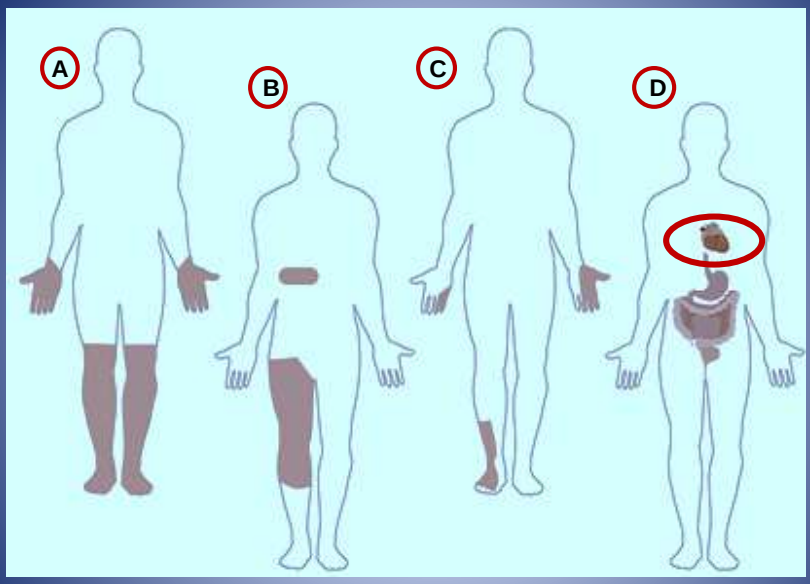
Cardiac Autonomic Neuropathy In Patients With Diabetes

FARID FAWZY, MD, PhD
Professor of Medicine, Diabetes & Endocrinology,
Zagazig University, Egypt

Case Presentation

- A 26 year old woman with brittle type 1 DM was brought dead to the ED.
- She had a 16-year history of poor glycemic control with wide B.G. fluctuations, severe hypoglycemic episodes, and hypoglycemia unawareness.
- Over time she developed persistent orthostatic hypotension with daily falls in systolic blood pressure ranging from 30–60 mmHg necessitating intermittent therapy with midodrine.
- Other complications included severe gastro-paresis, refractory diarrhea, and painful diabetic peripheral neuropathy.
- Clinical examination revealed a fixed heart rate of 115 bpm, BP 110/78 mmHg supine and 70/48 mmHg while standing, symmetrical absent pin brick and temperature sensation in stocking distribution and left Charcot joint.
- Pertinent laboratory findings were A1C 8.7%, creatinine 1.9 mg/dl, ACR 496 mg/g, and hemoglobin 10.8 g/dl.



(A) Diabetic sensorimotor polyneuropathy.
(B) Radiculoplexopathy or radiculopathy
(C) Momononeuropathy or mononeuritis multiplex
(D) Aautonomic neuropathy

Disclosure

- I have honoraria and sponsored conferences with Novartis, Novo-Nordisk, Eli-Lilly, Astra-Zeneca, MSD, HSO, Inspire, Takeda, Janssen, Merck Serono, and Global-Napi

- No potential conflict of interest relevant to this presentation

Agenda

- Epidemiology
- Risk Factors and Pathogenesis
- Clinical Consequences
- Screening and Diagnosis
- Therapeutic Approaches

American Diabetes Association. Diabetes Care

Diabetes Care. 2010 Feb; 33(2): 434–441. PMCID: PMC2809298
doi: 10.2337/dc09-1294

Cardiac Autonomic Neuropathy in Diabetes
A clinical perspective

Rodica Pop-Busui, MD, PHD

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
Fisher VL & Tahrani AA, 2017 Oct 6;10:419-434.

REVIEW

Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives

Epidemiology of CAN

- Prevalence of CAN varies greatly from one study to another depending on the diagnostic criteria and study population.
- Prevalence varies from 1.6–2.6% in the DCCT to 90% in long standing type 1 patients waiting for a pancreas transplant.
- In a large cohort Ziegler et al. reported prevalence of 25.3% in patients with type 1 DM and 34.3% in those with type 2DM.
- Established risk factors for CAN are glycemic control in type 1 diabetes, and a combination of hypertension, dyslipidemia, obesity and glycemic control in type 2 diabetes.

