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Tips and Tricks for Endomyocardial Biopsy

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Demographic features and prevalence of myocarditis in patients undergoing transarterial endomyocardial biopsy for unexplained cardiomyopathy

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INTRODUCTION

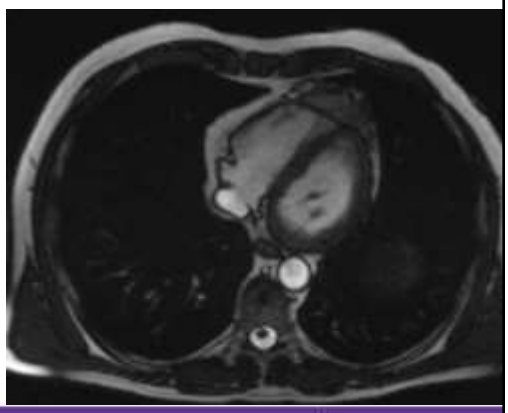
- Myocarditis is an inflammatory disease of the myocardium associated with cardiac dysfunction.
- Three forms of inflammatory CMP are recognized:
  Infectious,
  Autoimmune, and
  Idiopathic
- The true incidence and diagnosis of myocarditis is a challenge due to a great variation in clinical manifestations from asymptomatic changes on ECG to fulminant CHF , arrhythmias and sudden cardiac death.

Leone O , et al. Cardiovasc Pathol 2012;21:245–74.

IMAGING TECHNIQUES

Cardiac magnetic resonance (CMR) is the ideal technique to detect soft tissue changes such as edema and inflammation.

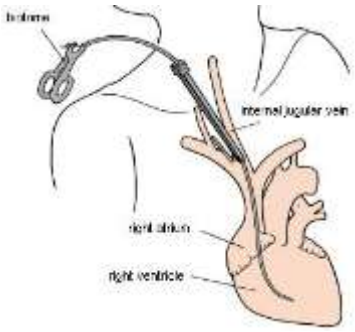
However, imaging techniques such as CMR or ECHO can only provide non-invasive tissue characterization but fail in revealing the true underlying causes that determine prognosis and treatment of the disease.



Mavrogeni S, et al. Int J Cardiol 2012;159:e37–8.

Endomyocardial biopsy (EMB)

- Its an invasive, diagnostic technique, which obtain histological samples from the myocardium using a biopsy forceps.
- Cardiac biopsy was initially performed in the 1950s by means of limited thoracotomy.
- EMB is the gold standard for heart disease when the common non-invasive methods do not make precise histopathological diagnosis possible.



Sekiguchi M, et al. Kokyu To Junkan 1988;36:1155.
Cooper LT, et al. Circulation 2007;116:2216–33.

REVIEW

Current Status of Endomyocardial Biopsy

Aaron M. From, MD; Joseph J. Maleszewski, MD; and Charanjit S. Rihal, MD

TABLE. **Indications for Endomyocardial Biopsy**

Monitor cardiac transplant rejection status
Diagnose unexplained cardiomyopathies
Suspected myocarditis
Suspected infiltrative cardiomyopathy
Diagnose cardiac tumors
Detect suspected anthracycline toxicity
Use in research

Mayo Clin Proc. 2011;86(11):1095-1102

Endomyocardial biopsy (EMB)

- EMB can be taken from the RV or LV. via the venous, or arterial route.
- EMB may be guided by Fluoroscopy, ECHO, or both .


