 2-D: Post ablation study: Earliest retrograde conduction recorded at PCS (another AP location) with induction of non-sustained SVT.

Figure 2-E: Successful RF ablation of the RPSAP with VA dissociation during VP denoting interruption of the retrograde conduction in the AP.

Figure 2-F: Normal Post ablation ECG.

Discussion

This Study was a retrospective cohort study from January 1992 to January 2007. It was carried out at The Critical Care Medicine department of Cairo University reporting the efficacy and safety of the conventional RF catheter ablation in a rare subset of pts having SVT with multiple mechanisms and pathways (36 pts). It was our second registry in Egypt after the first published on which was conducted on 21 pts (18). Up to our knowledge no available data or series on most of the research sites reporting the efficacy of RF catheter ablation in pts having double tachycardia (AVNRT & AVRT).
however there are data available reporting the efficacy of RF catheter ablation in pts with SVT utilizing multiple APs [13,14,15].

It is very important to identify pts with multiple APs because of the risk of atrial and may be ventricular fibrillation [13,16]. Electrophysiologic findings suggesting multiple APs include: [10,12,16].

1- Changing antegrade delta waves (changing morphology of delta waves): This is uncommon during sinus rhythm. Occasionally, the change becomes apparent after the use of class I drugs or amiodarone. Atrial fibrillation (induced or spontaneous) may show different patterns of preexcitation, over more than one AP.

2- Multiple retrograde atrial activation sequences with different P waves and VA intervals during orthodromic AVRT or ventricular pacing in the same pt.

3- Orthodromic AVRT with antegrade fusion, producing single "fused" beats, or changing progressively to a run of antidromic tachycardia.

4- Preexcited AVRT in a patient with a posterior septal AP indicates a second AP. This is because; antidromic AVRT was never documented in posterior septal accessory pathways.

5- Atypical preexcitation during sinus rhythm or pre-excited tachycardia which does not conform to a specific location suggests the presence of multiple accessory pathways, causing a fused pattern of pre-excitation.

6- Mismatch between the atrial (P) and ventricular (delta wave) insertions of the AP during orthodromic and antidromic AVRT, respectively.

**The main findings of our present study:**

Our study documented the safety and efficacy of catheter ablation of SVT. Our results demonstrate that catheter ablation of APs & AVNRT can be performed with high level of success (100%). The recurrence was documented in 7 cases, 6 had AVRT utilizing multiple APs with recurrence rate 28.6% (6 out of 21 cases) and one pt (7%, one out of 13 cases) with dual mechanisms (AVNRT+AVRT). The increased risk of arrhythmia recurrence in pts having multiple APs was reported also in literature [14,15]. Stellbrink et al, had reported the high efficacy and curative rate more than 90% of RF catheter ablation in pts having symptomatic SVT with APs & AVNRT [17]. They have reported recurrence rate 3 to 10% for APs & 0 to 15% for AVNRT. The reported higher recurrence rate in pts with multiple APs (28%; 6 of 21 pts) was attributed to the critical location of the accessory pathways (4 with RAS AP) and the possible occurrence of inadvertent heart block during attempt at RF catheter ablation.

**Factors affecting ablation success and recurrence:**

Successful ablation with RF energy requires accurate mapping and adequate tissue heating together with technical expertise. The probability of arrhythmia recurrence after a successful ablation in our study was strongly influenced by ablation target, with recurrence being more likely after ablation of septal APs either posterior and/or anterior. These data are comparable with the data reported by Calkins et al [14] and by Iturralde et al [15].

**Complications:**

The incidence of major complications in our study group is around 6% including complete heart block in one pt which needed permanent implantation of pacemaker after ablating midseptal AP and acute lower limb ischemia after ablating left lateral AP. No reported pt deaths. Higher incidence of complications in our study group compared to 3% in multi-center clinical trial reported by Calkins et al in 1998 [14] attributed to small sample size.

**Limitations of this study:**

1- It is a small sample size study conducted on 36 pts but it is not considered as severe limitation because most of the reported data from literature concerning SVT with multiple APs were conducted on small sample size pts [16].

2- Some intra-catheter data were not probably assessed like, the procedure time, mean number of RF energy applications and the fluoroscopy time.

