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Ruolo della Biopsia Miocardica nelle Miocarditi

Fabrizio Oliva

VII Congresso di ECOCARDIOCHIRURGIA

Milano, 5-7 Maggio 2014

Background

- Challenging diagnosis (extreme diversity of clinical manifestations).

- Actual incidence is difficult to determine as endomyiocardial biopsy (EMB), diagnostic gold standard, is used infrequently.

Richardson *Circulation 1996*
Kindermann *J Am Coll Cardiol 2012*

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Ruolo della BEM nelle Miocarditi

- Cosa è in grado di fornire la BEM rispetto agli altri accertamenti diagnostici
- Quando eseguirla
- Aspetti operativi

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Documento di Consenso sulle Indicazioni alla Biopsia Endomiocardica

SIC
ANMCO
Società Italiana Cardiologia Invasiva
Società Italiana di Cardiologia Pediatrica

O. Leone, C. Rapezzi, G. Sinagra, A.Angelini, E. Arbustini, G.Bartoloni, C.Basso, A. Caforio, F, Calabrese, F. Coccolo, G.D'Amati, O. Milanesi, S. Nodari, F.Oliva, D. Prandstaller, A.Pucci, A. Ramondo, M. Valente, G Thiene.

G Ital di Cardiol 2009; 10 (9 suppl 1): 3S-50S.

Documento di Consenso sulle Indicazioni alla BEM

Condizione patologica sospettata	Potenzialità diagnostiche della BEM	Annotazioni tecniche	Standards diagnostici della malattia
Miocarditi	**Diagnosi di certezza** **Altre informazioni:** -grading ed attività della malattia	**Importante** -timing della BEM -numero/ Rappresentatività BEM **Necessarie** -istochimica e immunoistochimica -indagini molecolari per genomi virali **Importante** -associare ricerca autoanticorpi anti-cardiaci nel siero	BEM NB: scintigrafia miocardica e RM possono contribuire a generare il sospetto diagnostico ma non sostituiscono la BEM La RM può guidare la sede topografica del prelievo

Giornale Italiano di Cardiologia 2009, in press

BEM: informazioni

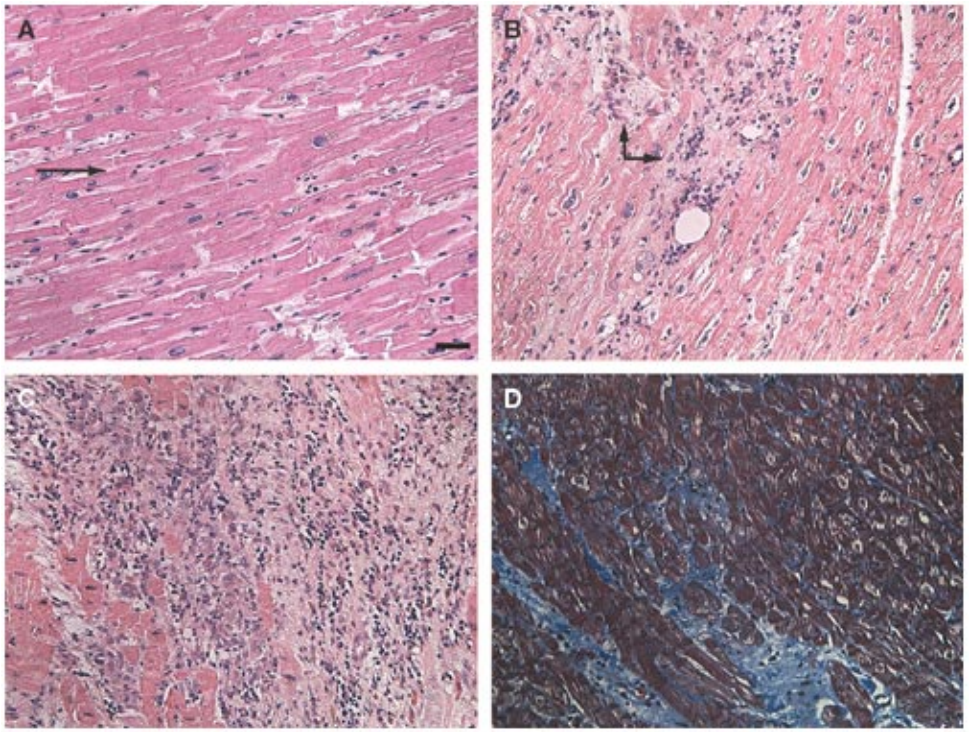
- Istologia
- Immunoistochimica
- Virologia

BEM: luci e ombre

- Analisi istopatologica (criteri di Dallas):
  - Standard di riferimento
  - Limiti di accuratezza: errori di campionamento, variabilità interosservatore
- Immunoistochimica: grado di attivazione immunologica
- Reazione polimerasica a catena in tempo reale (RT-PCR): presenza di genoma virale

Aretz *Am J Cardiovasc Patholog 1987*
Chow *J Am Coll Cardiol 1989*
Baugham *Circulation 2006*

Esame istologico



Diagnosis of Myocarditis: Death of Dallas Criteria
Kenneth L. Baughman
Circulation 2006;113;593-595

A. Miocardio "normale" senza evidenza di infiltrato cellulare o di necrosi
B. Miocardite "borderline con moderato infiltrato linfocitico
C. Miocardite "fulminante" con infiammazione miocardica intensa e necrosi
D. Miocardite "cronica" con importante fibrosi interstiziale e atrofia dei miociti

European Heart Journal (2013) 34, 2636–2648
doi:10.1093/eurheartj/eht210

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (*Table 1*).

Autoimmune myocarditis

Histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies (aabs) (*Table 2*).

N.B. There are autoimmune diseases (e.g. Hashimoto's thyroiditis) where aabs are mainly biomarkers, autoantibody-mediated forms (e.g. Graves' disease), in which aabs are pathogenic, and cell-mediated autoimmune diseases, which are negative for aabs. In all cases, autoimmune diseases are negative for infectious agents.

Viral and immune myocarditis

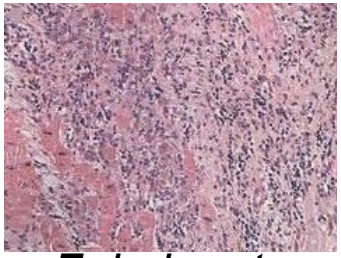
Histological myocarditis with positive viral PCR and positive cardiac aabs (*Table 2*).

Caforio *Eur Heart J 2013*

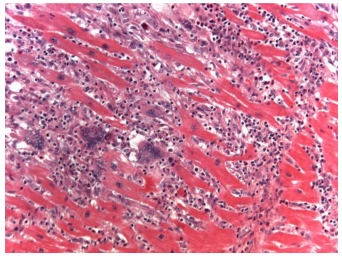
BEM: ruolo nell'iter diagnostico

Fornire la diagnosi eziologica

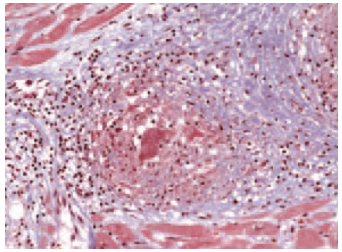
Miocardite infettiva Batteri/Virus/Protozoi	Miocardite non infettive di origine immunitaria/allergica	Altre



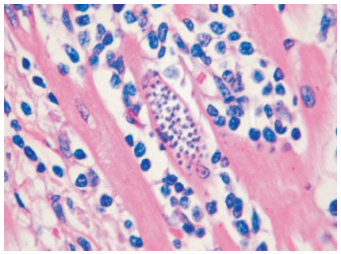
Fulminante



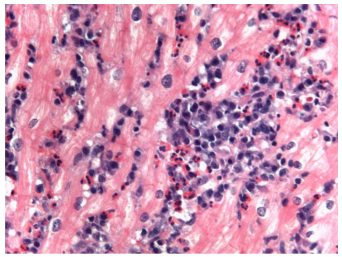
Cellule giganti



Sarcoidosi



Chagas



Ipereosinofilia

OPZIONI TERAPEUTICHE DIFFERENTI

BEM: risvolti gestionali sul malato

- Forme specifiche di Miocardite con responsività al trattamento immunosoppressivo:
  - Miocardite a cellule giganti
  - Miocardite eosinofila necrotizzante
  - Coinvolgimento cardiaco in sarcoidosi

BEM: ruolo nell'iter diagnostico

Fornire indicazioni sul grado di attività della malattia

- Quantificazione dell'infiltrato flogistico
  < o > 7 linfociti T/mm2

- Precisa misurazione dell'entità della fibrosi

BEM: informazioni prognostiche

- Infiltrato linfocitario, granulomatoso o gigantocellulare
- Attivazione immunologica

↓

Predittori indipendenti di prognosi severa

McCarthy *N Engl J Med 2000*
Kindermann *Circulation 2008*

BEM

- Numero congruo di prelievi
- Conservazione di un campione per indagini virologiche molecolari o di proteonomica
- Completa caratterizzazione istopatologica, immunoistochimica e virologia molecolare

Leone *Cardiovasc Pathol 2012*

Myocarditis
Diagnostic Evaluation

ECG

- It 's usually abnormal athough signs are neither specific nor sensitive

- Diffuse concave (rather than convex in myocardial ischemia) ST-T segment elevations without reciprocal changes and non-specific T-wave changes are suggestive for myocarditis

Morgera *Am Heart J 1992*
Caforio *Eur Heart J 2007*

Echocardiography

- It's useful to exclude other causes of heart failure but there are no specific echo features of myiocarditis
- LV dysfunction 69%
- LV cavity enlargement minimal or absent in Fulminant M.
- RV dysfunction 23% > predictor of death or HTx
- Segmental wall motion abnormalities 64% (hypokinetic, akinetic, dyskinetic) mimic AMI
- Useful to monitor changes in cardiac chamber size, wall thickness, ventricula function, pericardial effusion

Felker *JACC 200*

Cardiac Biomarkers

- CK or CK-MB not useful (low predictive value)

- <u>Only 35% of pts with suspected myocarditis had elevated troponin levels</u>
  - Using troponin T cutoff > 0.1 ng/mL :
    positive predictive value 93%
    negative predictive value 56%
  - Higher levels = prognostic value

Liu *Circulation 2001*
Smith *Circulation 1997*
Lauer *JACC 1997*

Virus serology

- Utility remains unproven
- Only in 5 of 124 patients (4%) there was serological evidence of an infection with the same virus detected by nested PCR in EMB
- …The patients are referred with a significant delay from the onset of the initial infection (from some weeks to a few months): acute phase has already resolved.

Mahfoud *Eur Heart J 2011*

Immunologic Approaches

- Mayor histocompatibility (MHC) antigens expression as criterion for diagnosing inflammatory CMP
- This approach has greater sensitivity than the Dallas criteria
- MHC class I e II expression was increased 10-fold in myocarditis cohort
- Sensitivity 80% Specificity 85%
- No correlation with hystopathological findings of active myocarditis in some studies
- MHC could represent a more chronic form of myocardial injury and may not be responsible for clinical presentation

Myocarditis
Diagnostic Evaluation

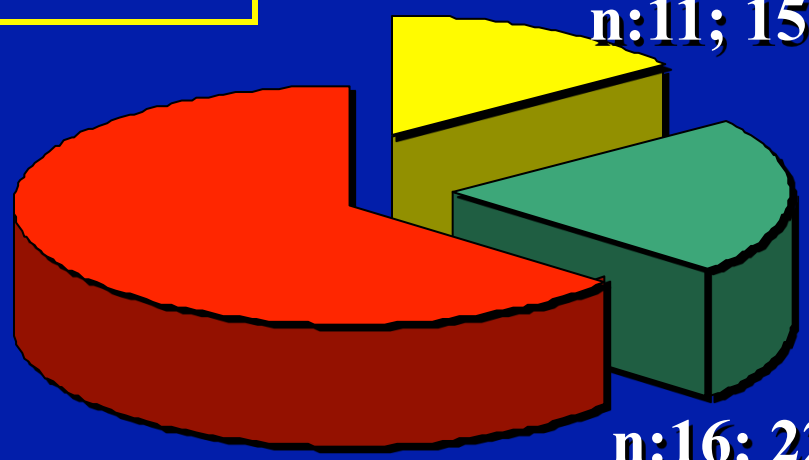
CMR

- It can localise tissue injury,it can quantitate tissue injury (oedema, hyperemia, fibrosis)
- When 2 or more Lake Louise criteria are positive > diagnosis accuracy 78%
- Biopsy of these specific myocardial regions ??
- Serial MRI for tracking the natural hystory of the disease

Abdel-Ary *JACC 2005*

Registro TS-CMP
MIOCARDITI: Presentazione clinica
(1978-2006)

TOTALE PAZIENTI
n: 74



n:11; 15%, (M 73%; 38±14 aa)

n:47; 63%, (M 57%; 38±16 aa)

n:16; 22%, (M 81%; 35±14 aa)

PSEUDO-IMA **ARITMIE** **SCC**

CRITERI DI CLASSIFICAZIONE:

✓ Sintomo clinicamente più rilevante all'esordio

CMR Sensitivity Varies With Clinical Presentation and Extent of Cell Necrosis in Biopsy-Proven Acute Myocarditis

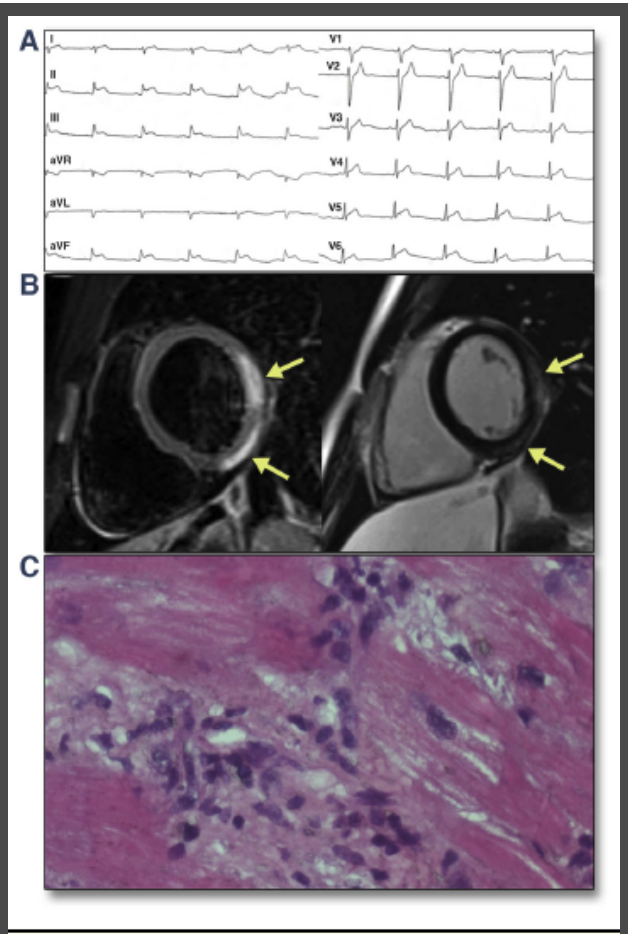


Figure 1. Acute Myocarditis in a 23-Year-Old Man Presenting With Fever and Chest Pain (Ischemic Pattern)

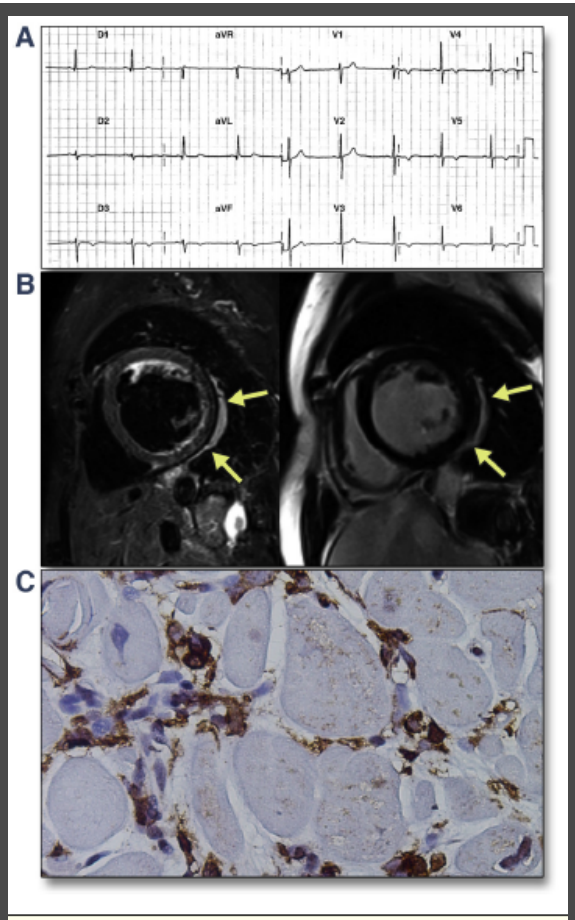


Figure 2. Acute Myocarditis in a 48-Year-Old Man Presenting With Recent-Onset Dyspnea and Left Ventricular Dysfunction (Cardiomyopathic Pattern)