Circulation

Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy

Differences in Complication Rate and Diagnostic Performance

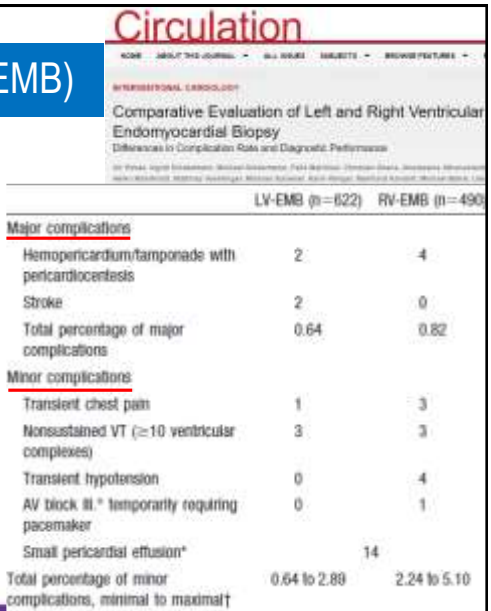
CLINICAL CARDIOLOGY

Safety of Transvenous Right Ventricular Endomyocardial Biopsy Guided by Two-Dimensional Echocardiography

- Because of the lack of available facilities and clinical experience, EMB appears to be infrequently used to diagnose myocarditis .

Endomyocardial biopsy (EMB)

- Reported complications range from minor site hematoma, to ventricular perforation.
- Incidence of complication was less than 1% of patients.
- LV-EMB was safer and more Diagnostic than RV-EMB.


Circulation

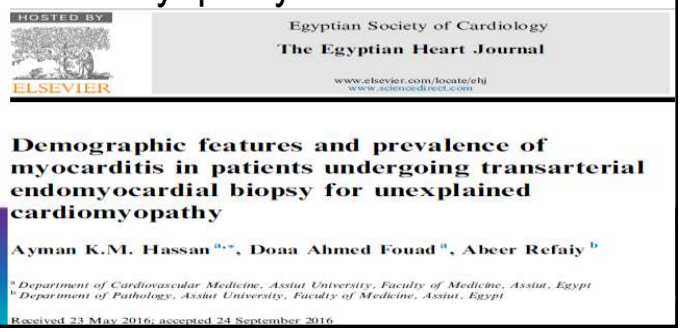
Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy

Differences in Complication Rate and Diagnostic Performance

	LV-EMB (n=622)	RV-EMB (n=490)
Major complications		
Hemopericardium/tamponade with pericardiocentesis	2	4
Stroke	2	0
Total percentage of major complications	0.64	0.82
Minor complications		
Transient chest pain	1	3
Nonsustained VT (≥10 ventricular complexes)	3	3
Transient hypotension	0	4
AV block III.* temporarily requiring pacemaker	0	1
Small pericardial effusion*	14	
Total percentage of minor complications, minimal to maximal†	0.64 to 2.89	2.24 to 5.10

The aim of our study

was to identify the demographic features and in-hospital prevalence of myocarditis in patients undergoing transarterial EMB for unexplained cardiomyopathy.



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15 patients with unexplained CM were included out of 1100 pts admitted 2014

The inclusion criteria :

- Acute symptoms of HF refractory to standard TTT,
- Worsening of EF despite optimized TTT,
- Development of significant arrhythmias, particularly progressive HB and VT,
- HF with concurrent rash, fever, or peripheral eosinophilia,
- New-onset CM in the presence of known amyloidosis, sarcoidosis, or hemochromatosis.

The exclusion criteria

- History of IHD,
- uncontrolled HTN,
- DM,
- Congenital HD or
- RHD,
- Familial CM,
- Peripartum CM,
- Cardiotoxic exposure
- Alcoholic patients

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Patients diagnosis protocol

All patients were subjected to

full history taking to identify the most common symptoms of myocarditis such as chest pain, breathlessness, fatigue, palpitations and fainting attacks. The history of flu-like symptoms (a cough, fever, malaise) and medications was used.

Then this was followed **by full physical examination, routine LAB tests,CXR** and **ECG**.

All patients had detailed **ECHO** study by an independent operator to analyze the suspected etiology of heart failure symptoms.