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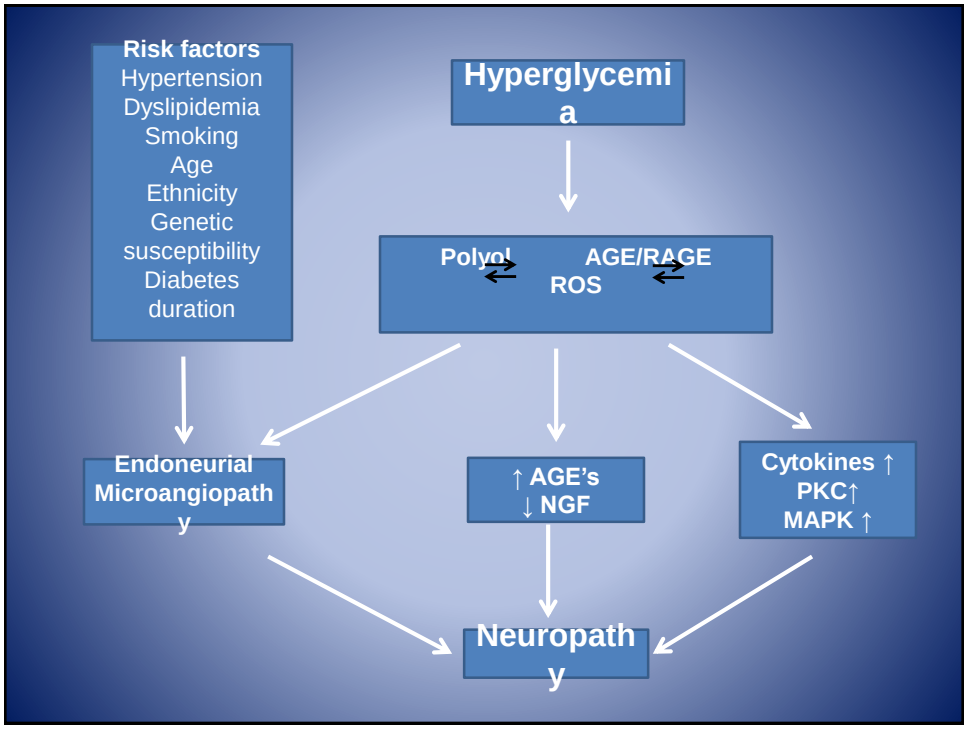
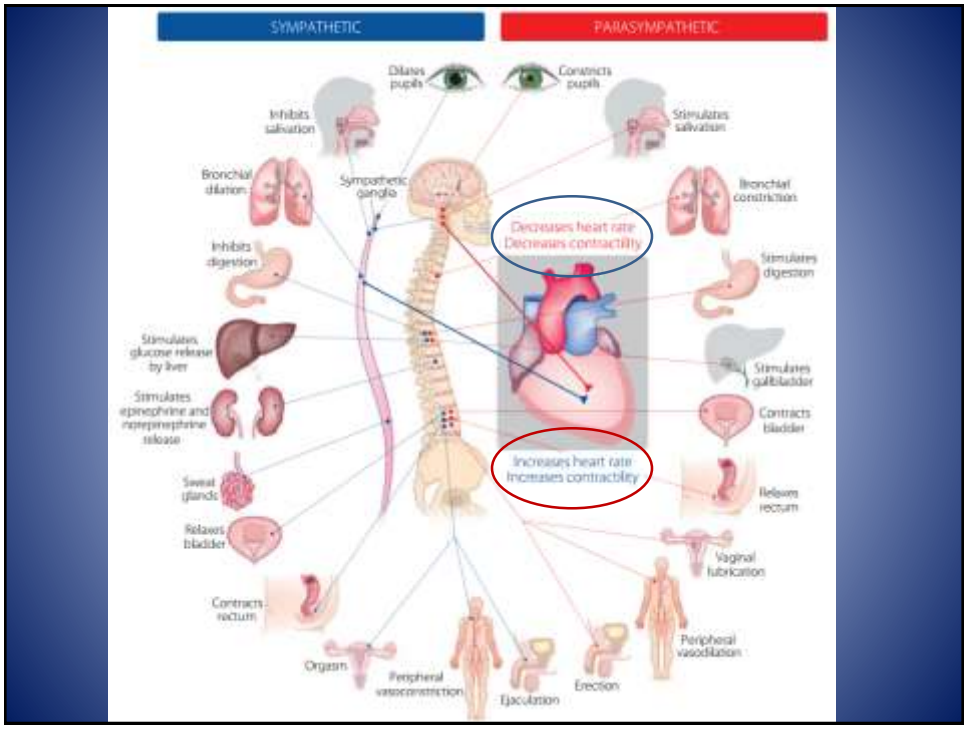