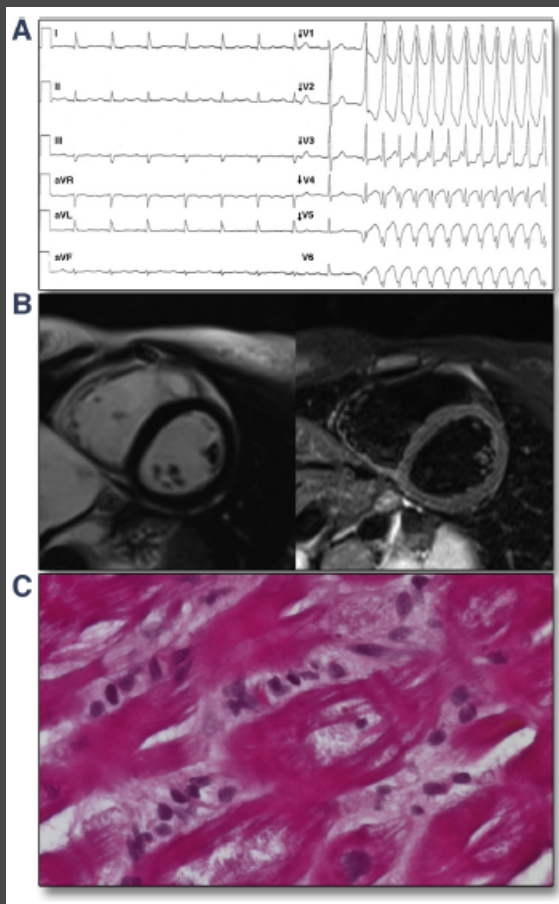


Figure 3. Acute Myocarditis in a 29-Year-Old Woman With Palpitations and Hypotension (Arrhythmic Pattern)

Francone *J Am Coll Img 2013*

CMR Sensitivity Varies With Clinical Presentation and Extent of Cell Necrosis in Biopsy-Proven Acute Myocarditis

RESULTS Three clinical myocarditis patterns were recognized: infarct-like (pattern 1, n = 21), cardiomyopathic (pattern 2, n = 21), and arrhythmic (pattern 3, n = 15). Tissue edema was observed in 81% of pattern 1, 28% of pattern 2, and 27% of pattern 3. Early enhancement was evident in 71% of pattern 1, 67% of pattern 2, and 40% of pattern 3. Late gadolinium enhancement was documented in 71% of pattern 1, 57% of pattern 2, and 47% of pattern 3. CMR sensitivity was significantly higher in pattern 1 (80%) compared with pattern 2 (57%) and pattern 3 (40%) ($p < 0.05$). Cell necrosis was the prevalent mechanism of death in pattern 1 compared with pattern 2 ($p < 0.001$) and pattern 3 ($p < 0.05$), whereas apoptosis prevailed in pattern 2 ($p < 0.001$ vs. pattern 1 and $p < 0.05$ vs. pattern 3).

CONCLUSIONS In acute myocarditis, CMR sensitivity is high for infarct-like, low for cardiomyopathic, and very low for arrhythmic clinical presentation; it correlates with the extent of cell necrosis–promoting expansion of interstitial space. (J Am Coll Cardiol Img 2014;7:254–63)

Francone *J Am Coll Img 2013*

CMR

- Good correlation CMR-EMB in troponine positive patients, correlation is worse in pts with a longer history of symptoms
- CMR cannot exclude viral forms of myocarditis
- It is reasonable to perform CMR prior to EMB in clinically stable patients
- It should not be performed in life-threatening presentations where EMB is urgently indicated

Cooper *Am Coll Cardiol 2007*
Caforio *Eur Heart J 2013*

- Anamnesi, indagini non invasive (sierologia, ECG, ECO, RM) sono importanti per caratterizzare il quadro e per una stima diagnostica pre-BEM e per la valutazione prognostica anche nel follow up seriato ..
- …ma BEM è il gold standard

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AHA/ACCF/ESC Scientific Statement

The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

Table 2 The role of endomyocardial biopsy in 14 clinical scenarios

Scenario number	Clinical scenario	Class of recommendation (I, IIa, IIb, III)	Level of evidence (A, B, C)
1	New-onset heart failure of *< 2 weeks'* duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
2	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	I	B
3	Heart failure of *> 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa	C
4	Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C
5	Heart failure associated with suspected anthracycline cardiomyopathy	IIa	C
6	Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
7	Suspected cardiac tumors	IIa	C
8	Unexplained cardiomyopathy in children	IIa	C
9	New-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	B
10	Heart failure of *> 3 months'* duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	C
11	Heart failure associated with unexplained HCM	IIb	C
12	Suspected ARVD/C	IIb	C
13	Unexplained ventricular arrhythmias	IIb	C
14	Unexplained atrial fibrillation	III	C

2007

European Heart Journal
doi: 10.1093/eurheartj/ehm456

The role of endomyocardial biopsy in the management of cardiovascular disease

2007

A Scientific Statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

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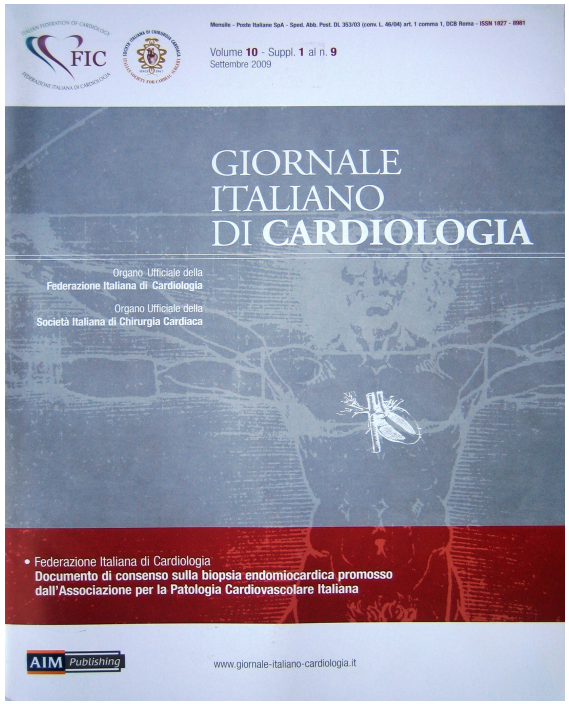
BEM: indicazioni



2009

Federazione Italiana di Cardiologia

Documento di consenso sulla biopsia endomiocardica promosso dall'Associazione per la Patologia Cardiovascolare Italiana

Associazioni e Società coinvolte

Associazione per la Patologia Cardiovascolare Italiana (APCI)

Società Italiana di Cardiologia (SIC)
Gruppo di Studio di Anatomia e Patologia Cardiovascolare
Gruppo di Studio Cardiomiopatie e Malattie del Pericardio
Gruppo di Studio Funzione Miocardica e Insufficienza Cardiaca

Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)
Area Scompenso Cardiaco

Società Italiana di Cardiologia Invasiva (SICI-GISE)

Società Italiana di Cardiologia Pediatrica (SICP)

Autori

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La specifica patologia che si vuole diagnosticare (o escludere)

La presenza/assenza di alternative diagnostiche non invasive

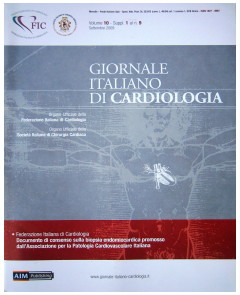
Le ricadute complessive di una diagnosi di certezza sulla gestione clinica del paziente

BEM: indicazione
gradi di raccomandazione

Grado 1	non esistono metodiche alternative capaci di fornire una diagnosi di certezza. Le ricadute cliniche della diagnosi sono certe.
Grado 2 a	non esistono metodiche alternative capaci di fornire una diagnosi di certezza. Le ricadute cliniche della diagnosi sono incerte
Grado 2 b	non esistono metodiche alternative capaci di fornire una diagnosi di certezza. Non ci sono tuttavia ricadute cliniche certe, ma solo conoscitive.
Grado 3	esistono metodiche diagnostiche alternative capaci di fornire una diagnosi di certezza.

Federazione Italiana di Cardiologia

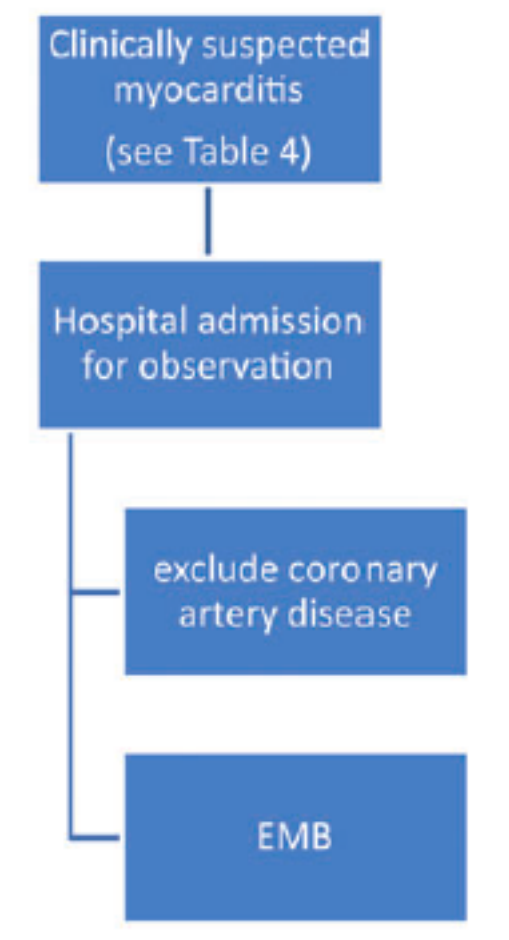
Documento di consenso sulla biopsia endomiocardica promosso dall'Associazione per la Patologia Cardiovascolare Italiana



Condizione patologica sospettata	Grado di raccomandazione
Miocarditi	
Situazioni cliniche:	
1. Scompenso cardiaco o sindrome equivalente ad esordio acuto/iperacuto insorto da <1 mese	1
2. Scompenso cardiaco insorto da <6 mesi, a coronarie indenni, con ipocinesia VS persistente	
a) malgrado un adeguato periodo (1-3 settimane) di terapia medica convenzionale "ottimale"	1
b) decisione presa ancor prima di verificare l'efficacia della terapia	2a
c) nonostante risposta clinica alla terapia	2a
3. Scompenso cardiaco insorto da >6 mesi, a coronarie indenni, con ipocinesia VS persistente	
a) malgrado un adeguato periodo (1-3 settimane) di terapia medica convenzionale "ottimale"	2a
b) decisione presa ancor prima di verificare l'efficacia della terapia	2a
c) nonostante risposta clinica alla terapia	2b
4. Dolore toracico cardiaco e rialzo degli enzimi di miocardiocitolisi, con esclusione angiografica di coronaropatia e FEVS depressa	2a
5. Dolore toracico cardiaco e rialzo degli enzimi di miocardiocitolisi, con esclusione angiografica di coronaropatia e normale FEVS	2b
6. Aritmie ipercinetiche ventricolari sostenute o "minacciose" in un contesto clinico compatibile con miocardite	1
7. Blocchi AV in presenza di disfunzione ventricolare in un contesto clinico compatibile con miocardite	2a
8. Blocchi AV in assenza di disfunzione ventricolare in un contesto clinico compatibile con miocardite	2b
9. Peggioramento clinico o della funzione ventricolare di una CMP dilatativa in precedenza migliorata, verosimilmente o sicuramente post-miocarditica	2a
10. CMP peripartum	2a

European Heart Journal (2013) **34**, 2636–2648
doi:10.1093/eurheartj/eht210

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases



Recommendation

10. All patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB.

Caforio *Eur Heart J 2013*

2013 ACCF/AHA Guideline for the Management of Heart Failure

6.5.3. Endomyocardial Biopsy

Endomyocardial biopsy can be useful when seeking a specific diagnosis that would influence therapy, and biopsy should thus be considered in patients with rapidly progressive clinical HF or worsening ventricular dysfunction that persists despite appropriate medical therapy. Endomyocardial biopsy should also be considered in patients suspected of having acute cardiac rejection status after heart transplantation or having myocardial infiltrative processes. A specific example is to determine chemotherapy for primary cardiac amyloidosis. Additional other indications for endomyocardial biopsy include in patients with rapidly progressive and unexplained cardiomyopathy, those in whom active myocarditis, especially giant cell myocarditis, is being considered (310). Routine endomyocardial biopsy is not recommended in all cases of HF, given limited diagnostic yield and the risk of procedure-related complications.

Endomyocardial biopsy can be useful in patients with HF when a specific diagnosis is suspected that would influence therapy	IIa	C

EMB ?

- How to find the desirable middle between these two extreme recommendations ?

Diagnostic approach of myocarditis: strike the golden mean

M. R. Hazebroek · K. Everaerts · S. Heymans

a more practical approach, particularly for patients presenting to GPs and/or regional hospitals that often have no access to state-of-the-art CMR or cannot safely perform EMB. Therefore, referral for EMB in acute suspected myocarditis patients (point 1, 2 & 4 in Table 1) is recommended in the case of:

- A life-threatening arrhythmia
- LV dysfunction that does not improve 4–5 days after onset of symptoms
- LV dysfunction that progressively deteriorates within 4–5 days after onset of symptoms
- Recurrent myocarditis

Neth Heart J (2014) 22:80–84

EMB : when ?

- Well-selected cases, placing the results in a management perspective and treatment of the patient.

Caso clinico

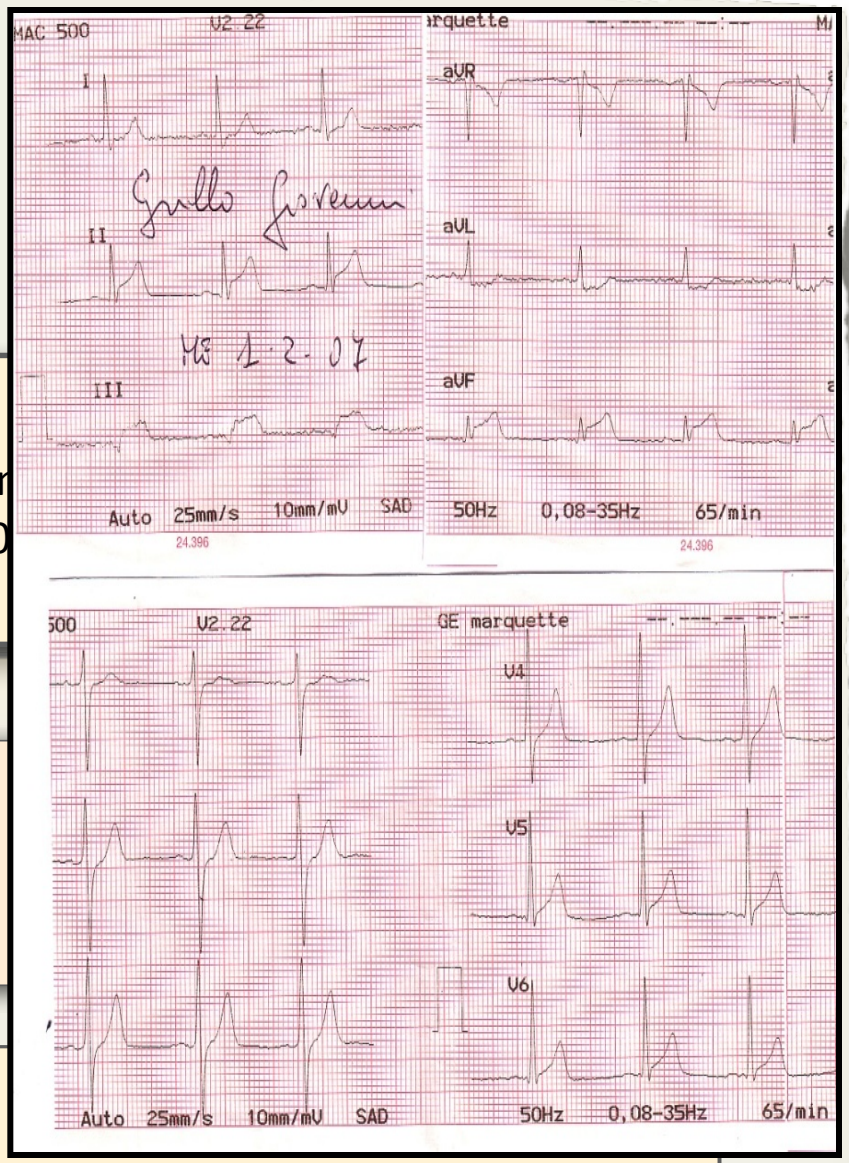
C.L.
43 aa
FR CV: Forte fumatore; familiarità per cardiopatia ischemica, dislipidemico
ANAMNESI PATOLOGICA REMOTA: Non precedenti di rilievo.

Ricovero per la comparsa di dolore retrosternale oppressivo non irradiato, insorto a riposo la mattina e non modificato da movimento, esacerbatosi in serata.