It was ***after ECHO assessment that patients were included into the study as suspected unexplained Cardiomyopathy for CA if –ve…. Do EMB***

Endomyocardial biopsy (EMB)

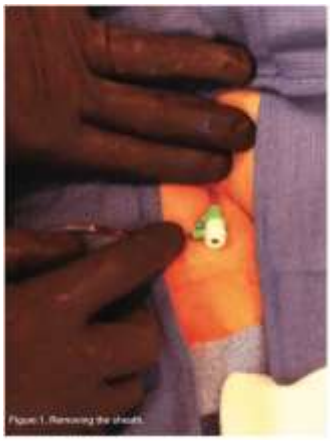
33 EMB samples were taken from the left ventricle of 11 patients.

Zero complication rate.

9 Tips & Trikes for safe and effective EMB

EMB : TIP 1 --- FA, ½ dose heparin

- Insert 6F femoral sheath in left or right common femoral artery .. Same as in CA
- Give 2500 IU of Heparin in the sheath only.

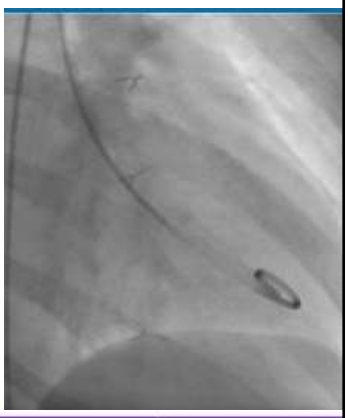


EMB : TIP 2 --- JR 3.5 guiding

- Insert JR 3.5 guiding cath
- Using the regular J tipped 0.038 GW
- Till the root of the Aorta

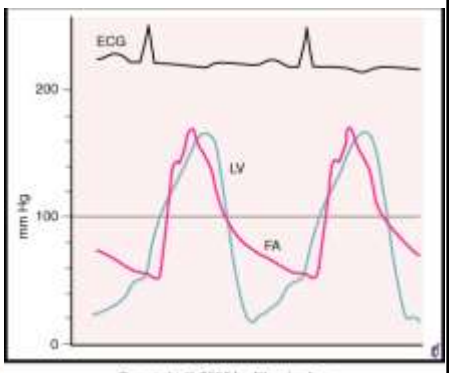
EMB : TIP 3 ---- reach the LV apex

- Push the JR3.5 into the LV during systole with AV opening.
- Push the wire in front of the guiding cath. till making a loop at the LV apex
  - Avoid inflow track ,chordae and papillary muscles .



EMB : TIP 4 ---- safety issues

- Remove the wire
- Measure the pressure in LV 1st (as a base line if perforation occur)
- Use a Y-connector



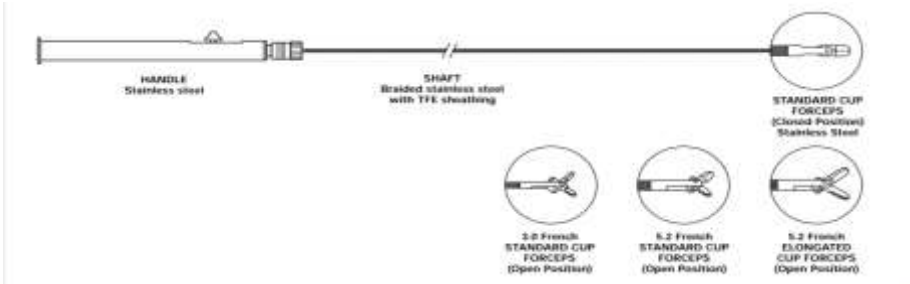
EMB : TIP 5… in-vitro preparation

- Prepare and test your Bioptome (Cook or small intestinal biopsy forceps compatible with 6 F guiding)
  - Check if it open and close smoothly
  - Push it in-vitro inside the JR guiding till it get out to measure the length relationship between both.