**Conclusion**

The presence of more than one arrhythmogenic mechanism should always be kept in mind. Meticulous EP diagnosis and careful post ablation analysis would obviously save effort to allow careful diagnosis of the unlikely situations of multiple pathways. Recurrence of SVT after an apparently successful RF ablation should always raise the issue of possible presence of multiple APs.

**References**

Supraventricular Tachycardia with Multiple Pathways


Thrombolysis or Acute PCI for STEMI. A Dilemma Solved by Acute Myocardial Perfusion Imaging (MPI)

AKRAM ABD EL-BARY, MD; AHMED ABD EL-AAL, MD; AHMED BATTAAH, MD; WAEL SAMI, MSc; MOHAMED EL-SHAFAE, MD; MOHAMED KHALED, MD; HELMY EL-GHAWABY, MD; MOHAMED ASHRAF, MD; MOHAMED ABDEL-AZIZ, MD; AHMED EL-SHERIF, MD; AYMAN EL-NAGGAR, MD; MAHMOUD EL-BADRY, MD; TAREK ALGOHARY, MD; AHMED MOWAIFI, MD; ALIA ABD EL-FATTAH, MD; SHERIF MOKHTAR, MD

Background: Over the past 10 years wide steps were taken in the management of acute myocardial infarction (MI). During these years, the goal was how to restore flow in the infarct-related artery (IRA) but in the last few years, the main concern was how to preserve a good microcirculation, through many therapies starting with heparin, passing through thrombolysis and ending with acute PCI. We are hereby reporting our experience over 10 years in acute myocardial perfusion imaging (MPI) as a tool for evaluating the different treatment modalities and their role in preserving actual perfusion at the tissue level.

Methods: A total of 208 patients (pts) with STEMI were enrolled in our study including 190 males (mean age 53.1 ± 10 yrs). DM was present in 35% of pts, HTN in 28%, Dyslipidemia in 56%, smoking in 43% and ±ve FH for CAD in 16% of pts. All pts were subjected to acute MPI by SPECT technique using triple head Gamma Camera with image acquisition of 20 frames, 30 seconds each. Every patient had two sets of images. The first set was done on admission by injecting 25mCi of Tc99m SestaMIBI before initiating therapy and acquisition was done after therapy within six hours of injection. A second set of images was done two days after therapy by injecting another 25 mCi of Tc99m SestaMIBI. Myocardium at risk (MAR) was calculated using 20 segment scoring system for the first set of images (0-4 scale). Final infarct size (IS) was calculated using the same scoring system for the second set of images. Salvage index (SI) was calculated (SI=MAR-RI/MAR x 100) and taken as an end point for successful reperfusion (SI≥30%). Patients were subdivided into two groups; Group I: 98 pts were treated medically (streptokinase in 86, combined SK 750.000 & Tirofiban in 11 pts), Group II: 110 pts subjected to acute PCI (rescue PCI in 34 pts, 1ry PCI in 64 pts and 1ry PCI & Acolysis in 12 pts).

Results: Mean MAR was 25.9 ± 11.46, IS 13.7 ± 10.46% & SI was 47.6 ± 34.4%. Overall successful reperfusion was achieved in 76.8% of pts. There was no significant difference between MAR in both groups (29.8±10.1 vs. 29.9±9.7 p=0.4). Group II showed higher SI (54.8±21 vs 43.5±27, p≤0.0001) and lower IS (13.9±8.8 vs 17.8±12.6, p=0.01) when compared to Group I. Reperfusion success was significantly higher in Group II when compared to Group I (88.9% vs 70.4%, p=0.001). Overall in hospital mortality was 8.2% (19 cases) and was higher in Group II (10.9% vs 7.1% p=0.09).

Conclusion: Acute MPI is useful in evaluating different strategies for achieving the success of reperfusion in acute STEMI. Acute PCI was shown by acute MPI to be superior to thrombolysis in achieving successful reperfusion with greater myocardial salvage.

Key Words: Acute myocardial perfusion imaging – STEMI.

Introduction

A critically important goal of reperfusion is to restore flow in the infarct artery as quickly and as completely as possible, but the ultimate goal of reperfusion in STEMI is to improve myocardial perfusion in the infarct zone. Despite adequate restoration of flow in the epicardial infarct artery, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury [1-3].