Alcuni giorni prima il ricovero infezione dell'orofaringe in assenza di febbre

Caso Clinico

- ECG: ST sopra in sede inferiore
- Esami ematochimici: positività dei markers di r
miocardica con CK MB max 83 mcg/l; Trop 1600
-Alterazione degli indici di flogosi, PCR 5.4



-Ecocardiogramma colordoppler all'ingresso:
ipocinesi infero-medio-basale
con FE conservata

Nel sospetto di uno STEMI infero-laterale
viene sottoposto a studio coronarografico in emergenza con evidenza di coronarie angiograficamente indenni
Alla ventricoloaortografia: FE 65% in assenza di alterazioni della cinesi

Caso Clinico

Durante la degenza sottoposto a RMN cuore con evidenza di immagini pre e post-contrasto indicative di miocardite acuta, con segni di flogosi attiva, FE V. sn. 54%

-Sierologia: negativa
-Durante la degenza paziente asintomatico e apiretico
- Trattamento con FANS

Rx Torace: Non evidenza di alterazioni parenchimali a focolaio in atto.
Seni costofrenici laterali pervi.
Cuore nei limiti volumetrici

Caso Clinico

ECG alla dimissione: T negative in sede inferiore
Terapia alla dimissione:
-Ramipril 5 mg 1/2 c ore 12
-Bisoprololo 1,25 mg 1 c ore 8
-Ibuprofene 400 mg 1 c ore 8 e 20 per 10 giorni, poi sospendere.

Ecocardiogramma di controllo ai 5 mesi: Ventricolo sinistro normale per dimensioni, spessori, cinesi segmentaria e funzione sistolica globale (FE 60%)

Follow up ambulatoriale: ai 3 -5 mesi, paziente asintomatico, in condizioni di compenso clinico ed emodinamico

THE CLINICAL CASE: Mr A.D.

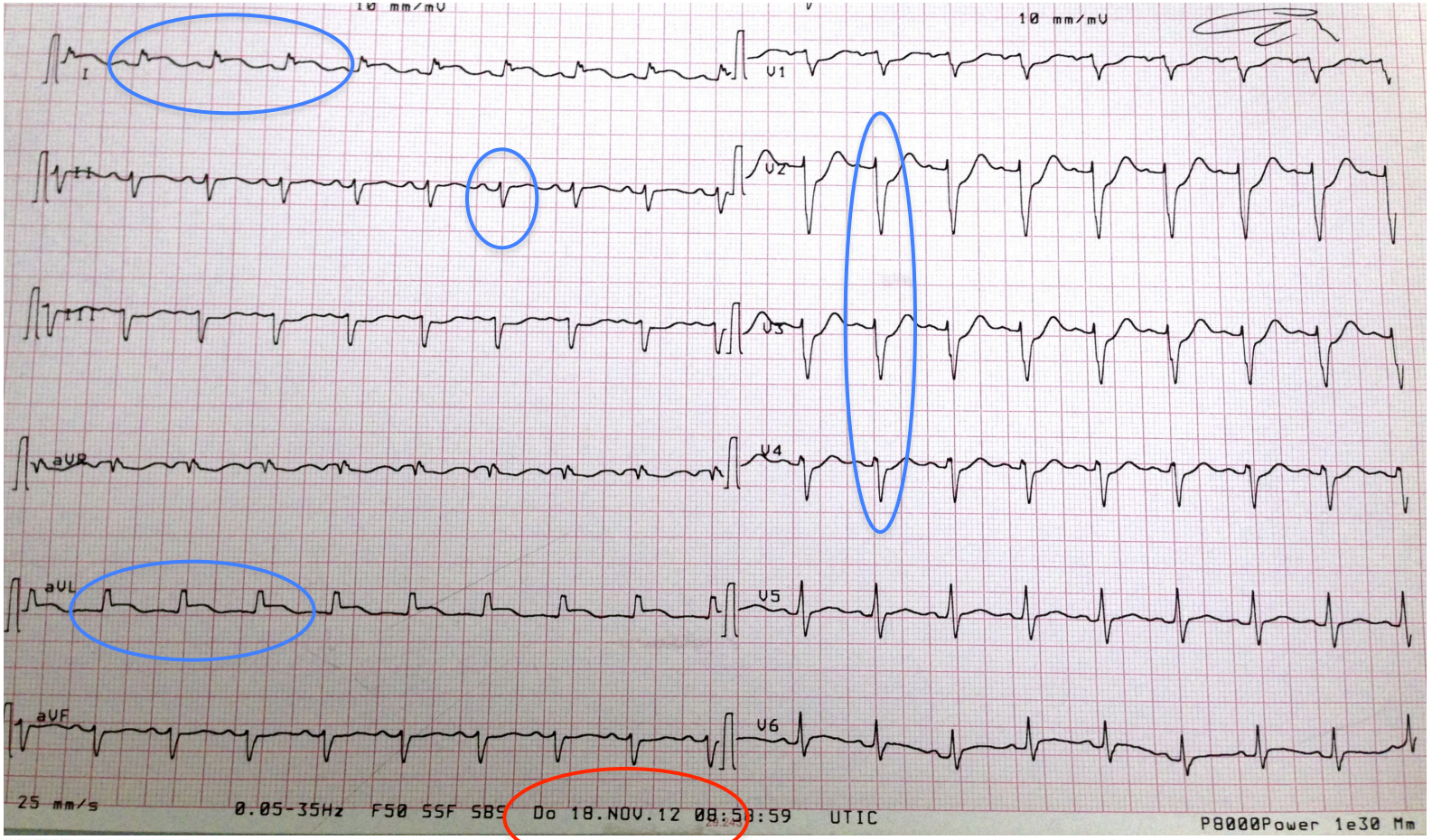
- A 31-year-old man with a history of multiple autoimmune disorders (thyroiditis, ulcerative colitis, autoimmune hepatitis)
  - Influenza-like illness 1 week before onset of cardiac symptoms
  - progressive dyspnoea and severe biventricular dysfunction (left ventricular ejection fraction –LVEF- of 30%)
  - Coronary angiogram was normal (SUSPECTED MYOCARDITIS)
  - VT treated with electrical cardioversion
  - After 24 hrs TRANSFERRED TO OUR CENTRE (HTx/ MCS REFERRAL CENTRE in Milan)

Day 2

ECG in Coronary Care Unit

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

Sinus tachycardia, left anterior hemiblock, low voltage of R wave V1-V4, mild ST-T elevation in D1-aVL



Day 2

CLINICAL AND ECO DATA

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

BP: 85/40 mmHg with Dopamine

HR 122 bpm → + Adrenaline

$SatO_2$ 90% → NIMV

ECHO: LVEF 20%,EDD 53 mm MR ++
IVS 12 PW 12 mm, RV: TAPSE 16 mm
No pericardial effusion
No aortic regurgitation

ABG analysis pH 7.4 Lactate 7
BP 80/40 HR 135 bpm
OLIGURIA 70 ml/2hrs (<0.5 ml/kg/hr)
UNRESPONSIVE cardiogenic shock
after 48hrs since the onset
1:1 IABP +A 0.12+D in CCU

SUNDAY NIGHT

Day 3

THE DAY AFTER

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

Morning, 19th November 2012:

BP 105/50 mmHg HR 105 bpm on IABP + Adrenaline + Dopamine

CVP 8 mmHg T 37.2°C

Urinary output >100 ml/h ABG: lactate 1.5

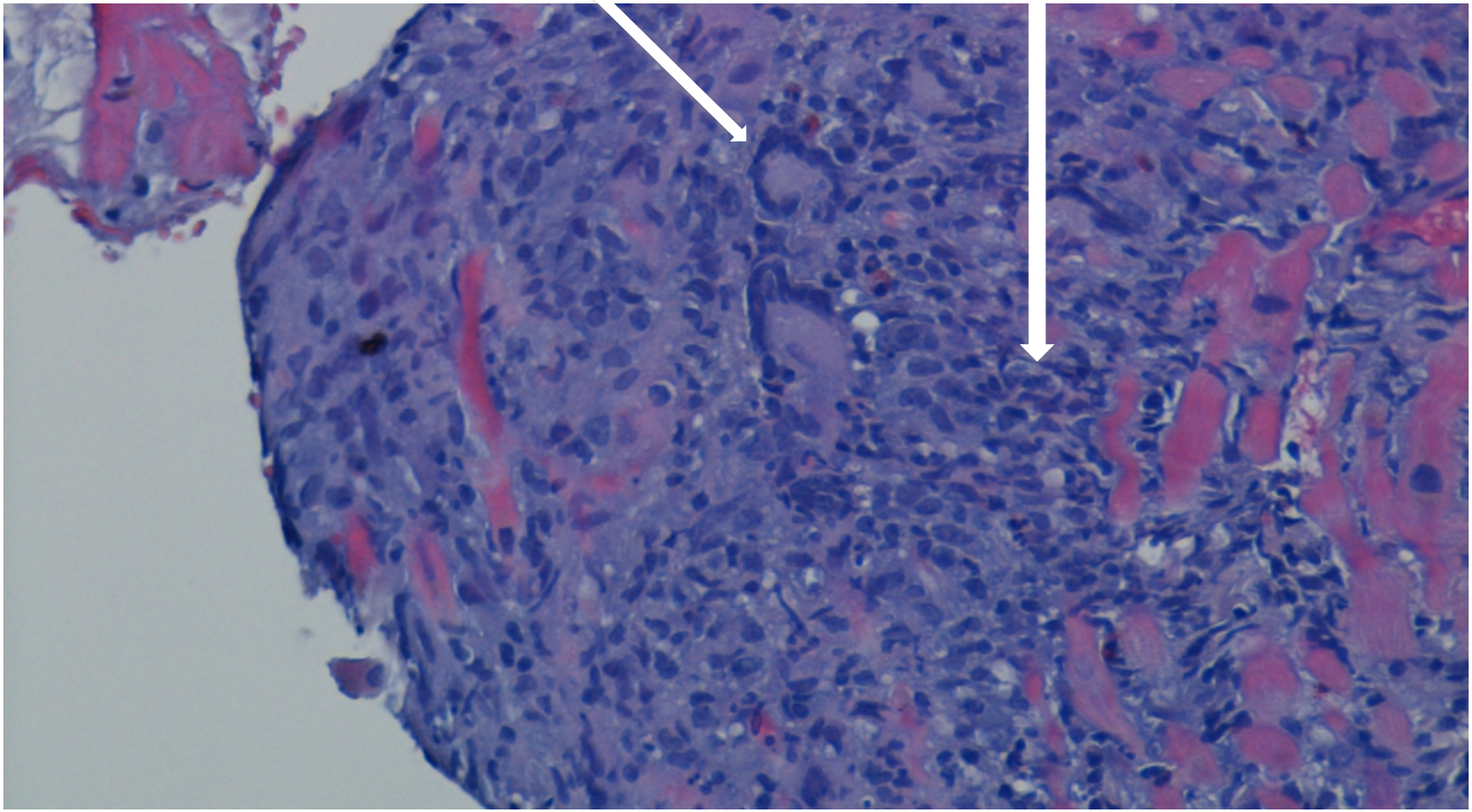
NT-proBNP 32,126 ng/L (n.v. 0-121) Troponin T hs 2,065 ng/L (n.v. 0-14)	**SEVERE MYOCARDIAL INJURY**
C-reactive protein 24.6 (n.v. 0-0.5 mg/dL) WHITE BLOOD COUNT 15.5*10^9/L	**SYSTEMIC INFLAMMATORY RESPONSE**
Creatinin 1.26 mg/dL (n.v. 0.7-1.2) ALT 127 U/L (n.v. 3-45)	**RENAL and HEPATIC INJURY**

Day 4 ENDOMYOCARDIAL BIOPSY

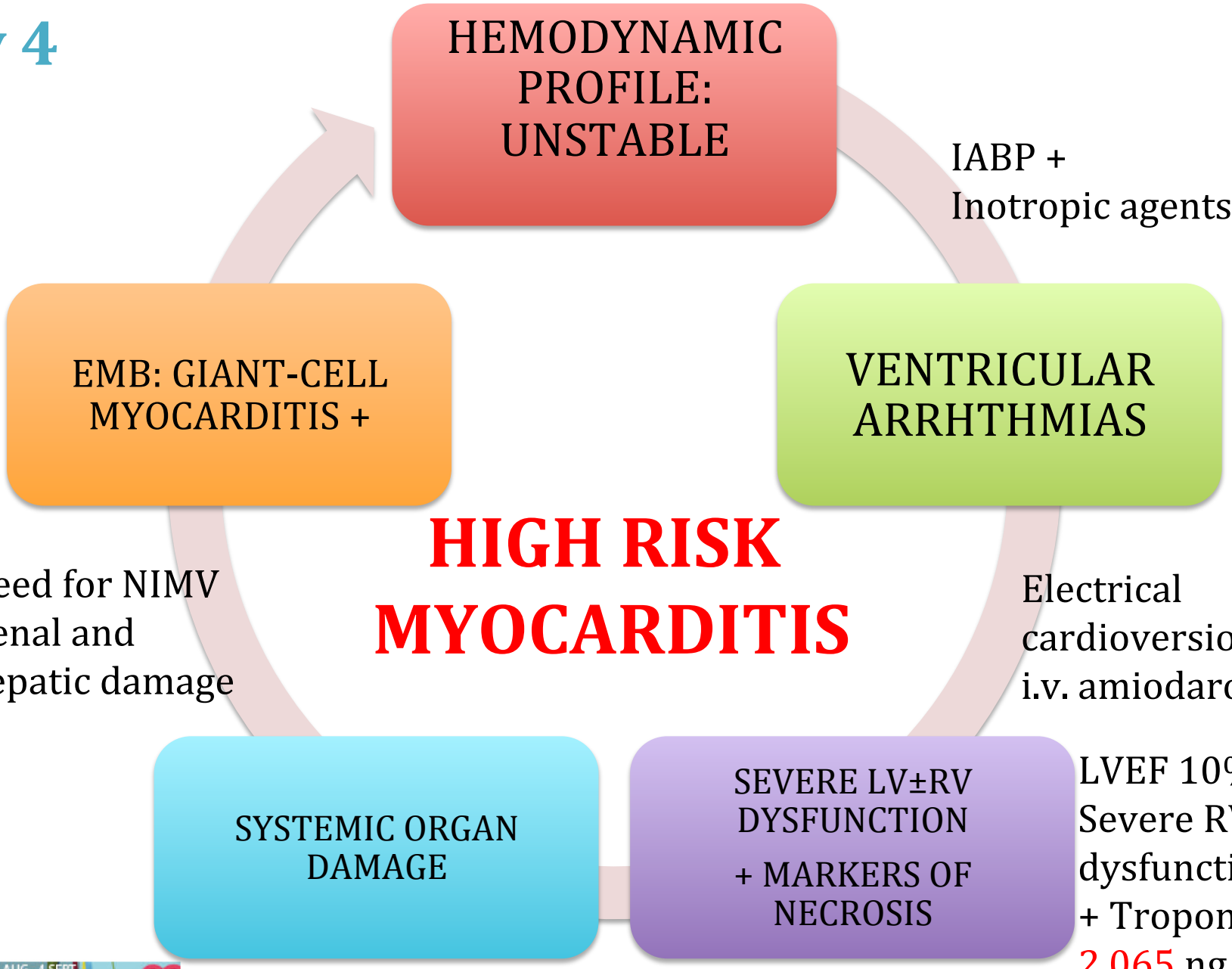
20th November: Tuesday morning (72hrs after the first hospital admission): RV biopsy
Tuesday 4 p.m. histological diagnosis: Giant-cell Myocarditis

multinucleated giant cells

widespread inflammatory infiltrate



Day 4


HEMODYNAMIC PROFILE: UNSTABLE
IABP + Inotropic agents
VENTRICULAR ARRHTHMIAS
Electrical cardioversion + i.v. amiodarone
SEVERE LV±RV DYSFUNCTION + MARKERS OF NECROSIS
LVEF 10% Severe RV dysfunction + Troponin T 2,065 ng/L
SYSTEMIC ORGAN DAMAGE
Need for NIMV Renal and hepatic damage
EMB: GIANT-CELL MYOCARDITIS +
HIGH RISK MYOCARDITIS