  Push the bioptom into the JR3.5 to the LV apex

EMB : TIP 5… in-vitro preparation

A Cook Flexible Biopsy forceps (with a standard cup for tissue sampling of 5.2 Fr volume 2.25 mm^3



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A Cook Flexible Biopsy forceps (with a standard cup for tissue sampling of 5.2 Fr volume 2.25 mm^3

COOK

ORDER NUMBER	French Size	Length	Forceps Volume mm^3	Quick Reorder Number[1]
STANDARD CUP FORCEPS				
FBF-3.0-60	3.0	60 cm	.86	158482
FBF-3.0-120	3.0	120 cm	.86	158481
FBF-5.2-60	5.2	60 cm	2.25	158483
FBF-5.2-120	5.2	120 cm	2.25	158484
ELONGATED CUP FORCEPS				
FBFE-5.2-60	5.2	60 cm	4.86	161067
FBFE-5.2-120	5.2	120 cm	4.86	161066

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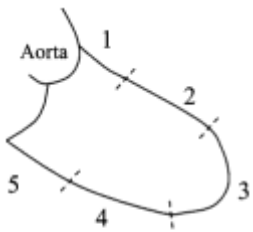
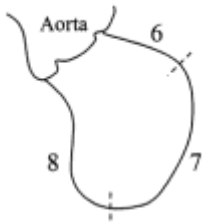
EMB : TIP 6 … fluoroscopic guidance

- Use RAO 35 standard view 1st
  - Tack the 1st biopsy from the apex
- Use the LAO 45 view
  - Then 2nd one form septum
  - To take the 3rd biopsy form lateral wall.



1 Anterobasaal
2 Anterolateraal
3 Apicaal
4 Inferior
5 Posterobasaal



6 Posterolateraal
7 Lateraal
8 Septaal

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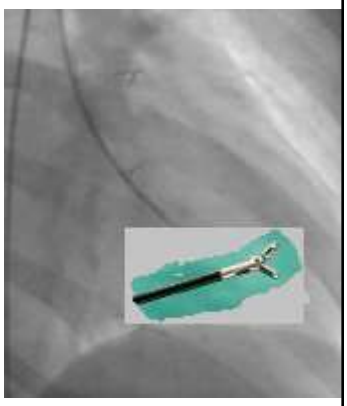
EMB : TIP 7… avoid perforation

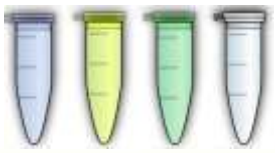
Avoid perforation of the LV ventricle

- After opening the forceps out side the guiding in the LV
- Push both till reach a resistance (this is the wall for biopsy)
- ***close the forceps till a grip is felt***
- ***Pull back the hole system (JR+ bioptome together)*** out side the LV into the aorta …..*if not the guiding will be advanced forward and perforate the LV.*
- Leave the JR, and get the bioptome outside the body



EMB : TIP 8… samples management

- Take 3 samples each = 2 mm --- Keep them safe
  - Use a green needle to get out your sample form the opened forceps tip.
  - Put it immediately into a bottle with saline better 10% formalin
  - Close it carefully and send it immediately to the pathologist
  - Each sample in a separate bottle with clear lable.
  - Better to have an epindorf tubes with preservative (PBS)
- Don't forget a blood sample 10 ml for viral and genetic testing.

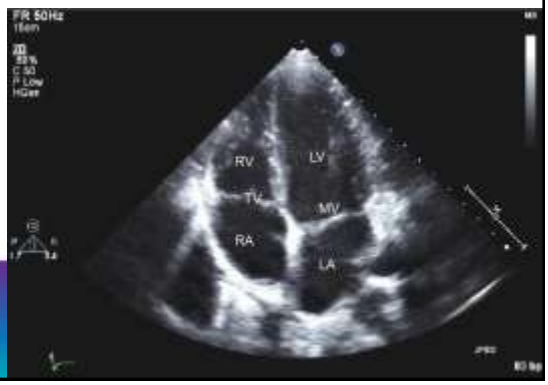


EMB : TIP 9 … safety post procedure

- **Final ECHO post procedure**

The main reported complications were

- pericardial effusion or
- new onset mitral incompetence due to chordal involvement.