There is controversy about which form of reperfusion therapy is superior in various clinical settings. Part of the uncertainty derives from the continual introduction of new agents, devices, and strategies, which quickly make previous studies
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less relevant to contemporary practice. With pharmacological reperfusion therapies, there are new agents, dosing regimens, adjunctive treatments, and combined strategies with procedures that are in a continual process of refinement and evaluation. Similarly, with catheter-based approaches, there are new devices, adjunctive therapies, technologies, and combined strategies with medications that are becoming introduced and evaluated. As a result, the evidence base regarding the best approach to reperfusion therapy is quite dynamic. Several issues should be considered in selecting the type of reperfusion approach, as discussed below. Given the current literature, it is not possible to say definitively that a particular reperfusion approach is superior for all patients, in all clinical settings, at all times of day [4-6].

The most comprehensive assessment of ST segment elevation myocardial infarction (STEMI) with radionuclide imaging was developed with the Technetium$^{99m}$ methoxyisobutylisonitrile (Tc$^{99m}$ sestaMIBI) single photon emission tomography (SPECT) approach [7]. This technique has been validated extensively and offers the opportunity for both early and late imaging to initially assess the area of ischemic risk as opposed to the ultimate infarct size. This approach is well delineated in the ACC/AHA/ASNC Guidelines on Cardiac Radionuclide Imaging [8].

**Aim:** Comparing thrombolysis to acute PCI as reperfusion modalities in the setting of STEMI by using acute myocardial perfusion imaging (MPI) to determine their scintigraphic success rate & impact on final infarct size.

**Patients and Methods**

The study involved 208 patients presenting years 1996-2006 to the critical care department, Cairo University by acute STEMI & eligible for thrombolytic therapy or acute PCI.

**All patients were subjected to:**
- History taking with special emphasis on onset & duration of chest pain, known contraindications to thrombolytic therapy & risk factors for coronary artery disease (CAD).
- Clinical examination.
- Twelve lead ECG.
- Cardiac enzymes.
- Acute myocardial perfusion imaging: Each patient had two sets of images.

**First set:**

Patients were injected on admission by 25 mCi Tc$^{99m}$ sestaMIBI Acquisition of images was delayed after stabilization & thrombolysis or acute PCI.

- Myocardial perfusion imaging was done using triple head Siemens Gamma camera, 20 frames 30 seconds each, with 120° arc.
- Processing and filtering was done using back-projection technique to get the classic short axis, vertical long axis and horizontal long axis slices; The acquired data were analyzed and processed using the Emory tool box version 1. The detected defect represented the myocardium at risk (MAR) & was quantitated using the 20 segment scoring system, 9-10 each segment received scores 0-4 where:
  - 0 → normal perfusion.
  - 1 → mild defect
  - 2 → moderate defect
  - 3 → severe defect
  - 4 → No photon activity.

The score was summed and divided by 80 to get the MAR as a percent of the myocardium.

**Second set:**

After 48 hours, another rest image was acquired, analyzed and the defect size quantified in same way used in the first set of perfusion images to calculate the final infarct size (IS) as a percent of the myocardium.

**End point:**

We used salvage index (SI) as an end point to our study.

\[ \text{SI} = \frac{\text{MAR} - \text{IS}}{\text{MAR}} \times 100 \]

Salvage index >30% pointed towards a successful reperfusion.

**Adjunctive therapies:**

**All patients received:**
- 300 mg of Aspirin on admission and continued on 150 mg of ASA daily thereafter.
- IV nitroglycerin started on admission, dose adjusted according to response and hemodynamics. IV nitroglycerin was withdrawn 12-24 hours after resolution of chest pain in a gradual manner.
- Morphine sulphate.
- Supplemental oxygen.
Other medications including b-blockers, calcium channel blockers, ACEI & other drugs were prescribed according to patients condition & associated co morbidities.

According to availability of intervention and referrals, patients were subjected to either:

- **Thrombolytic therapy:**
  - Streptokinase 1.5 million IU intravenous infusion over 60 minutes started within 30 minutes of admission.
  - Streptokinase 750,000 IU intravenous infusion over 30 minutes followed by tirofiban 0.4 ug/kg bolus then 0.1 ug/kg/hr for 24 hours.