Day 4

INTENSIVE SUPPORT

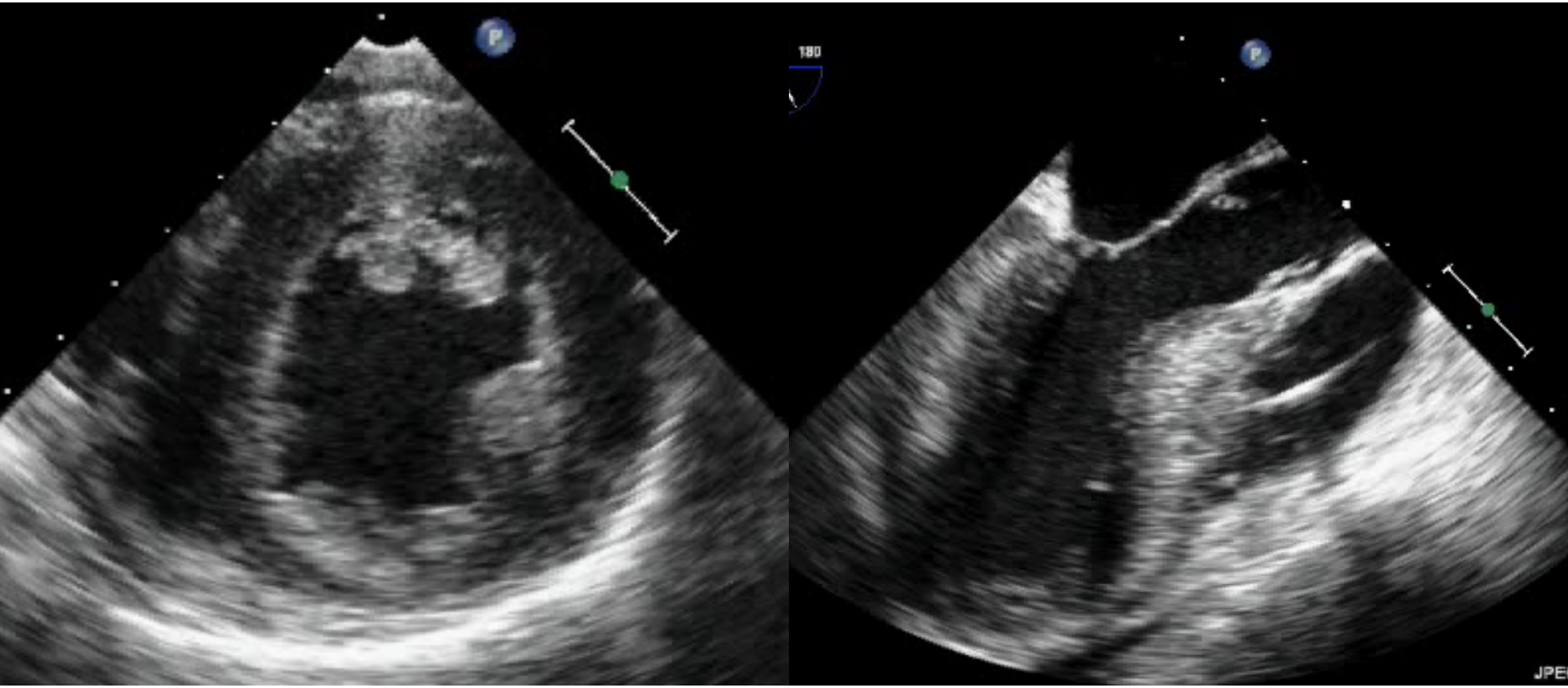
Repeated Sustained VT →TRANSFERRED to CARDIAC INTENSIVE UNIT
Hemodynamically unstable on IABP →
HD A + Noradrenaline + Intubation +
Mechanically assisted ventilation

20th November 4p.m.
Report of the EMB:
GIANT-CELL MYOCARDITIS

5:15 p.m. OPERATING THEATER
Femoral Veno-arterial
Extracorporeal membrane
oxygenation (va-ECMO)

TE ECHO DURING SURGERY

Severe biventricular dysfunction – increased wall thickness –
non homogeneous myocardium texture



IABP
+inotropic agents

Av ECMO (CO: >4 L/min) positioned 20/Nov 11/Dec: 21 days

ECMO removal

Extubated 1 day after surgery

Combined Immunosuppression:
1gx3days methylprednisolone
RATG 2.5mg/kg in 1 week
Cyclosporine 200 mg/d (basal level 200)

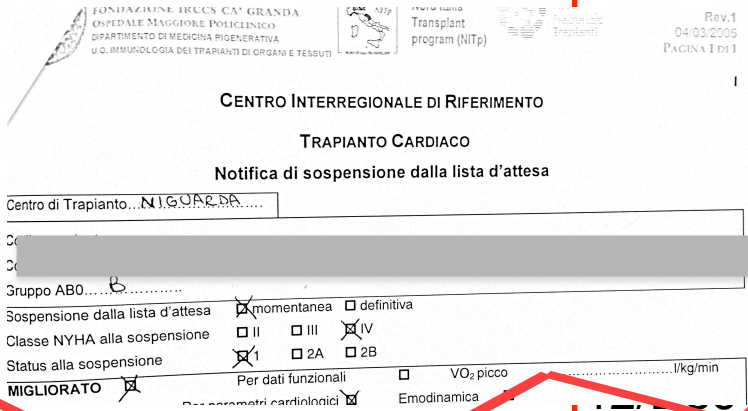
EMB:
GCM

LVEF 10%

HTx screening

8/Dec.:
LVEF 50%

IABP
removal


FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO
DIPARTIMENTO DI MEDICINA RIGENERATIVA
U.O. IMMUNOLOGIA DEI TRAPIANTI DI ORGANI E TESSUTI

Transplant program (NITp)

Rev.1
04/03/2005
PAGINA 1 DI 1

CENTRO INTERREGIONALE DI RIFERIMENTO

TRAPIANTO CARDIACO

Notifica di sospensione dalla lista d'attesa

Centro di Trapianto...NIGUARDA.....

Gruppo AB0.....B.....

Sospensione dalla lista d'attesa ☒ momentanea ☐ definitiva

Classe NYHA alla sospensione ☐ II ☐ III ☒ IV

Status alla sospensione ☒ I ☐ 2A ☐ 2B

MIGLIORATO ☒ Per dati funzionali ☐ VO_2 picco .....l/kg/min

Emodinamica

WEANING AND FURTHER INVESTIGATIONS

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

ECMO and IABP were removed after day 21
After additional 11 days the patient was discharged
(Hospital stay 34 days)

Viral Abs: All NEGATIVE
→HHV6, CMV, EBV, HSV 1/2, VZV,
→Adenovirus, Coxsackie A9, A24, B 1-6,
→Parvovirus B19, echovirus
Bacterial: Chlamydia pneumoniae, Borrelia Burgdorferi, Mycoplasma pneumoniae

Antibody serum testing: POSITIVE: anti-nDNA (1:160), anti-dsDNA, ANA (1:320 homogeneous pattern) → Suspected LUPUS

IMMUNOSUPPRESSIVE REGIMEN

Induction

Methylprednisolone (Solumedrol) i.v. 1 g od x 3 days

Thymoglobuline i.v. 70 mg (1 mg/kg, day 1) + 56 mg (0.8 mg/kg day 4) + 45 mg (0.6 mg/kg, day 7) [with CD 3+ T cell count monitoring]

Cyclosporine 35 mg bd (day 2), 50+75 mg (day 3)+ 75 mg bd (day 4), 75+100 mg (day 5)

IMMUNOSUPPRESSIVE REGIMEN

Mantenence

Methylprednisolone i.v. 60 mg od → 35 mg → oral prednisone 35 mg

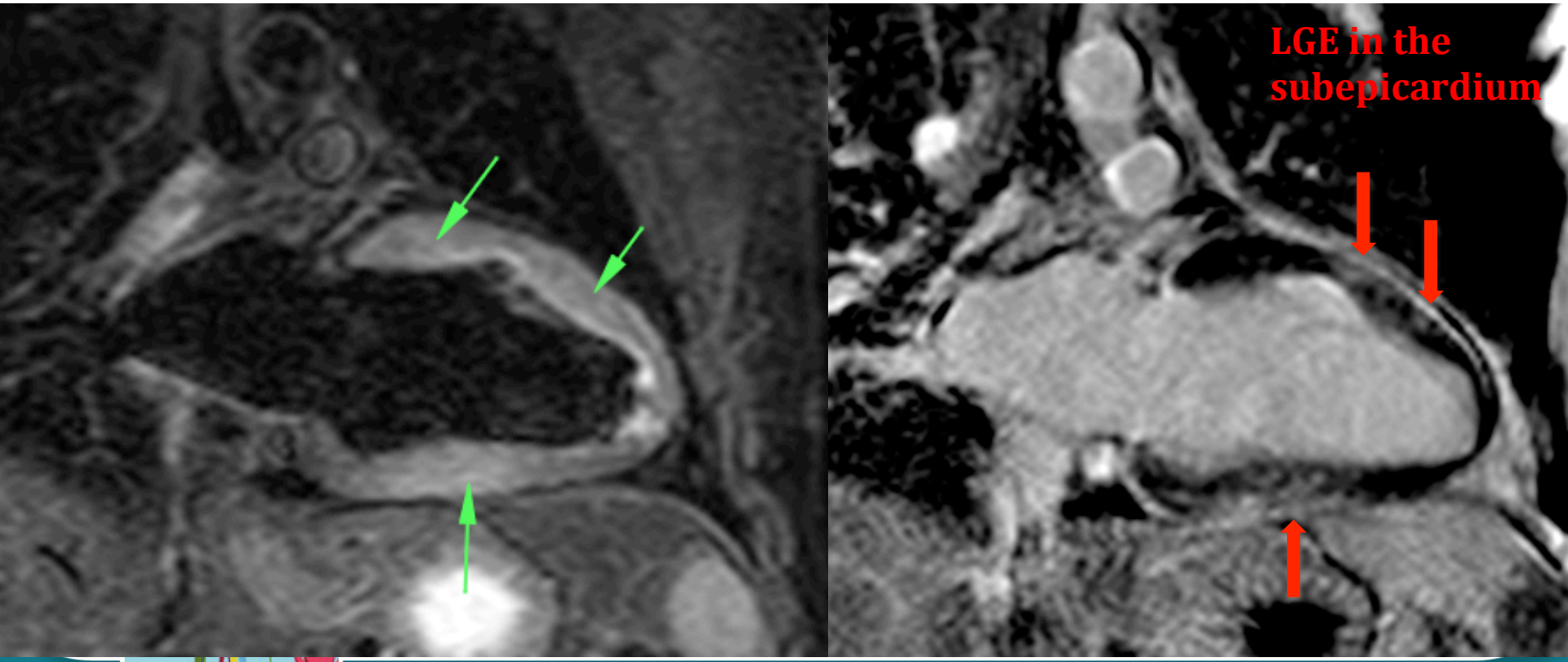
Cyclosporine (S. Neoral) Dosage 3-5 mg/kg/die

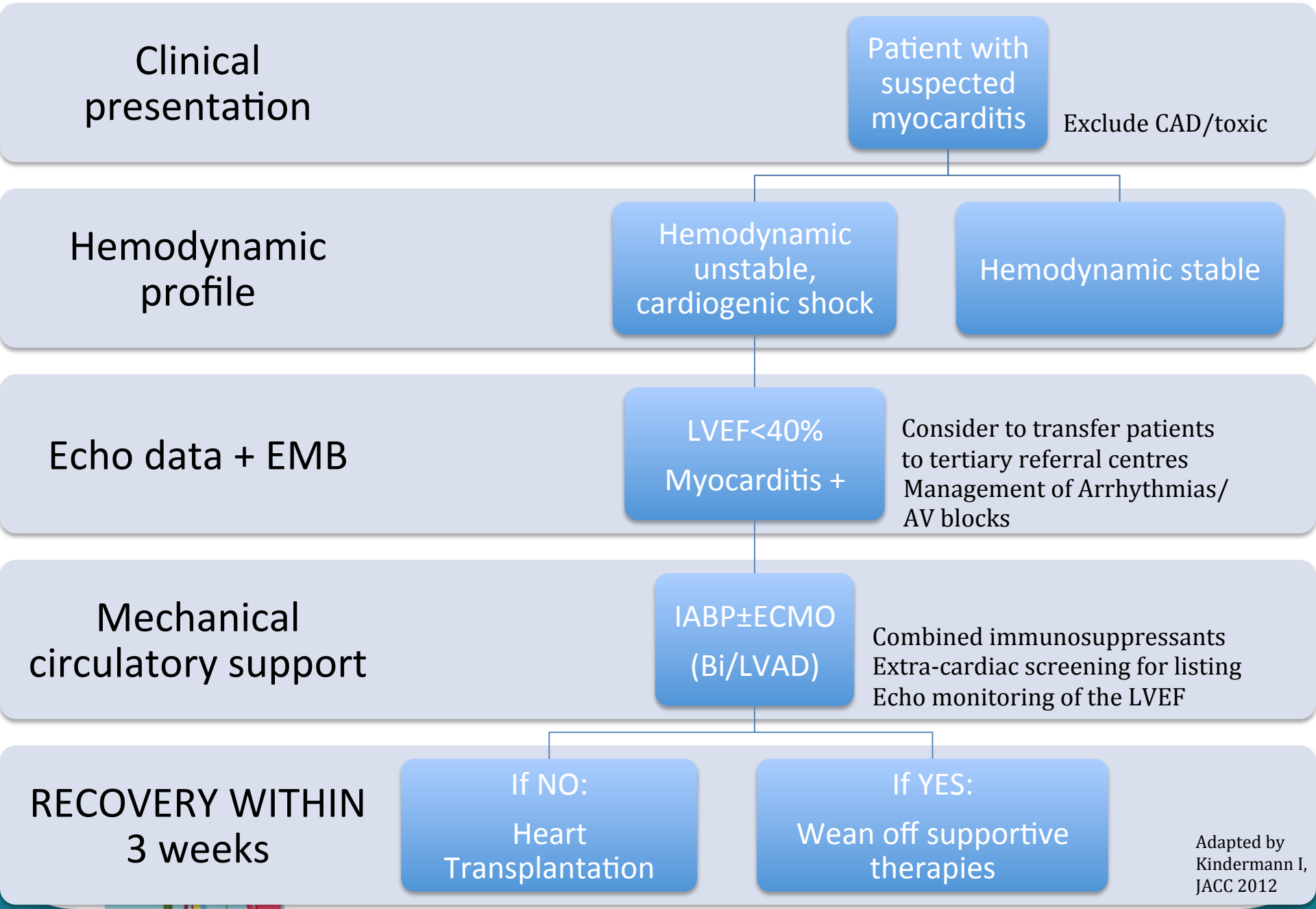
CARDIOVASCULAR MR

One week after discharge (4 January 2013): LVEF 60% (proBNP 1.591 ng/L)

Diffuse myocardial oedema in the mid-sub-epicardium in T2-weithed STIR sequences

Diffuse areas of late gadolinium enhancement (LGE)




Clinical presentation
Patient with suspected myocarditis
Exclude CAD/toxic
Hemodynamic profile
Hemodynamic unstable, cardiogenic shock
Hemodynamic stable
Echo data + EMB
LVEF<40%
Myocarditis +
Consider to transfer patients to tertiary referral centres
Management of Arrhythmias/ AV blocks
Mechanical circulatory support
IABP±ECMO
(Bi/LVAD)
Combined immunosuppressants
Extra-cardiac screening for listing
Echo monitoring of the LVEF
RECOVERY WITHIN 3 weeks
If NO:
Heart Transplantation
If YES:
Wean off supportive therapies
Adapted by Kindermann I, JACC 2012

IMPLICATIONS TO CLINICAL PRACTICE

- Cardiac function may recover completely in GCM

  → but circulatory support (IABP+ECMO) to maintain hemodynamics and oxygenation

- Immunosuppression may require days or weeks to allow resolution of myocardial damage and transplant-free survival

  → but no specific raccomandation regarding drug combination/dosage/duration

IMPLICATIONS TO CLINICAL PRACTICE

- In the setting of GCM + multiorgan manifestations of autoimmunity

→ long term treatment with a drug combination with a well-known safety and toxicity profile, such as cyclosporine and low-dose prednisone, may be a reasonable choice.