Risk factors
Hypertension
Dyslipidemia
Smoking
Age
Ethnicity
Genetic susceptibility
Diabetes duration
Hyperglycemia
Polyol
AGE/RAGE
ROS
Endoneurial Microangiopathy
↑ AGE's
↓ NGF
Cytokines ↑
PKC↑
MAPK ↑
Neuropathy


SYMPATHETIC
PARASYMPATHETIC
Dilates pupils
Constricts pupils
Inhibits salivation
Stimulates salivation
Bronchial dilation
Sympathetic ganglia
Bronchial constriction
Decreases heart rate
Decreases contractility
Inhibits digestion
Stimulates digestion
Stimulates glucose release by liver
Stimulates gallbladder
Stimulates epinephrine and norepinephrine release
Contracts bladder
Increases heart rate
Increases contractility
Sweat glands
Relaxes rectum
Relaxes bladder
Vaginal lubrication
Contracts rectum
Peripheral vasodilation
Orgasm
Peripheral vasoconstriction
Ejaculation
Erection

Clinical Consequences of CAN

- ***Resting tachycardia & Impaired HRV***
- ***Exercise intolerance***
- ***Perioperative cardiovascular instability***
- **Orthostatic Hypotension**
- ***Non-dipping blood pressure profile***
- ***Silent myocardial ischemia***
- ***Sudden cardiac death***
- ***Autonomic cardiomyopathy***

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- Cardio-Autonomic Response Tests (CART's):
- Heart rate response to respiration
- Heart rate response to standing
- Heart rate response to Valsalva
- Blood pressure response to standing
- Blood pressure response to hand grip

- Resting heart rate
  >100 bpm is abnormal.
- Beat-to-beat HRV*
  With the patient at rest and supine (not having had coffee or a hypoglycemic episode the night before), heart rate is monitored by ECG or autonomic instrument while the patient breathes in and out at six breaths per minute, paced by a metronome or similar device. A difference in heart rate of >15 bpm is normal, <10 bpm is abnormal. The lowest normal value for the expiration-to-inspiration ratio of the R-R interval is 1.17 in people 20–24 years of age. There is a decline in the value with age†.
- Heart rate response to standing*
  During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing. Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio is >1.03.
- Heart rate response to the Valsalva maneuver*
  The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R to shortest R-R should be >1.2.

- Systolic blood pressure response to standing
  Systolic blood pressure is measured in the supine subject. The patient stands, and the systolic blood pressure is measured after 2 min. Normal response is a fall of <10 mmHg, borderline is a fall of 10–29 mmHg, and abnormal is a fall of >30 mmHg with symptoms.
- Diastolic blood pressure response to isometric exercise
  The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min. The normal response for diastolic blood pressure is a rise of >16 mmHg in the other arm.
- ECG QT/QTc intervals
  The QTc should be <440 ms.

Other diagnostic tools

- Scintigraphic evaluation of sympathetic innervation of the heart with Positron Emission Tomography (PET) scans.
- Microneurography which records electrical activity from the peroneal, tibial or radial sympathetic nerves.
- Corneal confocal microscopy (CCM).