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Results of EMB are usually affected by two opponents

- the 1st opponent is the fading of infiltration of inflammatory cells after treatment or in the late stage of the disease.
- The 2nd opponent is sampling errors

These factors made us to adopt the methodology in this study by taking the biopsies during the **early stage** of the disease and taking biopsies from **different areas of LV** which may help to get higher results.

Veinot JP. Cardiovasc Pathol 2011;20:291–6.

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Histopathological analysis

- Tissue specimens were processed and 5 ml sections were cut and stained with **hematoxylin and eosin** or other specific stains according to each case.
- Sections were examined by **light microscopy** and the following features were evaluated:
  - the presence of inflammatory cells,
  - number, and distribution of inflammatory cells,
  - the presence of necrosis or fibrosis.

Dallas criteria

The confirmed diagnosis of myocarditis was according to the Dallas criteria

Definition of idiopathic myocarditis: "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease"

Classification

First biopsy
- Myocarditis with/without fibrosis
- Borderline myocarditis (repeat biopsy may be indicated)
- No myocarditis

Subsequent biopsy
- Ongoing (persistent) myocarditis with or without fibrosis
- Resolving (healing) myocarditis with or without fibrosis
- Resolved (healed) myocarditis with or without fibrosis

Descriptors

	Inflammatory infiltrate	Fibrosis
Distribution	Focal, confluent, diffuse	Endocardial, interstitial
Extent	Mild, moderate, severe	Mild, moderate, severe
Type	Lymphocytic, eosinophilic, granulomatous, giant cell, neutrophilic, mixed	Perivascular, replacement

Leone O , et al. Cardiovasc Pathol 2012.

Limitations of Dallas criteria

- High inter-observer variability in interpreting biopsy (especially borderline myocarditis).
- EMB is considered to be positive for inflammation by immunehistochemical detection of focal or diffuse mononuclear infiltrates with >14 cells/mm^2.

Leone O , et al.

ELSEVIER

Cardiovascular Pathology 21 (2012) 245 - 274

CARDIOVASCULAR PATHOLOGY

Original Article

2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology

- S: published peer-reviewed evidence SUPPORTS the utility of the test.
- M: published peer-reviewed evidence is MIXED concerning the utility of the test.
- N: there is NO published peer-reviewed evidence assessing the utility of the test.

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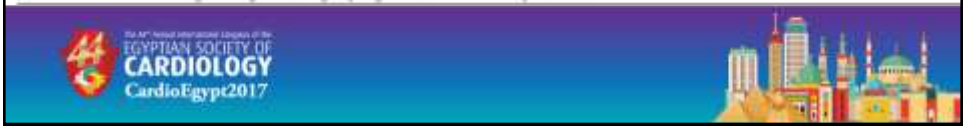
EMB diagnostic potential in cardiac dis.

Endomyocardial biopsy diagnostic potential in cardiac diseases with grading of recommendation