CAVEATs

Increased risk of ventricular arrhythmias after GCM (consider ICD if ventricular arrhythmias are documented – 59% of GCM transplant-free survivors experienced a sustained VT).[2]

Risk of recurrence of GCM when immunosuppressive agents are weaned off (documented recurrence of GCM in native heart[4] and also documented in Htx).[2]

Risk of subsequent dilated cardiomyopathy (DCM)

(Transplant free survival: 69% at 1 year, 52% at 5 years ,[2] in the GMC Study Group: 22% at 5 years)[3]

2. Kandolin R, CIRC HF, 2013
4. Cooper, AJC 2008
3. GMC Study Group, JACC 2003

AT DISCHARGE

Maintenance immunosuppression + HF treatment

- **CyA 125 mg bd (plasmatic CYA 143 ng/ml) - prednisone 30 mg od**
- Furosemide 37.5 mg - bisoprololo 3.75 mg - enalapril 10 mg bd - spironolactone 25 mg - aspirin 100 mg

Surveillance with CMR

Cardiac rehabilitation

AFTER 3 MONTHS

Prednisone Tapering →30 mg→ 25mg →15 mg →…

E.D. : Ventricular tachycardia → amiodarone+lidocaine

→Cardioversion (180 bpm/hemodynamically stable)

→Methylprednisolone (Solumedrol) i.v. 1 g + 500 mg + 500 mg od x 3 days

Repeated CMR → reduced inflammation (STIR)

and LGE

Repeated EMB → negative

FOLLOW UP CMR

At discharge

EDV 116 ml ESV 46 ml LVEF 60

IVS 14 mm LV mass 162 g

RVEDV 113 ml

After 3 months

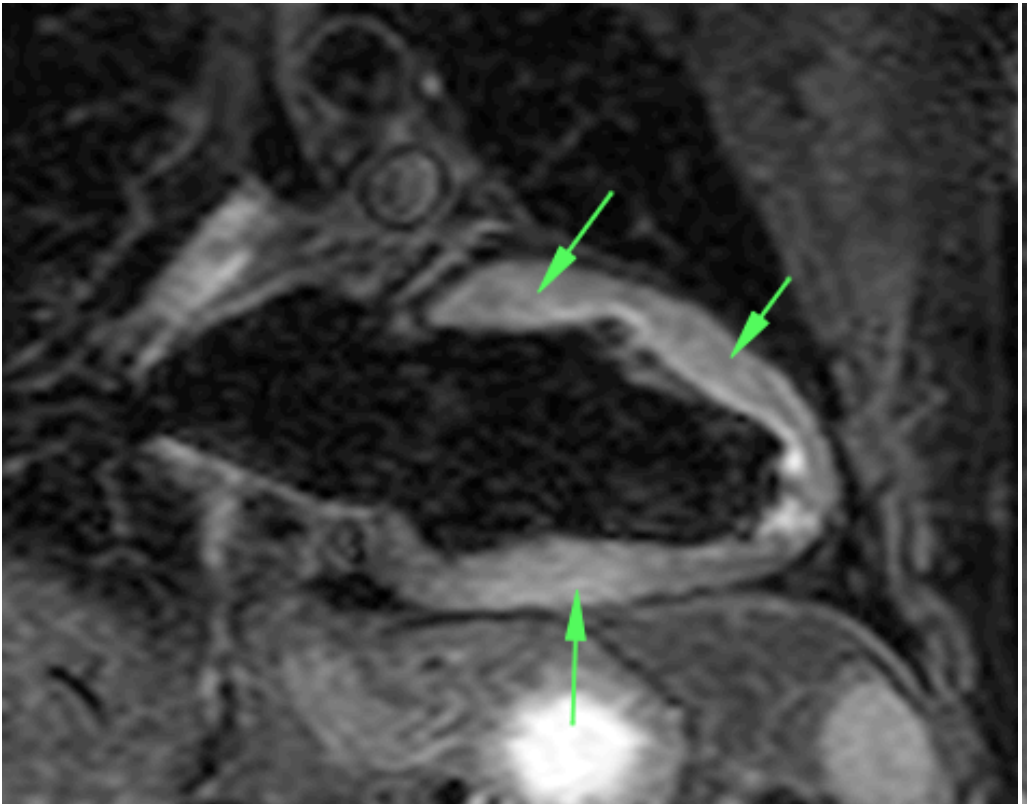
EDV 142 ml ESV 63 ml LVEF 56

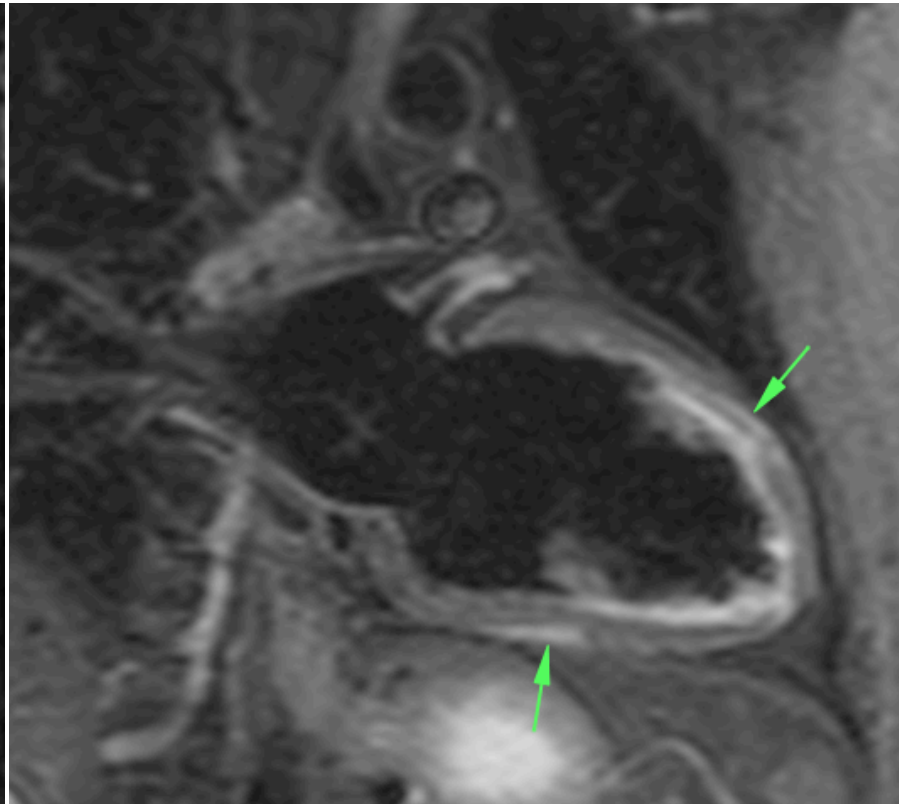
IVS 9 mm LV mass 110 g (signs of ameliorated inflammatory edema) RVEDV 124 ml

FOLLOW UP CARDIOVASCULAR MR

At discharge

After 3 months





DIFFERENT TREATMENT ALTERNATIVES

Other immunosuppresants:[5]

- Steroids associated with azathioprine

Evidence to support this treatment

- Case report of a patient with GCM weaned off biVAD with OKT3 (anti-CD 3 T cells)+HD steroids.[4]
- OKT3+Cya+steroids used in the GCM Clinical trial.[6]

5. Caforio A, EHJ 2013
4. Cooper, AJC 2008
6. Pinderki, JHLT, 2002

DIFFERENTIAL DIAGNOSIS BASED ON CLINICAL PRESENTATION AT OUR HOSPITAL

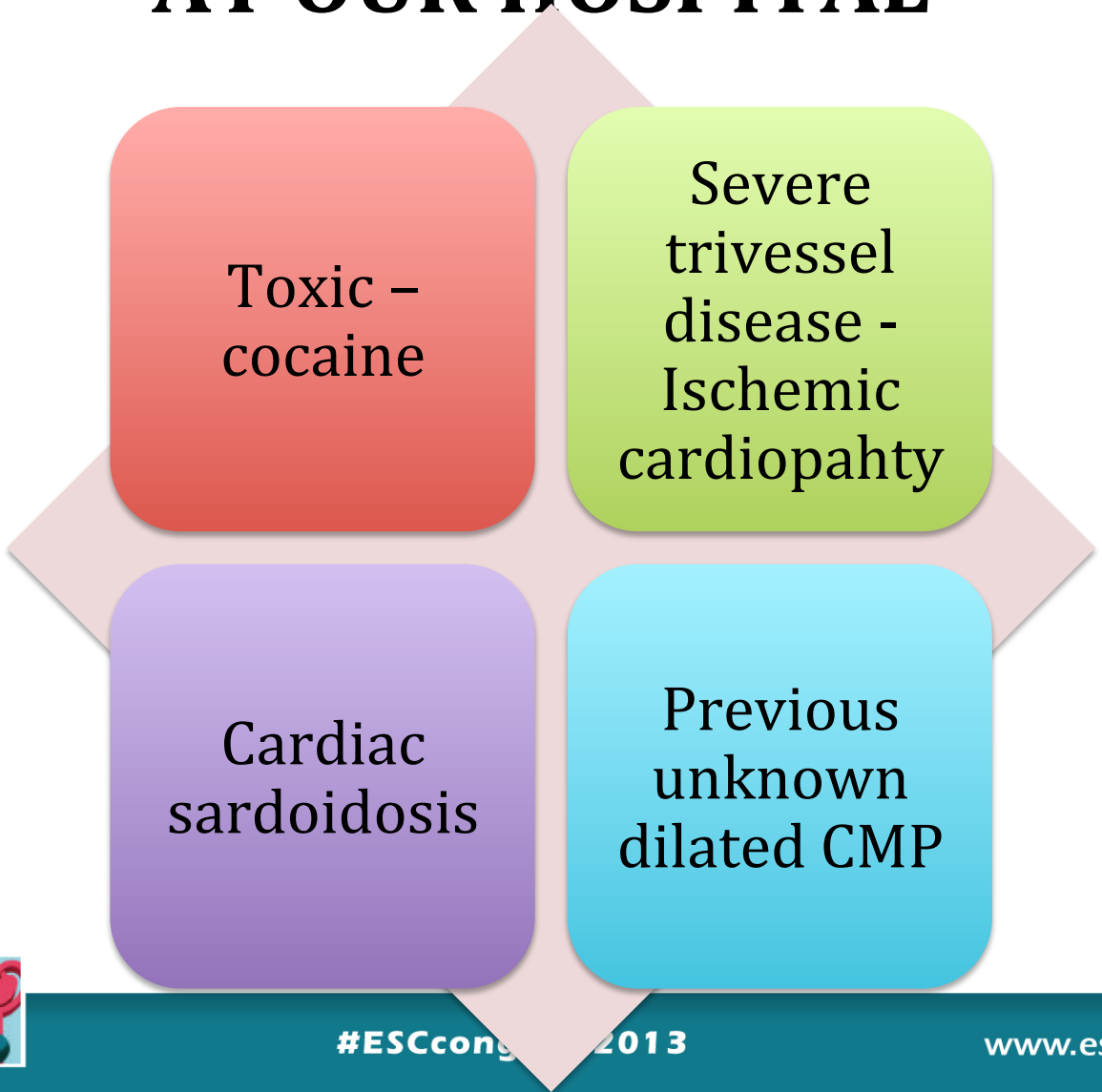


Table 4 **Diagnostic criteria for clinically suspected myocarditis**

Clinical presentations[a]

- Acute chest pain, pericarditic, or pseudo-ischaemic
- New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
- Unexplained cardiogenic shock

Diagnostic criteria

I. ECG/Holter/stress test features

- Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

II. Myocardiocytolysis markers

- Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

- New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

- Oedema and/or LGE of classical myocarditic pattern (see text)

Caforio *Eur Heart J 2013*

EMB: When ?

A proposal

- Fulminant myocarditis
- Moderate-severe LV dysfunction, recent onset
- Recurrent myocarditis

eccellenza collaborazione

CONVENTION CENTRI SCOMPENSO LOMBARDIA

sostenibilità innovazione

16 e 17 MAGGIO 2014
Antico Borgo La Muratella
Cologno al Serio (BG)

La collaborazione tra centri di eccellenza è fondamentale per dimostrare la sostenibilità delle cure e proseguire sulla strada dell'innovazione

SEGRETERIA SCIENTIFICA

Dr. Fabrizio Oliva
Dipartimento A. De Gasperis
Ospedale Niguarda Ca' Granda - Milano

COMITATO SCIENTIFICO

Dr. Manlio Cipriani, *Milano*
Dr. Giuseppe Di Tano, *Cremona*
Dr. Andrea Mortara, *Monza*
Dr. Michele Senni, *Bergamo*

LA PROPOSTA

Moderatori: *Antonello Gavazzi, Bergamo - Gabriella Malfatto, Milano*

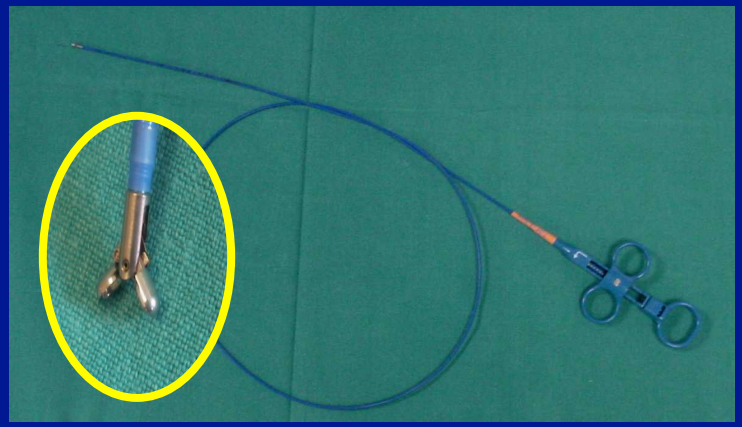
11.00 Miocarditi: proviamo a vedere quante sono e a capirle e curarle meglio. Idee per un registro lombardo
Manlio Cipriani, Milano

11.25 Discussione
Discussant: *Luca Bettari, Cremona - Marco Aroldi, Mantova - Massimo Puoti, Milano*

Biopsia Endomiocardica

- Tecnica di esecuzione:
  - Ventricolo dx (approccio venoso anterogrado giugulare o femorale)
  - Ventricolo sin (approccio arterioso retrogrado brachiale o femorale)

- Complicanze:
  - Rischio tamponamento con necessità pericardiocentesi 0.12%
  - Mortalità 0% (*Holzmann Circulation 2008, BEM n. 3048)*



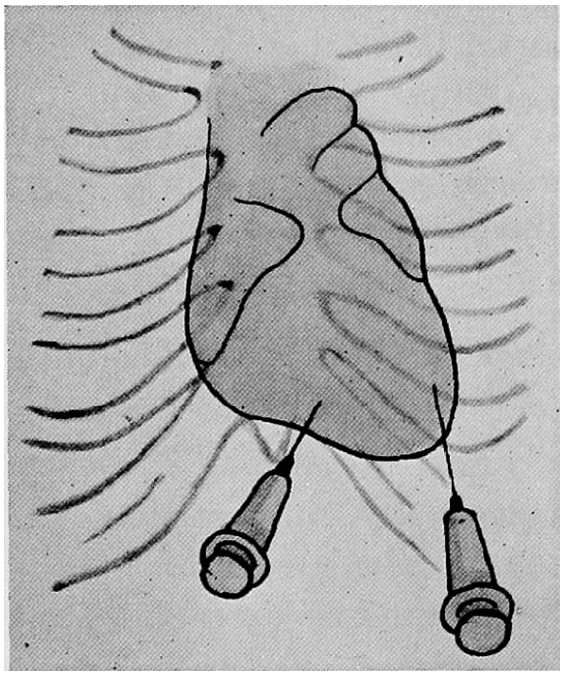
Ruolo della BEM nelle Miocarditi

- Cosa è in grado di fornire la BEM rispetto agli altri accertamenti diagnostici
- Quando eseguirla
- Aspetti operativi

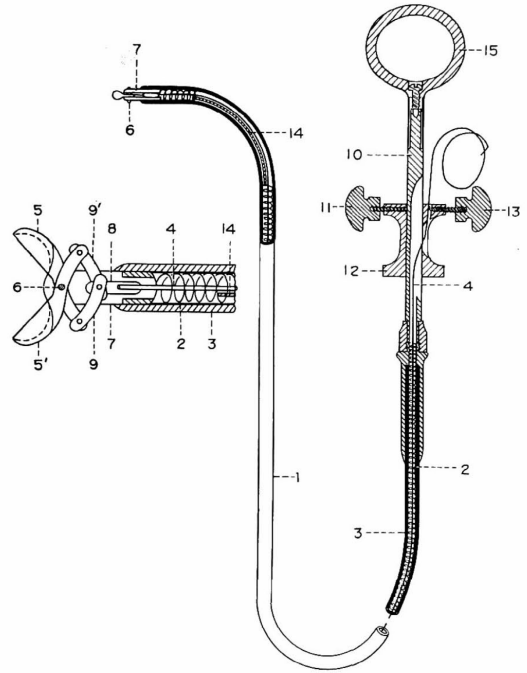
.....once upon a time.....

Sigeru SAKAKIBARA, M.D. *and*
Souji KONNO, M.D.

A new instrument to obtain biopsy specimen of endocardium and myocardium was devised. More than 10 biopsy specimens were obtained from 5 patients without any untoward effect. The method is quite safe and useful in making an accurate diagnosis in cases in which the causes of diseases were uncertain.