- **Acute PCI:**
  - Primary PCI according to standard protocols with door to balloon time <90 minutes.
  - Rescue PCI for patients referred with acute MI & failed thrombolytic therapy based on standard clinical and ECG criteria within 90 min.
  - Primary PCI preceded by ultrasound thrombolysis (Acolysis, Angiosonics inc., USA) which is an intracoronary probe positioned at proximal end of occlusion site to deliver low frequency high energy ultrasound waves aiming at disintegration of coronary thrombus to debris subcapillary in size.

All patients subjected to acute PCI received IV infusion of tirofiban starting on admission and continuing for 24 hours.

All patients signed an informed consent about their plan of management and inclusion in the study.

**Statistical methods:**
- All data were expressed as mean and standard deviation unless otherwise needed.
- Descriptive statistics for all continuous data, and frequencies for all categorical data.
- For data that was normally distributed unpaired t-test has been performed.
- When the mean value was violated Mann-Whitney test has been performed.
- Chi-Square for testing the association.
- Pearson coefficient correlation to confirm the strength of an already existing relationship between 2 continuous variables.

- A p value <0.05 has been considered significant.
- Statistical package used SPSS II under windows.

**Results**

**Patients characteristics:**

Two hundred & eight patients (190 males) mean age 53.1±10 years (Table 1).

According to treatment received patients were subdivided into two groups (Table 2):
- Group I: 98 patients (thrombolytic therapy group).
- Group II: 110 patients (acute PCI group).

<table>
<thead>
<tr>
<th>Table 1: Patients characteristics.</th>
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</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>HTN</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>+ve family history of CAD</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 2: Patients according to therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>Thrombolytic</td>
</tr>
<tr>
<td>Streptokinase</td>
</tr>
<tr>
<td>Streptokinase ± tirofiban</td>
</tr>
<tr>
<td>Streptokinase ± tirofiban</td>
</tr>
<tr>
<td>Acute PCI</td>
</tr>
<tr>
<td>Primary PCI (primary PCI)</td>
</tr>
<tr>
<td>Rescue PCI (r PCI)</td>
</tr>
<tr>
<td>Primary PCI ± acolysis</td>
</tr>
<tr>
<td>PCI: Percutaneous coronary intervention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Scintigraphic data in all patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scintigraphic parameter</td>
</tr>
<tr>
<td>MAR</td>
</tr>
<tr>
<td>IS</td>
</tr>
<tr>
<td>SI</td>
</tr>
</tbody>
</table>

MAR: Myocardium at risk. IS: Infarct size. SI: Salvage index.

**Endpoint:**

Overall scintigraphically successful reperfusion (SI >30%) was achieved in 76.8% of patients.

**Risk factors in both groups:**

There was no significant difference between both groups as regards the prevalence of risk factors for CAD (Table 4).
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There was no significant difference between both groups as regards time of presentation, gender and age (Table 5).

Scintigraphic data in both groups:

Despite similar MAR, group II patients showed significantly higher SI & lower IS (Table 6).

Successful reperfusion was significantly higher in group 1 compared to group 2 (Fig. 1).

Subgroup analysis:

There was no statistically significant difference between the cases with successful reperfusion in both groups as regards the MAR, IS, SI (Table 7).

On comparing the major subgroups of patients namely the streptokinase group (86 pts) vs the primary PCI group (64 pts) as regards the acute MPI results we found a clear superiority of primary PCI over streptokinase in achieving scintigraphically successful reperfusion with significantly smaller infarct size despite similar MAR (Table 8).

In cases with scintigraphically successful reperfusion in the streptokinase and primary PCI groups there was no significant difference between both subgroups as regards MAR, SI or final infarct size (Table 9).

Mortality:

Overall mortality rate reached 8.2% & was higher in the PCI group when compared to the thrombolysis group however this difference was statistically insignificant (Fig. 2), (Table 10).