Clinically suspected disease	EMB diagnostic potential and histological notes	Technical aspects and tissue triage	Grading of recommendation
Myocarditis/inflammatory cardiomyopathy	Definite diagnosis: lymphocytic, granulocytic, polymorphous, eosinophil, necrotizing eosinophilic, giant cell, granulomatous myocarditis, with or without associated myocyte damage/ necrosis. Histological findings alone or together with molecular techniques may be able to specify the etiology of the inflammatory disease.	Recommended: In addition to formalin fixation, two fragments (or one if greater than 1 mm^3) could be snap-frozen or preserved in RNA-later for virus molecular investigation. One peripheral blood sample (5 - 10 ml) collected in EDTA or sodium citrate tubes. NB: Timing and number of EMB and serial histological sections are important for sensitive detection of myocarditis.	S
Cardiac sarcoidosis	Definite diagnosis: noncaseous granulomatous myocarditis. Histological findings pathognomonic or highly suggestive of the disease.	Possible increased utility with guided biopsy procedure.	S
Myocardial diseases due to drugs and chemical/"toxic" substances	Probable/possible diagnosis: hypersensitivity myocarditis (histological findings suggestive of the disease), toxic damage.	Glutaraldehyde or Karnovsky solution fixed fragment for electron microscopy may be useful for cardiotoxicity evaluation of some drugs.	S: hypersensitivity myocarditis M: cardiotoxicity
Peripartum cardiomyopathy	Probable diagnosis: myocarditis/borderline myocarditis. Histological findings give some indications of probable disease.	Fresh sample may be useful for virus molecular biology. Important: EMB timing	M
Cardiac amyloidosis	Definite diagnosis: amyloid infiltration. Histological findings/histomorphological stains are pathognomonic.	Recommended: Congo red, modified sulfated alcian blue, or thioflavin T stains. IHC, IF, immunoelectron microscopy, protein sequencing, and/or mass spectrometry to establish the type of amyloid. Frozen tissue is required for IF and protein sequencing	S
Iron overload	Definite diagnosis: iron extracellular deposition. Histological findings/iron staining are pathognomonic.	Iron staining is advisable for all diagnostic EMBs from patients with unexplained DCM.	S



EMB diagnostic potential in cardiac dis.

Mitochondrial cardiomyopathies	Probable/possible diagnosis: morphologically altered mitochondria by electron microscopy Nonspecific histological findings: enlarged myocytes with extensive cytoplasmic vacuolization	Recommended: Fresh sample is needed for histoenzymatic stainings. Glutaraldehyde or Karnovsky solution fixed fragment is needed for ultrastructural tests.	M (especially in isolated MIC)
Arrhythmogenic right ventricle cardiomyopathy	Probable diagnosis: fibrous or fibrofatty replacement and myocardial atrophy. Nonspecific histological findings.	IF or IHC for plakoglobin and other cellular junction proteins is promising test (being validated). EMB from the interventricular septum may not be informative. Diagnostic accuracy increases if EMB sampling site is guided by imaging (MRI) or electrophysiological (electroanatomic mapping) techniques.	S (in selected cases having no clear-cut diagnosis with noninvasive and other invasive procedures)
Loeffler fibroplastic endocarditis/ endomyocardial fibrosis	Definite diagnosis in the acute phase: endomyocardial infiltrates rich in degranulated eosinophils and endocardial thrombosis. Specific histological findings. Possible diagnosis in the chronic phase: evidence of endocardial fibrous thickening and subendocardial myocyte abnormalities. Nonspecific histological findings.	EMB timing is important as the utility of biopsy probably decreases with disease time course.	S in the acute–subacute phase
Cardiac tumors	Definite diagnosis	IHC useful for tumor typing	S
Hypertrophic cardiomyopathy (sarcomeric mutations)	Possible diagnosis: myocyte hypertrophy, interstitial and/or substitutive fibrosis, disarray, and possible small vessel disease. Nonspecific histological findings.		M: The clinical diagnosis of HCM usually relies on noninvasive diagnostic tools, and EMB is not recommended in the diagnostic workup. However, in selected cases, EMB may be helpful in excluding infiltrative or storage diseases with variable diagnostic degree of certainty.
Idiopathic restrictive cardiomyopathy	Possible diagnosis: normal myocardium, and/or fibrosis and/or disarray. No other identifiable diseases causing restrictive phenotype. Nonspecific histological findings.		M: EMB is unable to give a specific diagnosis. However, in selected cases, EMB may be helpful in excluding infiltrative or storage diseases. Useful in the workup of constriction versus restriction.
Idiopathic dilated cardiomyopathy	Possible diagnosis: myocyte hypertrophy, nuclear alterations, perinuclear halo, with or without fibrosis. Nonspecific histological findings.		M: EMB is unable to give a diagnostic picture, but may be helpful in excluding other diseases.
Heart transplantation	Definite diagnosis: acute cellular rejection, some infectious disease, PTLD, and nonrejection posttransplant findings. Specific histological findings.	Recommended: C4d IHC/IF staining for AMR. Fresh sample is required for IF staining.	S