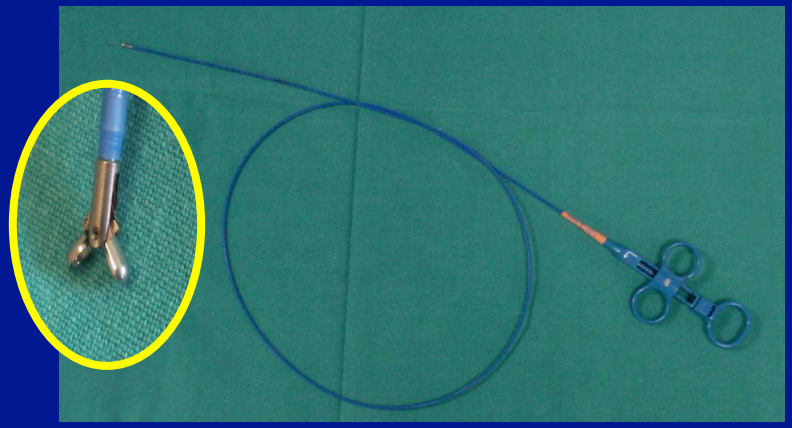
Idiopathic myocarditis
Myocarditis of collagen diseases
Endomyocardial fibrosis
Idiopathic cardiac hypertrophy
Sarcoidosis
Carcinomatosis
Primary myocardial tumors



Jap. Heart J.
November, 1962

Biopsia Endomiocardica

- Tecnica di esecuzione:
  - Ventricolo dx (approccio venoso anterogrado giugulare o femorale)
  - Ventricolo sin (approccio arterioso retrogrado brachiale o femorale)



BEM: profilo di sicurezza

- Tasso di complicanze maggiori: 0% - 0,82%
- Tasso di complicanze minori: 0,20% - 5,10%

Ragionevole rapporto rischio beneficio se motivato da solida indicazione clinica

Ylmaz *Circulation 2010*
Holzman *Circulation 2008*

BEM: limiti

- Limite di sensibilità diagnostica comune a tutte le metodiche bioptiche nei confronti di patologie multi-microfocali.

- Possibilità di risultati falsi negativi per errore di campionamento la cui reale incidenza non è nota.

Accorgimenti per ottimizzare l'accuratezza diagnostica

Attinenti al cardiologo

- Timing adeguato
- Campionamento bioptico adeguato
- Contestualizzare la BEM in un programma diagnostico completo

Attinenti al patologo

- Training formativo specifico
- Affiancare all'esame istologico classico altre tecniche di indagini tissutali
- Processare accuratamente i prelievi

Attinenti al Centro

Lettura integrata clinico-patologica

Biopsia Endomiocardica

- Cardiologo
  - BEM sec. timing appropiato
  - Campionamento bioptico adeguato (n.3-4 prelievi)
  - Contestualizzare BEM in programma diagnostico completo

- Patologo
  - Training formativo
  - Es. istologico tradizionale + tecniche di indagine tissutale
  - Utilizzare criteri diagnostici istopatologici univocamente definiti e periodicamente aggiornati

Consensus Indicazioni BEM 2009

"Lettura integrata clinico-patologica"

Cardiologo: timing appropriato

…la scomparsa dei tradizionali segni istologici di infiammazione può avvenire in tempi molto brevi……

Histological changes with time

*Day**	*Biopsy changes*
0	Lymphocytes, plasma cells, eosinophilic infiltrate, myocyte necrosis
5	Focal lymphocytic infiltrate, less myocyte necrosis, granulation tissue, fibrosis
16	Rare eosinophils, fibrosis
39	Focal lymphocytic infiltrate, fibrosis
59	Focal lymphocytic infiltrate
111	Focal lymphocytic infiltrate, fibrosis, myocyte hypertrophy
158	Interstitial fibrosis, myocyte hypertrophy
229	Interstitial fibrosis, myocyte hypertrophy
425	Rare lymphocytes only

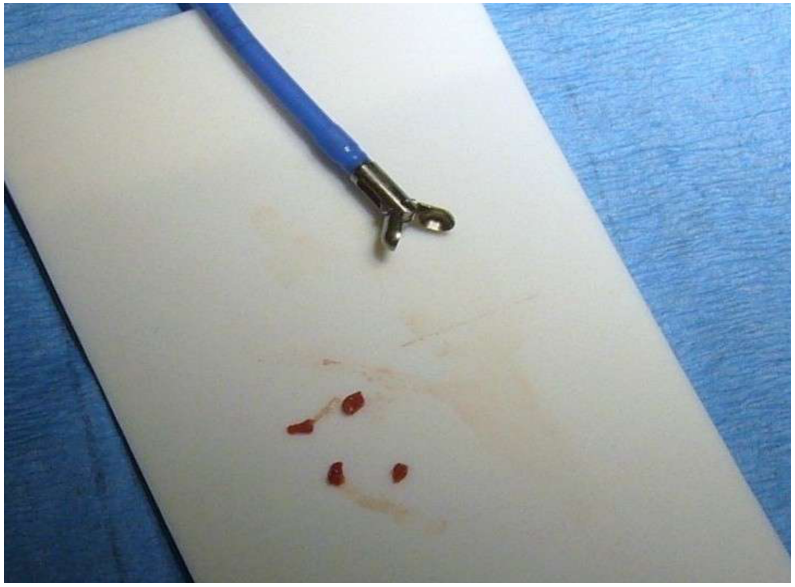
Br Heart J 1990;64:406–8

Rapid histological changes in endomyocardial biopsy specimens after myocarditis

Anne M Keogh, Margaret E Billingham, John S Schroeder

Cardiologo: campionamento bioptico adeguato

Esecuzione prelievi multipli (4 prelievi con dimensioni minime di 2 mm^2) ed in sedi diverse al fine di incrementare la sensibilità diagnostica della metodica.



- Almeno 3 frustoli in formalina per esame istologico, istochimico ed immunoistochimico
- 1 o 2 frammenti da congelare in azoto liquido per ev indagini molecolari
- 5-10 ml di sangue periferico per ev studi molecolari

Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy

Differences in Complication Rate and Diagnostic Performance

Table 2. Major and Minor Complications (n=755)

	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

Histopathological Diagnosis Based On	Either Positive LV- or Positive RV-EMB	Only Positive LV-EMB	Only Positive RV-EMB	Positive LV- and RV-EMB
Myocarditis and/or virus genome presence	254 (100)	32 (12.6)	18 (7.1)	204 (80.3)
Myocarditis (≥14 leukocytes/mm^2)	203 (80.0)	38 (18.7)	16 (7.9)	149 (73.4)
Virus genome presence	181 (71.3)	30 (16.6)	31 (17.1)	120 (66.3)

Ylmaz et al. Circulation 2010

Contribution and Risks of Left Ventricular Endomyocardial Biopsy in Patients With Cardiomyopathies

A Retrospective Study Over a 28-Year Period

Cristina Chimenti MD, PhD; Andrea Frustaci MD

Background—Use of left ventricular (LV) endomyocardial biopsy (EMB) to investigate cardiomyopathies is currently discouraged because it is considered riskier than and as contributive as right ventricular (RV) biopsy. The aim of our study is to report our experience with this option and to discuss its advantages and disadvantages.

Methods and Results—In our center from 1983 to 2010, 4221 patients underwent diagnostic EMB. In particular, 2396 (56.8%) underwent biventricular EMB, 1153 (27.3%) underwent selective LVEMB, and 672 (15.9%) underwent selective RVEMB. The rate of complications and histological findings were retrospectively analyzed. The periprocedural major complication rate (perforation with or without cardiac tamponade, embolization) was 0.33% for LVEMB and 0.45% for RVEMB, with a significant decrease in the rate of major complications with time (from 1.6% and 1.9% in 1983–1988 to 0% and 0.3% in 2007–2013, respectively; $P<0.001$ for both), denoting a steep learning curve. No patients died. When the structural and functional abnormalities affected exclusively the LV, the diagnostic yield of LVEMB was 97.8% compared with 53% for RVEMB. Conversely, when the echocardiographic presence of increased wall thickness, local or global ventricular dilation, or dysfunction also involved the RV, the diagnosis was reached in 98.1% of LVEMBs and 96.5% of RVEMBs. This discrepancy was particularly evident for myocarditis, whereas in infiltrative and storage diseases, the histological abnormalities were always detectable in both ventricles.

Conclusions—LVEMB is a safe procedure with very low transient complications, comparable to RVEMB. It appears diagnostically more contributive than RVEMB in patients with cardiomyopathies and clinically preserved RV. (***Circulation***. **2013;128:1531-1541.**)

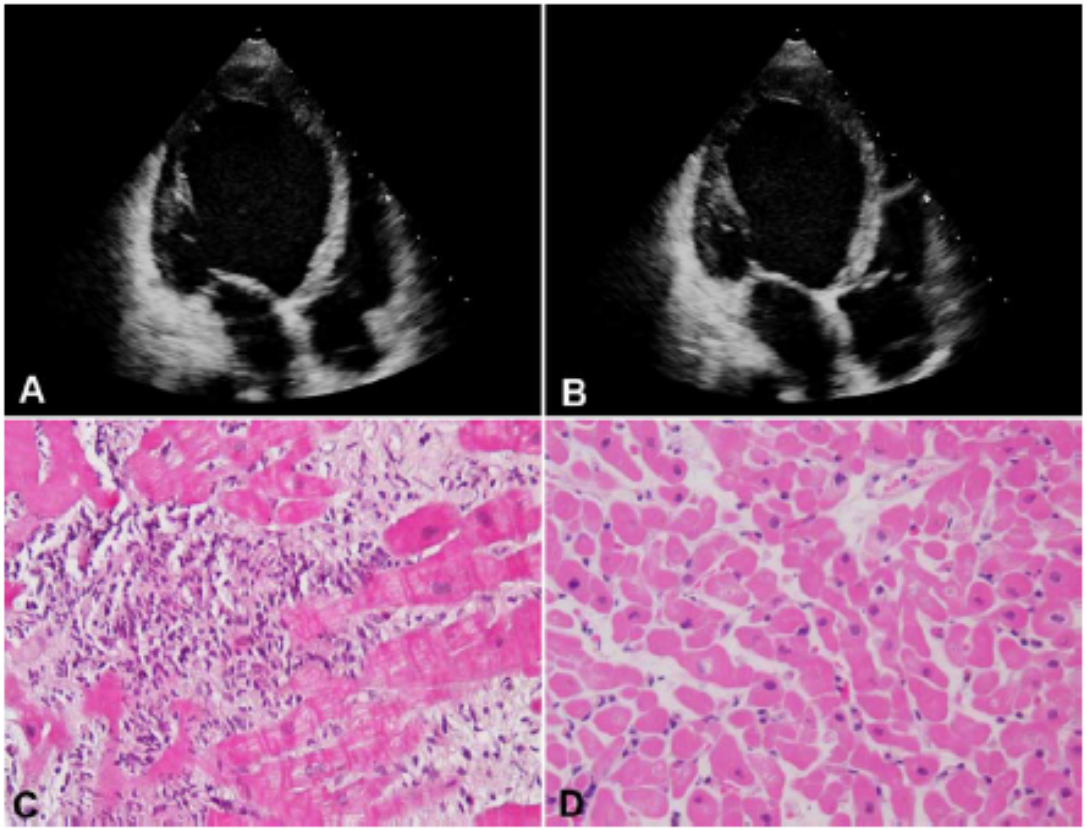


Figure 3. Echocardiographic (**A**, diastole; **B**, systole in 4-chamber apical view) and histological (**C**, left ventricle; **D**, right ventricle; hematoxylin and eosin, ×200) comparisons of left ventricular (LV) and right ventricular (RV) involvement in a patient with heart failure. Shown are LV dilation and dysfunction as a result of active myocarditis and a normal RV.

Contribution and Risks of Left Ventricular Endomyocardial Biopsy in Patients With Cardiomyopathies

A Retrospective Study Over a 28-Year Period

Cristina Chimenti MD, PhD; Andrea Frustaci MD

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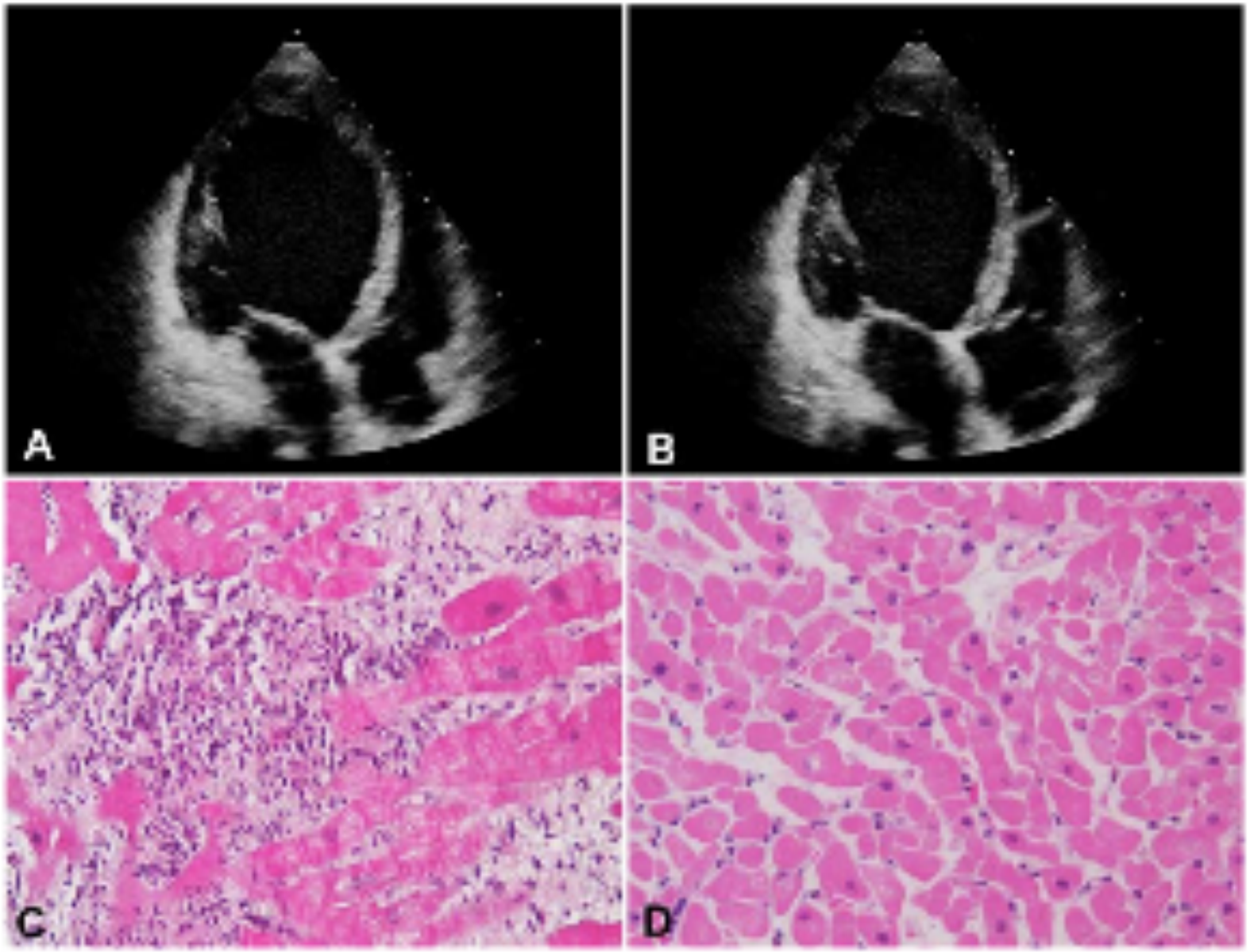
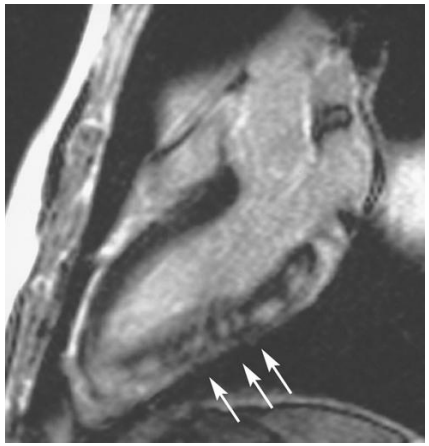
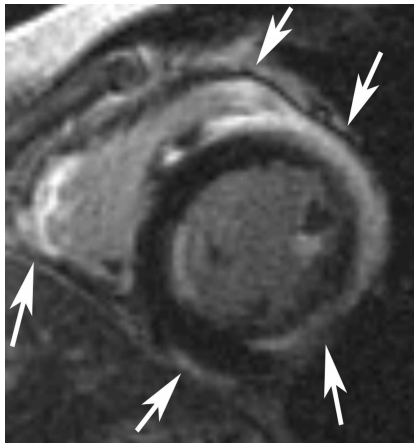
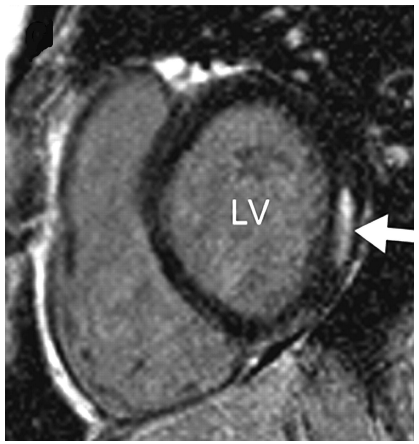

A
B
C
D

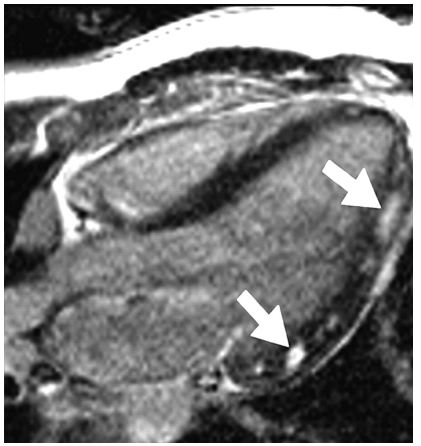
BEM: VD o VS?