SCREENING FOR CAN

- **Whom?**
  - Patients with type 2 diabetes at the time of diagnosis.
  - Patients with type 1 diabetes after 5 years of diagnosis.
  - Earlier screening in type 1 with suggestive symptoms of CAN.
  - Pre-operative assessment for all patients with diabetes.
  - Patients with diabetes planning an intense exercise program.
- **How?**
  - Standard Clinical Testing (CART's)
  - Electrophysiological and imaging studies
  - Corneal Confocal Microscopy (CCM)
  - Risk assessment scores (Age, BMI, HTN, & resting heart rate)
- **When?**
  - Screening should be repeated annually if negative

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General Measures

- Timely diagnosis for effective management.
- Lifestyle changes including graded supervised exercise program.
- Optimizing glycemic control in patients with type1 DM. (Framingham Heart Study, DCCT & EDIC)
- Correction of CV risk factors specially in patients with type 2 DM.

Pathogenesis-based pharmacotherapy

Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (AE)
	Lidorestat		Withdrawn (AE)
	Fidarestat		Effective in RCTs, trials ongoing
	AS-3201	Nerve sorbitol ↓	Effective in RCTs, trials ongoing
	Epalrestat		Marketed in Japan
Myo-inositol ↓	Myo-inositol	Nerve myo-inositol ↑	Equivocal
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in RCTs, trials ongoing
Nerve hypoxia ↑	Vasodilators	NBF ↑	
	ACE inhibitors		Effective in one RCT
	Prostaglandin analogs		Effective in one RCT
	phVEGF$_{165}$ gene transfer	Angiogenesis ↑	RCTs ongoing
Protein kinase C ↑	Protein kinase C-β inhibitor (ruboxistaurin)	NBF ↑	RCTs ongoing
C-peptide ↓	C-peptide	NBF ↑	Studies ongoing
Neurotrophism ↓	Nerve growth factor (NGF)	Nerve regeneration, growth ↑	Ineffective
	BDNF	Nerve regeneration, growth ↑	Ineffective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
GLA synthesis ↓	γ-Linolenic acid (GLA)	EFA metabolism ↑	Withdrawn
NEG ↑	Aminoguanidine	AGE accumulation ↓	Withdrawn

AE, adverse event; AGE: advanced glycation end product; BDNF, brain-derived neurotrophic factor; EFA: essential fatty acid; LCFA, long-chain fatty acid; NBF, nerve blood flow; NEG, nonenzymatic glycation; RCT, randomized clinical trial.

Treatment of orthostatic hypotension

- **Nonpharmacologic interventions:**
- Increased water consumption
- Lower extremity stockings
- Avoid sudden postural changes to standing up
- Avoid vasodilators, diuretics, α-blockers, phenothiazine (Largactil) and TCA.
- Eating frequent, small meals.
- Avoid maneuvers that increase intra-abdominal and intra-thoracic pressure.

- **Pharmacological therapy:**
- Midodrine: selective α1-adrenergic agonist and the only FDA-approved drug.
- Fludrocortisone: a synthetic mineralocorticoid
- Octreotide: inhibits gut vasoactive peptides leading to splanchnic vasoconstriction.
- Erythropoietin: increases intravascular volume and blood viscosity
- Pyridostigmine: a cholinesterase inhibitor.
- Nonselective beta blockers: antagonizing the hyperactive sympathetic drive.

Summary & Conclusion

- Although common and serious, CAN is frequently overlooked.
- Clinical consequences of CAN include resting tachycardia, intraoperative C.V. instability, absent nocturnal dipping, orthostatic hypotension, silent ischemia and arrhythmias.
- Patients may have subclinical CAN for years and screening with CART's and CCM is strongly recommended.
- Treatment principles include control of glycemic control & CV risk
- Pathogenesis-based medications like aldose reductase inhibitors, ACE inhibitors, c-peptide and ALA are promising.
- Orthostatic hypotension, indicates advanced CAN and

Thank You