DCM, dilated cardiomyopathy; EDTA, ethylenediaminetetraacetic acid; EMB, endomyocardial biopsy; IF, immunofluorescence; IHC, immunohistochemistry; MRI, magnetic resonance imaging; M, mixed; N, not supported; PTLD, posttransplant lymphoproliferative disorders; S, supported.

Results of our study

The in-hospital prevalence of
Unexplained CM =1.4%
Myocarditis =0.63%.

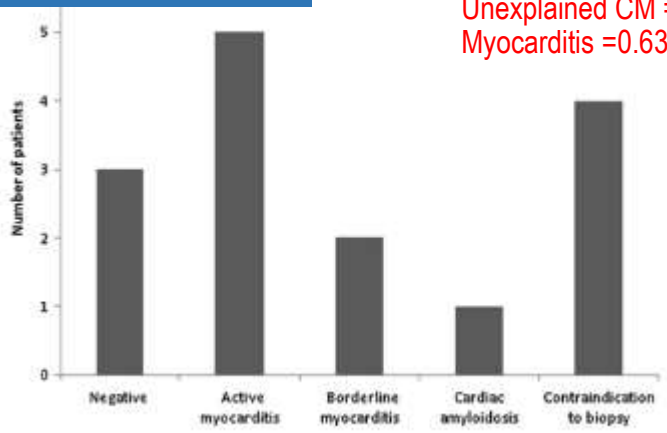


Figure 1 Distribution of patient according to biopsy result.

EMB showing the absence of inflammation or necrosis and diagnosed as **negative for myocarditis** (H&Ex400)

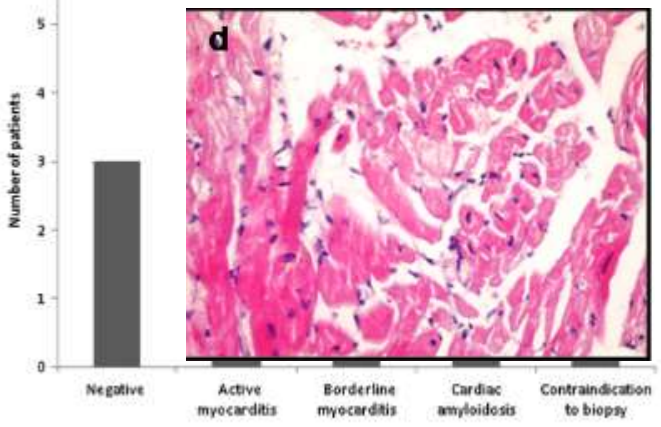


Figure 1 Distribution of patient according to biopsy result.

Acute myocarditis showing diffuse infiltrate by mixture of polymorphs and lymphocytes (arrows) with cardiomyocyte necrosis.

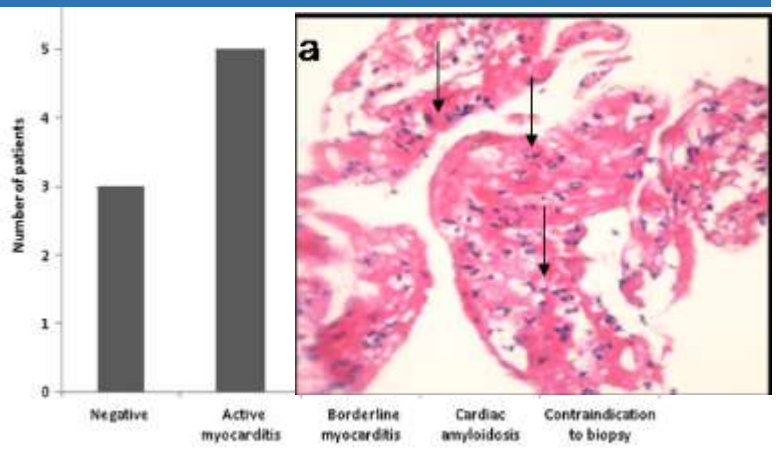


Figure 1 Distribution of patient according to biopsy result.