BEM VD





BEM VS

Biopsia Endomiocardica

Requisiti di minima

- Centro
  - Sede di emodinamica con elevato volume attività (> 500 procedure/anno) in collegamento operativo con cardiochirurgia e con centro qualificato di patologia
- Operatore
  - Esperienza documentata di training (≥ 50 BEM)
- Centro di Patologia Cardiovascolare
  - Patologo con esperienza validata lettura BEM
  - Laboratorio istologia, diagnostica molecolare e ultrastrutturale

Consensus Indicazioni BEM 2009

Biopsia Endomiocardica
Percorsi

- Pz. degente in Ospedale non dotato di emodinamica

➡ invio presso Centro qualificato

- Pz. Degente in Ospedale con emodinamica (ripondente ai requisiti di minima e collegata a cardiochirurgia) senza esperienza in BEM

➡ invio presso Centro qualificato

oppure

➡ intervento e tutoraggio di operatore qualificato nel Centro dove è ricoverato il pz.

Consensus Indicazioni BEM 2009

Attinenti al Patologo: esame istologico

Prima biopsia	
Miocardite attiva:	cellule infiammatorie con necrosi e/o degenerazione delle miocellule adiacenti
Miocardite borderline: (la biopsia andrebbe ripetuta)	presenza di solo infiltrato flogistico senza alterazioni necrobiotiche miocitarie
Biopsie successive	
Miocardite persistente:	l'assetto istopatologico riproduce quello della prima biopsia, con o senza la presenza di fibrosi
Miocardite in via di risoluzione:	l'infiltrato flogistico e la necrosi miocitaria risultano ridotti, con o senza la presenza di fibrosi
Miocardite risolta:	il processo flogistico-necrobiotico appare spento, con o senza la presenza di fibrosi

Aretz et al. Am J Cardiovasc Pathol 1987

Attinenti al Patologo: indagini immunoistochimiche

Anticorpo	Evidenziazione
CD45RO	Linfociti T-memory
CD45RA	Linfociti T-unmemory
CD4	Linfociti T-helper
CD8	Linfociti T-suppressor
CD68-PGM1	Istiociti
LN3	Antigeni HLA
CD54	Molecole di adesione
HEAT SHOCK PROTEIN	Fenomeni apoptotici

Attinenti al Patologo: indagini molecolari

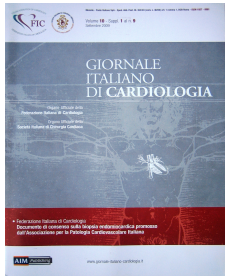
PCR e nested-PCR: *amplificano in modo esponenziale le molecole di DNA e RNA presenti consentendo l'identificazione anche di poche copie di genoma virale presenti nelle piccole quantità di tessuto miocardico della BEM*

Tabella 6. Virus cardiotropi da indagare nei casi di sospetto clinico di miocardite.

Virus	Sequenza (5'→3')	T° di *annealing*	Gene target	Prodotto di amplificazione
EV/RV	AAGCACTTCTGTTTCC CATTCAGGGGCCGGAGGA	50°C	5' untranslated region (5'-UTR)	297
CMV (DNA)	CACCTGTCACCGCTGCTATATTGC CACCACGCAGCGGCCCTTGATGTTT	52°C	Phosphorylated matrix protein (pp65 e pp71)	399
CMV (RNA)	GTGACCTTGACGGTGGCTTT CGTCATACCCCCCGGAGTAA	57°C	Early gene	275
PVB19	GGTAAGAAAAATACACTGT TTGCCCGCCTAAAATGGCTTT	57°C	NS1 VP1 e VP2	218
HSV	CATCACCGACCCGGAGAGGGA GGGCCAGGCGCTTGTTGGTA	60°C	DNA polimerasi	92
HCV	GGAACTACTGTCTTCACGCAGA TGCTCATGGTGCACGGTCTA GTGCAGCCTCCAGGACCC GGCACTCGCAAGCACCCTAT	54°C 56°C	5' untranslated region (5'-UTR)	210
EBV	TTCGGGTTGGAACCTCCTTG GTCATCATCATCCGGGTCTC	64°C	Nuclear antigen 1 (EBNA 1)	268
AV	GCCGCAGTGGTCTTACATGCACATC CAGCACGCCGCGGATGTCAAAGT	65°C	Exon protein	308
INF A	AAGGGCTTTCACCGAAGAGG CCCATTCTCATTACTGCTTC	50°C	Non structural protein 1 and 2 (NS1 and NS2)	190
INF B	ATGGCCATCGGATCCTCAAC TGTCAGCTATTATGGAGCTG	57°C	Non structural protein 1 and 2 (NS1 and NS2)	241

AV = adenovirus; CMV = cytomegalovirus; EBV = virus di Epstein-Barr; EV/RV = enterovirus/rinovirus; HCV = virus dell'epatite C; HSV = herpes simplex virus; INF A = virus dell'influenza A; INF B = virus dell'influenza B; PVB19 = parvovirus B19.

Attinenti al Centro:



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Conclusioni

Nonostante i recenti avanzamenti della cardio-Risonanza, la biopsia endomiocardica (BEM) rimane la metodica che permette, pur con limiti di sensibilità ed al prezzo di una procedura invasiva, una diagnosi di certezza ed una caratterizzazione di tipo istologico e molecolare

Conclusioni

QUANDO?

……as soon as possible……

COME?

prelievi adeguati, sedi accurate, analisi accurata

CON QUALI OBIETTIVI?

diagnosi di certezza e definizione eziologica precisa con ricadute sulla gestione clinica complessiva del paziente

eccellenza collaborazione

CONVENTION CENTRI SCOMPENSO LOMBARDIA

sostenibilità innovazione

16 e 17 MAGGIO 2014
Antico Borgo La Muratella
Cologno al Serio (BG)

La collaborazione tra centri di eccellenza è fondamentale per dimostrare la sostenibilità delle cure e proseguire sulla strada dell'innovazione

SEGRETERIA SCIENTIFICA

Dr. Fabrizio Oliva
Dipartimento A. De Gasperis
Ospedale Niguarda Ca' Granda – Milano

COMITATO SCIENTIFICO

Dr. Manlio Cipriani, *Milano*
Dr. Giuseppe Di Tano, *Cremona*
Dr. Andrea Mortara, *Monza*
Dr. Michele Senni, *Bergamo*

LA PROPOSTA

Moderatori: *Antonello Gavazzi, Bergamo – Gabriella Malfatto, Milano*

11.00 Miocarditi: proviamo a vedere quante sono e a capirle e curarle meglio. Idee per un registro lombardo
Manlio Cipriani, Milano

11.25 Discussione
Discussant: *Luca Bettari, Cremona – Marco Aroldi, Mantova – Massimo Puoti, Milano*

SCOMPENSO ACUTO: A CHE PUNTO SI DOVE STIAMO PUNTANDO...

Moderatori: *Giancarlo Marenzi, Milano – Gaetano De Ferrari, Pavia*

09.00 Il trattamento dello scompenso cardiaco acuto
Fabrizio Oliva, Milano
09.15 Come ripartire dai bisogni
Andrea Mortara, Monza

09.30 Discussione
Discussant: *Alice Sacco, Milano – Claudia Vittori, Milano*

ARITMIE E DEVICE

Moderatori: *Salvatore Pirelli, Cremona – Giovanni Battista Perego, Milano*

09.45 Fibrillazione atriale nello scompenso cardiaco: lo spazio e i vantaggi dei nuovi anticoagulanti orali
Antonio Cirò, Monza
10.00 CRT: ruolo della modalità di stimolazione nell'aumento della responsiveness
Antonio Curnis, Brescia
10.15 Sistemi di assistenza ventricolare meccanica long term
Luigi Martinelli, Milano

10.30 Discussione
Discussant: *Alessandro Verde, Milano – Luigi Moschini, Cremona – Attilio Iacovoni, Bergamo*

10.45 Coffee break

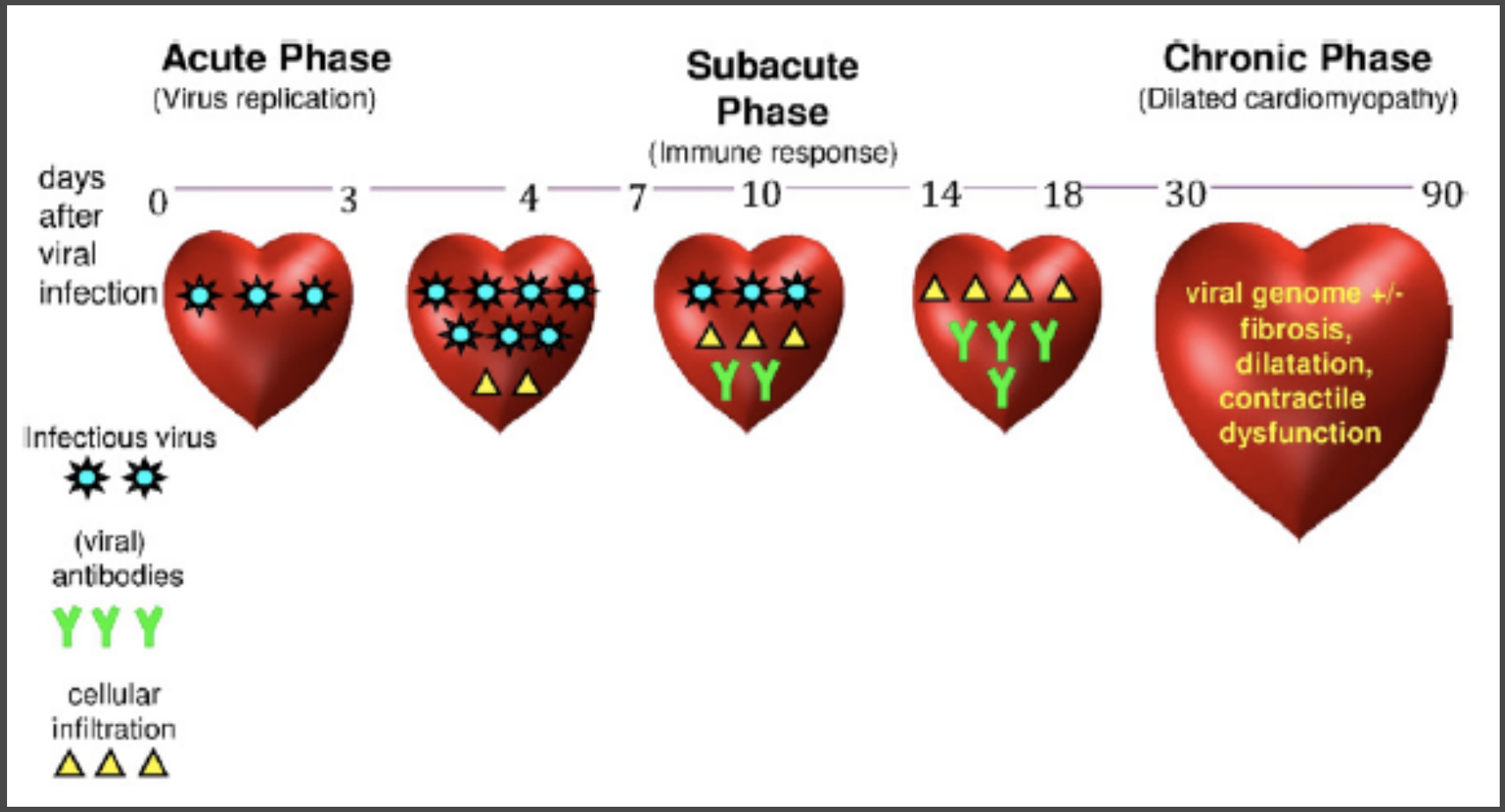
Trend temporale dei ricoveri per insufficienza cardiaca in Lombardia dal 2000 ad oggi.
Moderatori: *Fabrizio Oliva, Milano – Luigi Oltrona Visconti, Pavia*

11.45 Cosa può imparare il clinico
Maria Frigerio, Milano
12.00 Quali indicazioni per il decisore
Maurizio Bersani, Milano

12.15 TAVOLA ROTONDA
Discussant: *Jorge Salerno Uriarte, Varese – Roberto Pedretti, Tradate*
Carlo Campana, Como – Tommaso Diaco, Rivolta d'Adda
Francesco Gentile, Cinisello Balsamo – Michele Senni, Bergamo

13.00 Termine dei lavori

Time Course of Viral Myocarditis



Myocarditis
Clinical Presentation

- Clinical presentations range from nonspecific systemic symptoms (fever, myalgias, palpitations, exertional dyspnea) to fulminant hemodynamic collapse and sudden death.

- Myocarditis in sudden cardiac death in young adults: 8,6%-12% (1,2)

- Myocarditis as a cause of dilated CMIO in 9% (3)

1. Fabre *Heart 2005*
2. Doolan *Med J Aus 2004*
3. Felker *Medicine 1999*

Myocarditis: clinical presentation

- Mild symptoms
  - palpitation, atypical chest pain, SOB
- Minor ECG abnormalities
  - Conduction disturbance, ST-T changes
- Major arrhythmia
  - SVT, complete A-V block
- Syncope, sudden death
- Cardiogenic shock
- Heart failure resembling DCM
  - Recent onset
  - Up to 2 years
- Infarct-like with normal coronary arteries

Myocarditis
Clinical Presentation

- Transient ECG abnormalities commonly occur during community viral endemics; most pts remain enterely asymptomatic (1)
- Incidence of a reported infectious viral prodrome is highly variable, ranging from 10% to 80% of pts with documented myocarditis(2)
- Acute dilated CMIO is one of the most dramatic and clinically relevant presentation of acute lymphocitic myocarditis (9%-16% new onset CMIO) (3)
- HF symptoms is the primary presentation in 75% of giant cell myocarditis(4)

1.Mason *N Engl J Med 1995*
*2.*Babonian *heart 1997*
*3.*Felker *N Engl J Med 2000*
*4.*Cooper *N Engl J Med* 1997

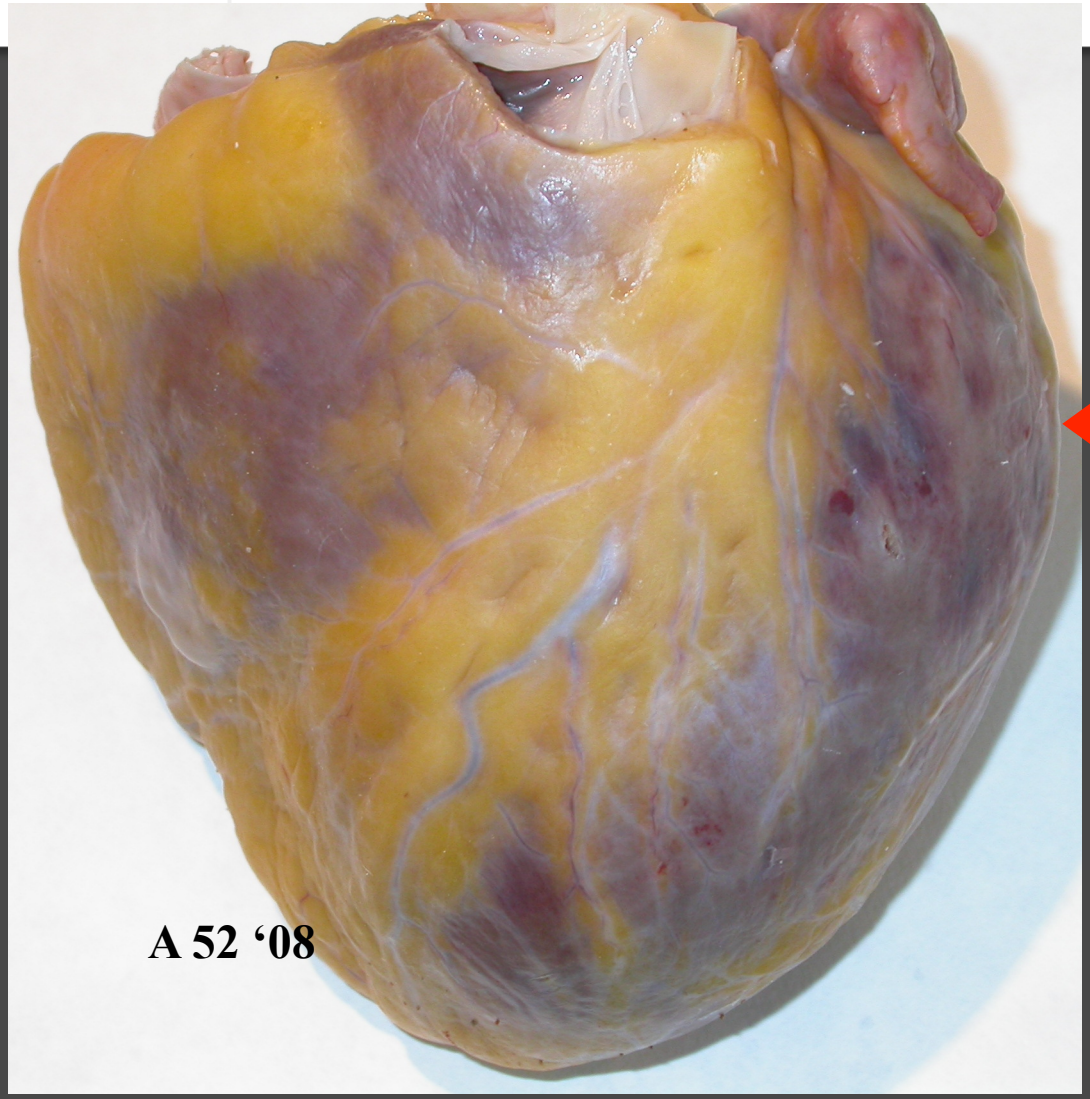
Myocarditis
Clinical Presentation

- Fulminant myocarditis
  - 10,2%
  - Severe hemodynamic compromise
  - Viral prodrome
  - Abrubt onset (< 3 days)
  - Global left ventricular dysfunction and minimally increase LVED dimensions
  - Either borderline or active lynphocitic myocarditis