---

**Table 4: Risk factors for CAD.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>35%</td>
<td>36.4%</td>
<td>0.844</td>
</tr>
<tr>
<td>HTN</td>
<td>32.9%</td>
<td>22.7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking</td>
<td>43.3%</td>
<td>43.6%</td>
<td>0.96</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>52.6%</td>
<td>60%</td>
<td>0.28</td>
</tr>
<tr>
<td>+ve FH for CAD</td>
<td>19.6%</td>
<td>13.6%</td>
<td>0.249</td>
</tr>
</tbody>
</table>


**Table 5: Age, sex and chest pain duration in both groups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.3±11.5 y</td>
<td>51.9±9.9 y</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90.7%</td>
<td>91.8%</td>
<td></td>
</tr>
<tr>
<td>Chest pain duration</td>
<td>5.1 hours</td>
<td>5.2 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: Scintigraphic data in both groups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAR</td>
<td>29.8±10.1</td>
<td>29.9±9.7</td>
<td>0.4</td>
</tr>
<tr>
<td>IS</td>
<td>17.8±12.6</td>
<td>13.9±8.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>SI</td>
<td>43.5±27</td>
<td>54.8±21</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

MAR: Myocardium at risk.   IS: Infarct size.   SI: Salvage index.

**Figure 1: Scintigraphic success in both groups. Group I: Thrombolytic therapy, Group II: Acute percutaneous coronary intervention.**

**Table 7: Subgroup analysis (cases with successful reperfusion).**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Successful cases in GI*</th>
<th>Successful cases in G II*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAR (mean) %</td>
<td>28.1±8.5</td>
<td>29.5±10.1</td>
<td>0.36</td>
</tr>
<tr>
<td>IS (mean) %</td>
<td>11.5±6.6</td>
<td>12.4±7.3</td>
<td>0.47</td>
</tr>
<tr>
<td>SI (mean) %</td>
<td>58.2±16</td>
<td>59.8±16</td>
<td>0.52</td>
</tr>
</tbody>
</table>

MAR: Myocardium at risk.   IS: Infarct size.   SI: Salvage index.   *: Salvage index >30%.

**Table 8: Comparison between streptokinase and primary PCI subgroups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Streptokinase (86 cases)</th>
<th>Primary PCI (64 cases)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scintigraphically successful reperfusion</td>
<td>73.3%</td>
<td>89.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MAR (mean) %</td>
<td>30.2±10</td>
<td>27.7±9.4</td>
<td>0.6</td>
</tr>
<tr>
<td>IS (mean) %</td>
<td>17.3±12.7</td>
<td>13.4±8.5</td>
<td>0.003</td>
</tr>
<tr>
<td>SI (mean) %</td>
<td>44.3±27.9</td>
<td>54±22.1</td>
<td>0.008</td>
</tr>
</tbody>
</table>


**Table 9: Comparison between cases with successful reperfusion* in both streptokinase and primary PCI subgroups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Streptokinase successful cases</th>
<th>Primary PCI successful cases</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAR (mean) %</td>
<td>27.9±8.5</td>
<td>27.7±9.4</td>
<td>0.3</td>
</tr>
<tr>
<td>IS (mean) %</td>
<td>11.4±6.7</td>
<td>11.9±7.4</td>
<td>0.3</td>
</tr>
<tr>
<td>SI (mean) %</td>
<td>58.8±15.7</td>
<td>59.4±16.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

MAR: Myocardium at risk.   IS: Infarct size.   SI: Salvage index.   PCI: Percutaneous coronary intervention.   *: Salvage index >30%.
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different adjunctive reperfusion techniques and comparing them to the standard PCI and thrombolytic therapies and that it is a single center study that reflects clearly our early contribution to mechanical reperfusion in Egypt in addition single ethnic patient group with possible special characteristics and different risk factors.

With the fear of the effect of microvascular obstruction by microthrombi that theoretically should be more evident with mechanically based reperfusion strategies through thrombus crushing and disintegration we found acute MPI to be the most suitable and available technique to evaluate myocardial reperfusion.

The introduction of technetium based isotopes was greatly helpful in this setting as obtaining a frozen image through rest injection of patients on admission and further delaying image acquisition after reperfusion did not delay starting the reperfusion strategy a crucial point in the setting of STEMI.

Our data showed the superiority of mechanical reperfusion over thrombolytic therapy patients not only had smaller infarct size and higher salvage index yet also had higher rate of scintigraphically successful reperfusion despite similar chest pain duration, risk factors for CAD and comparable age.