Borderline myocarditis: demonstrating few inflammatory cells without cardiomyocytes necrosis

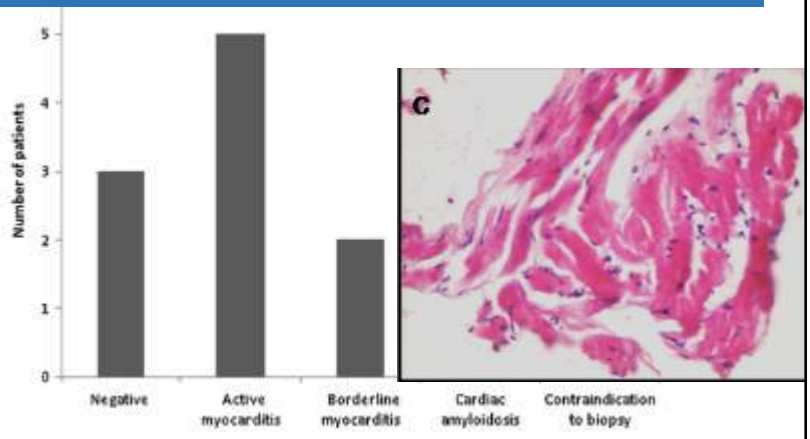


Figure 1 Distribution of patient according to biopsy result.

Cardiac amyloidosis showing homogenous structureless pink material (amyloid) in between cardiac muscles

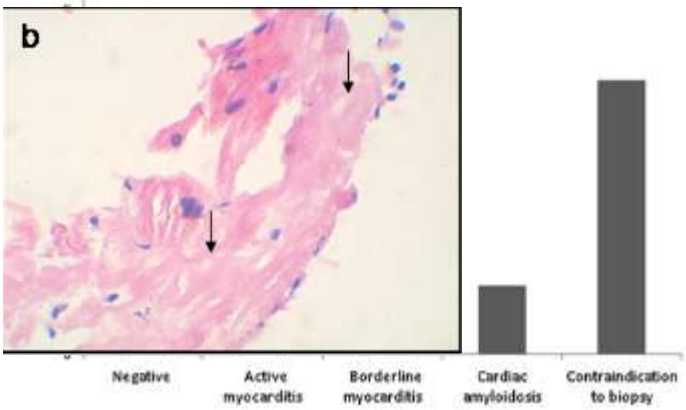


Figure 1 Distribution of patient according to biopsy result.

Limitations

- Small number of biopsy samples,
- No follow-up samples, Nor CMR .
- lack of immune histochemical analysis of biopsy samples and
- lack of molecular analysis with DNA-RNA extraction and
- RI-PCR amplification of the viral genome to rule in/out viral etiology was not performed.

However, this is our first report and our main concern was to **develop the system to implement EMB** sampling technique and set in motion the **process of the preservation** of samples and the onward **collaboration** with a specialist in the **pathology department** to handle and study all cardiac specimens in this **early report of our continuing project on unexplained CM patients**.

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THE MAIN FINDING IN OUR STUDY

1. **The in-hospital prevalence of**
   - **Unexplained CM was 1.4%**
   - **Myocarditis was 0.63%.**

2. Myocarditis proved by pathological examination of EMB represents 64% of these patients.

3. EMB from the LV using Cook bioptomes via transfemoral artery sheath is safe and essential in confirming the diagnosis.

THANKS

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