When comparing the subset of patients who had successful reperfusion in both groups there was no difference as regards the infarct size and salvage index. These results decreased our concerns about microvascular dysfunction caused by microthrombi resulting from thrombus disintegration; in addition it raised the question about the more powerful role of other claimed mechanisms to produce microvascular dysfunction with subsequent compromise of optimal reperfusion results.

We also compared the primary PCI patients alone to thrombolysis alone to exclude the impact of use of adjunctive therapies or devices on our results and the amazing was that primary PCI could achieve more optimal reperfusion in terms of higher salvage index and smaller infarct size in addition to higher success rate when compared to streptokinase alone.

The higher mortality in the PCI group represents the learning curve of the operators over years with highest mortality in the first 4 years of introduction of acute PCI, in addition the introduction of GP IIb/IIIa receptor antagonists and novel antiplatelet oral therapies by year 2000-2001 in Egypt namely
ticlopidine improved the results with less acute thrombosis and no reflow which are rarely observed in common practice nowadays.

Our results matched with the current update of the AHA/ACC guidelines update published in December 2007 as regards superiority of primary PCI over thrombolysis in management of STEMI [17].

In this study by using acute MPI we could clearly confirm the superiority of acute PCI over thrombolytic therapy in improving myocardial salvage & limiting the infarct size. Despite no difference found in the short term outcome as regards reduction of in hospital mortality in our study, yet long term follow-up is needed to assess the reduction of major adverse cardiac events with particular concern about mortality & heart failure development in both groups.

In conclusion

- Acute PCI is superior to thrombolysis in achieving better myocardial reperfusion as detected by acute MPI.
- Primary PCI is superior to thrombolytic therapy as a reperfusion strategy in the setting of STEMI.
- Acute MPI a useful & reliable tool for precise assessment of reperfusion therapies in the setting of acute STEMI.
- Successful reperfusion either achieved by thrombolytic therapy or acute PCI had comparable achievement in salvaging the myocardium & limiting the infarct size.

Case A: Patient with anterior MI subjected to primary PCI and Acolysis.

1-A: Coronary angiography: Proximal left anterior descending artery total occlusion

2-A: Acolysis probe, positioned at the proximal end of the thrombus and activated in successive sessions 60 seconds each.

3-A: After percutaneous coronary intervention: After stentind using bare metal stent at the site of the lesion with successful TIMI 3 flow and absent residual stenosis.

4-A: Acute myocardial perfusion imaging: Comparison display of short axis, vertical long axis and horizontal long axis slices for rest studies before and after primary PCI to LAD showing major reversibility in the inferoapical, anteroseptal, anterior and anterobasal segments with considerable reduction in LV size.

PCI: Percutaneous coronary intervention, LAD: Left anterior descending artery, LV: Left ventricle.
Case B: Thrombolytic therapy group.

1-B: Comparison display of short axis, vertical long axis and horizontal long axis slices for rest studies before and after streptokinase given after one hour of onset of chest pain in a patient with inferolateral STEMI, showing considerable filling in the lower septum, inferoapical, inferior, inferolateral, and posterolateral segments. SI=60% (Major salvage in myocardium at Lcx territory after successful thrombolytic therapy).

STEMI: ST elevation myocardial infarction, LCx: left circumflex artery.

2-B: Comparison display of polar maps for rest studies before and thrombolytic therapy in the setting of acute inferolateral MI, showing considerable filling in the inferoapical, inferior, inferolateral, lower septum, midlateral and posterolateral segments. SI=60%.

Case C: Successful primary PCI to LCx in a case of acute inferolateral MI.

1-C: Coronary angiography: Circumflex total occlusion artery total occlusion in the setting of acute inferior STEMI.

STEMI: ST elevation myocardial infarction, LCx: left circumflex artery.

2-C: After primary PCI and stenting of LCx: TIMI 3 flow with no residual stenosis.

PCI: percutaneous coronary intervention, LCx: left circumflex artery.

3-C: Comparison display of short axis, vertical long axis and horizontal long axis slices for rest studies before and after primary PCI to LCx showing considerable filling in the lower septum inferior, inferolateral, and posterolateral segments. SI=50%.

References


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