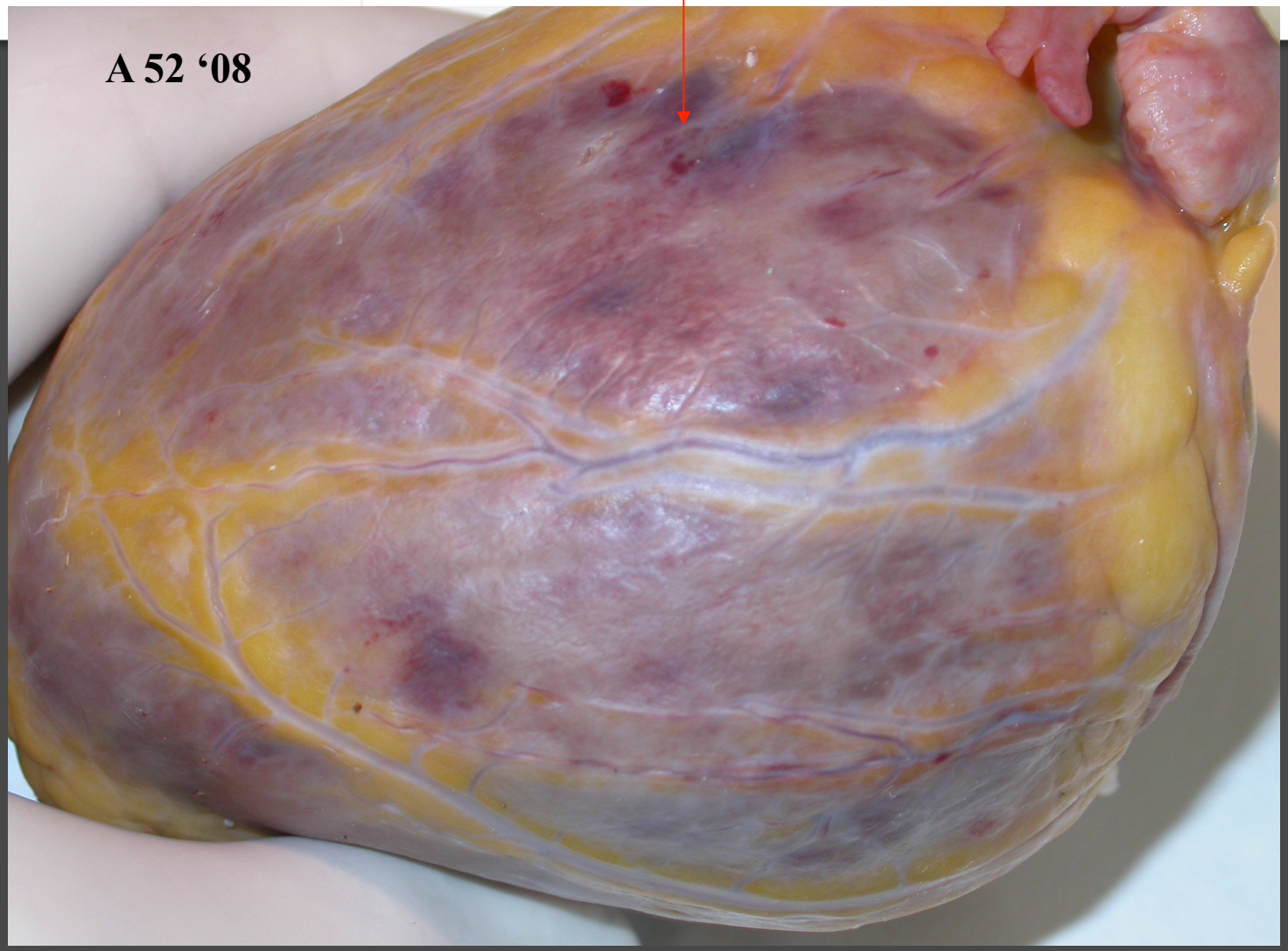
McCarthy *N Engl J Med 2000*

Miocardite acuta
Case Report

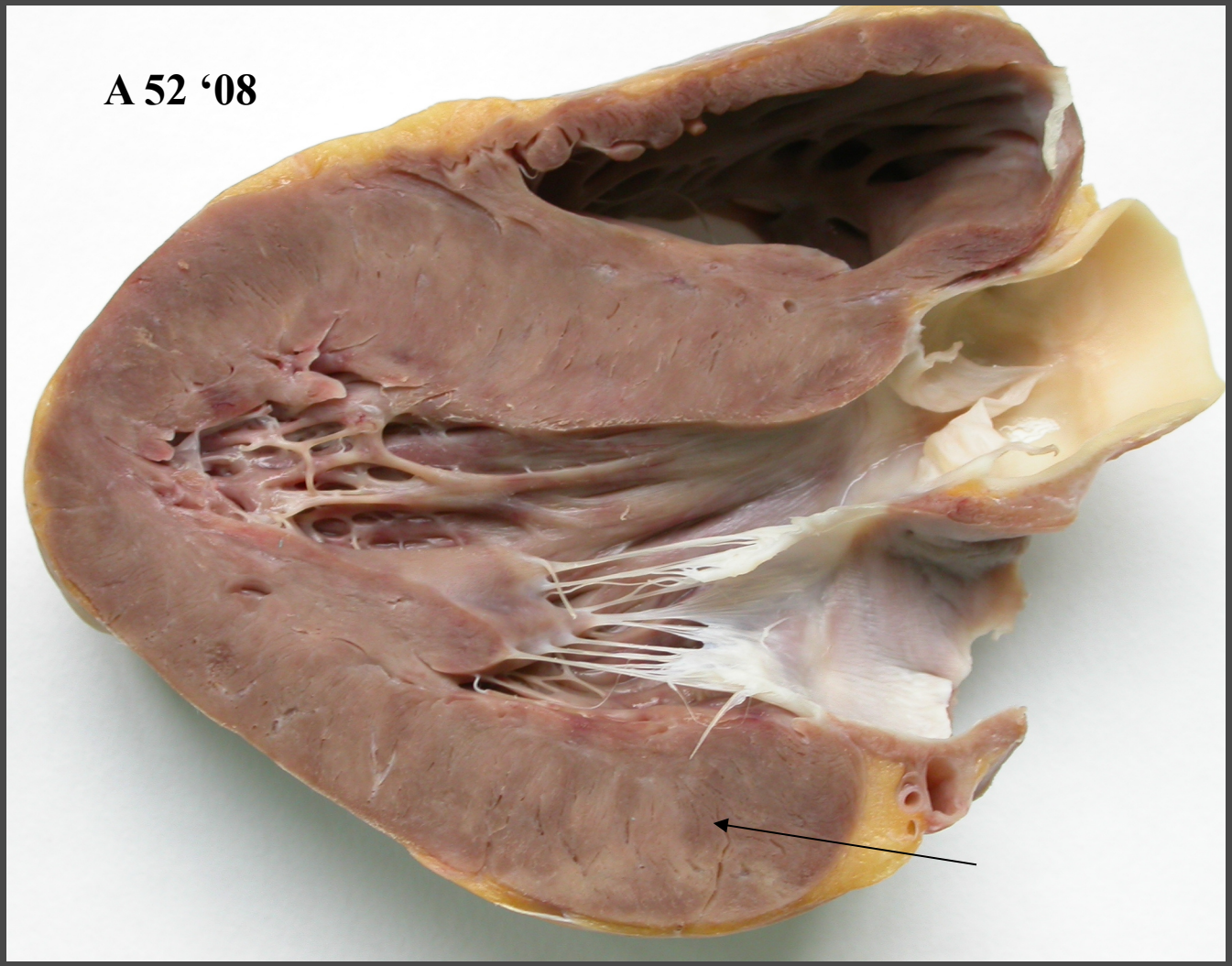
- Esordio acuto con dolore toracico in maschio di aa. 46
- Progressione di insufficienza cardiaca e respiratoria
- Sopraslivellamento ST diffuso all'ECG
- Aumento CPK e Troponina
- Exitus alla manovra di intubazione



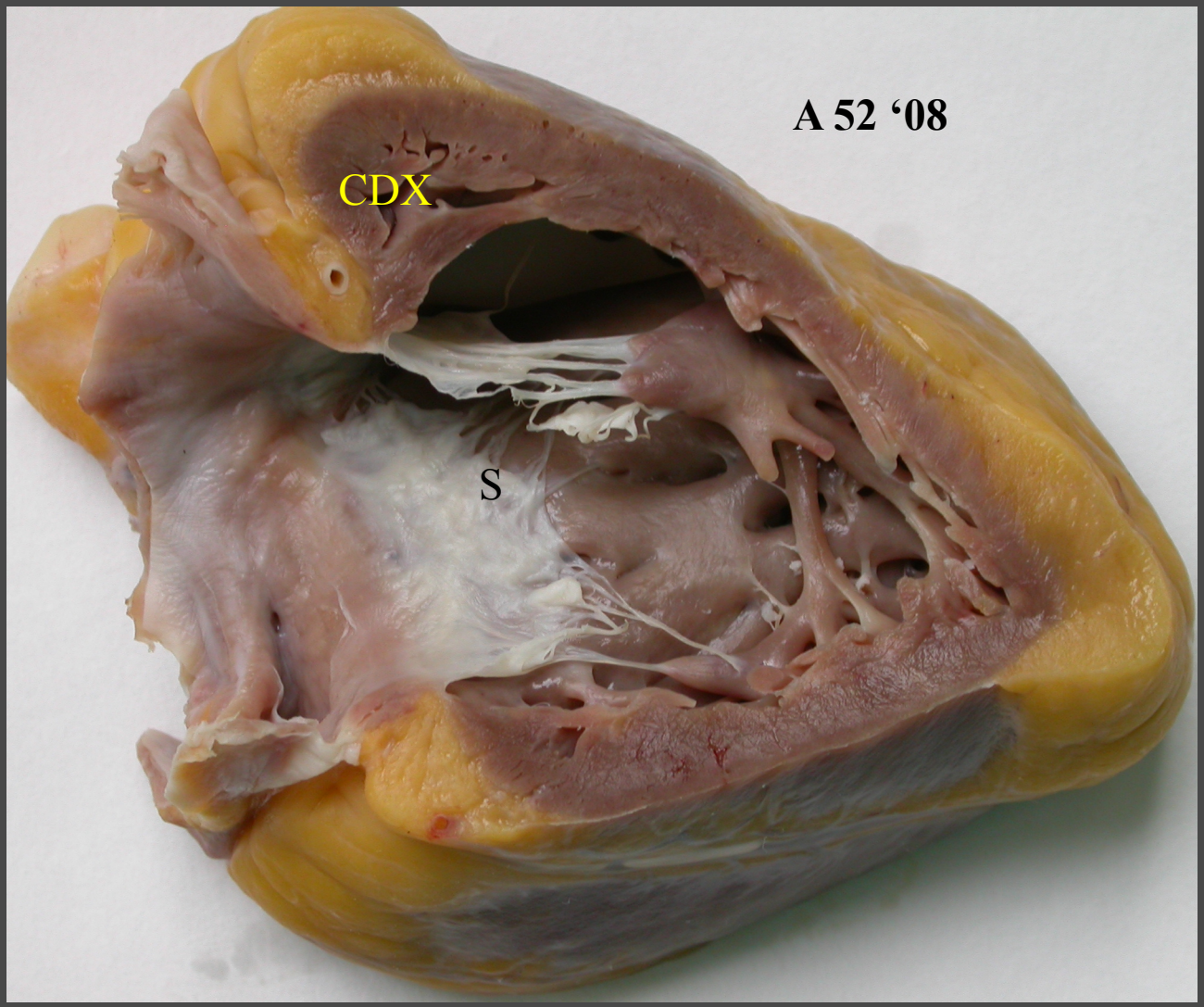
Cuore di dimensioni globalmente aumentate, con ispessimento parietale sinistro
Marezzatura emorragica epicardica con lieve opacamento fibrinoso



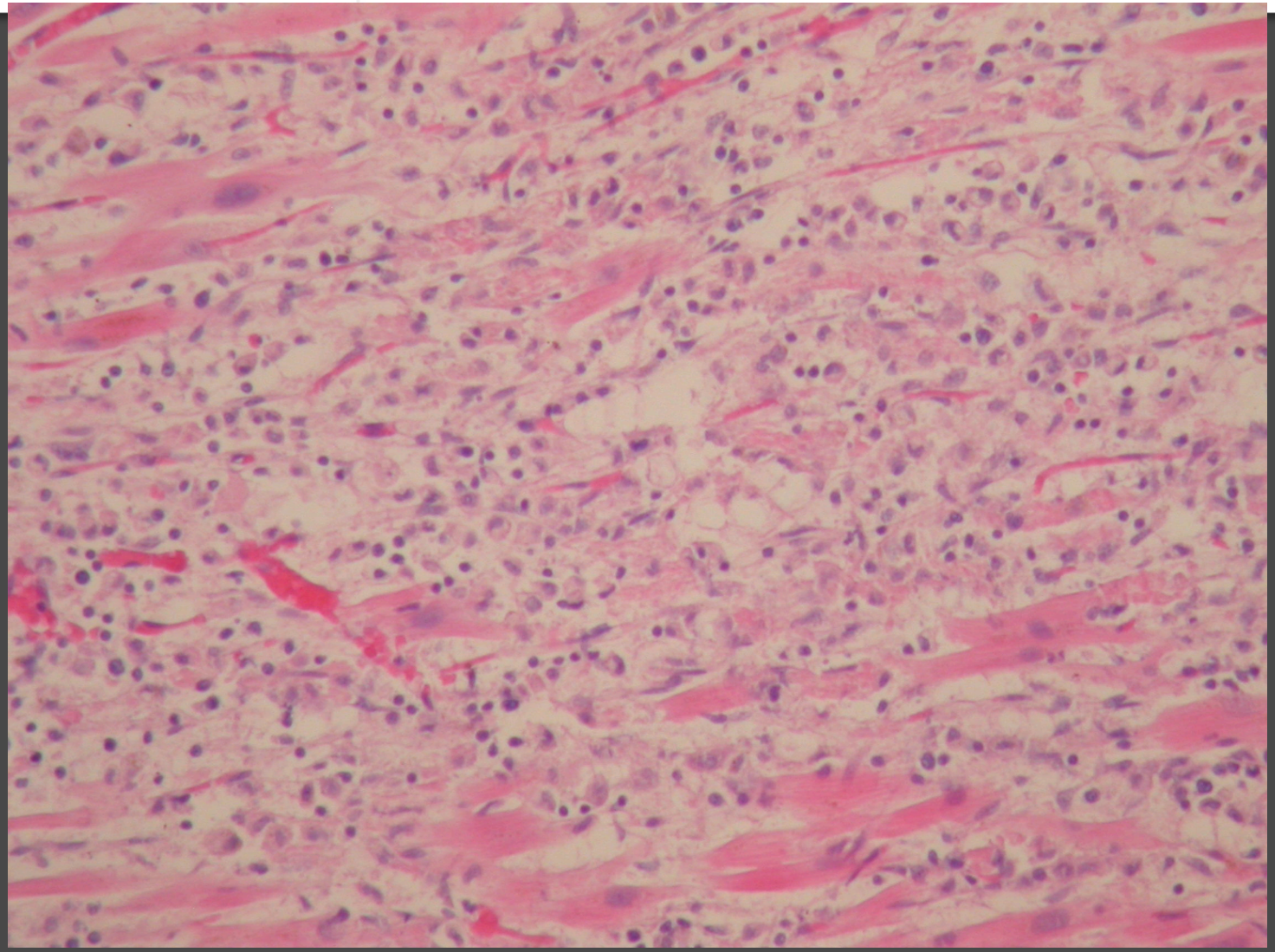
La fotografia laterale del VS dimostra una parete di spessore aumentato ed la variegatura emorragica



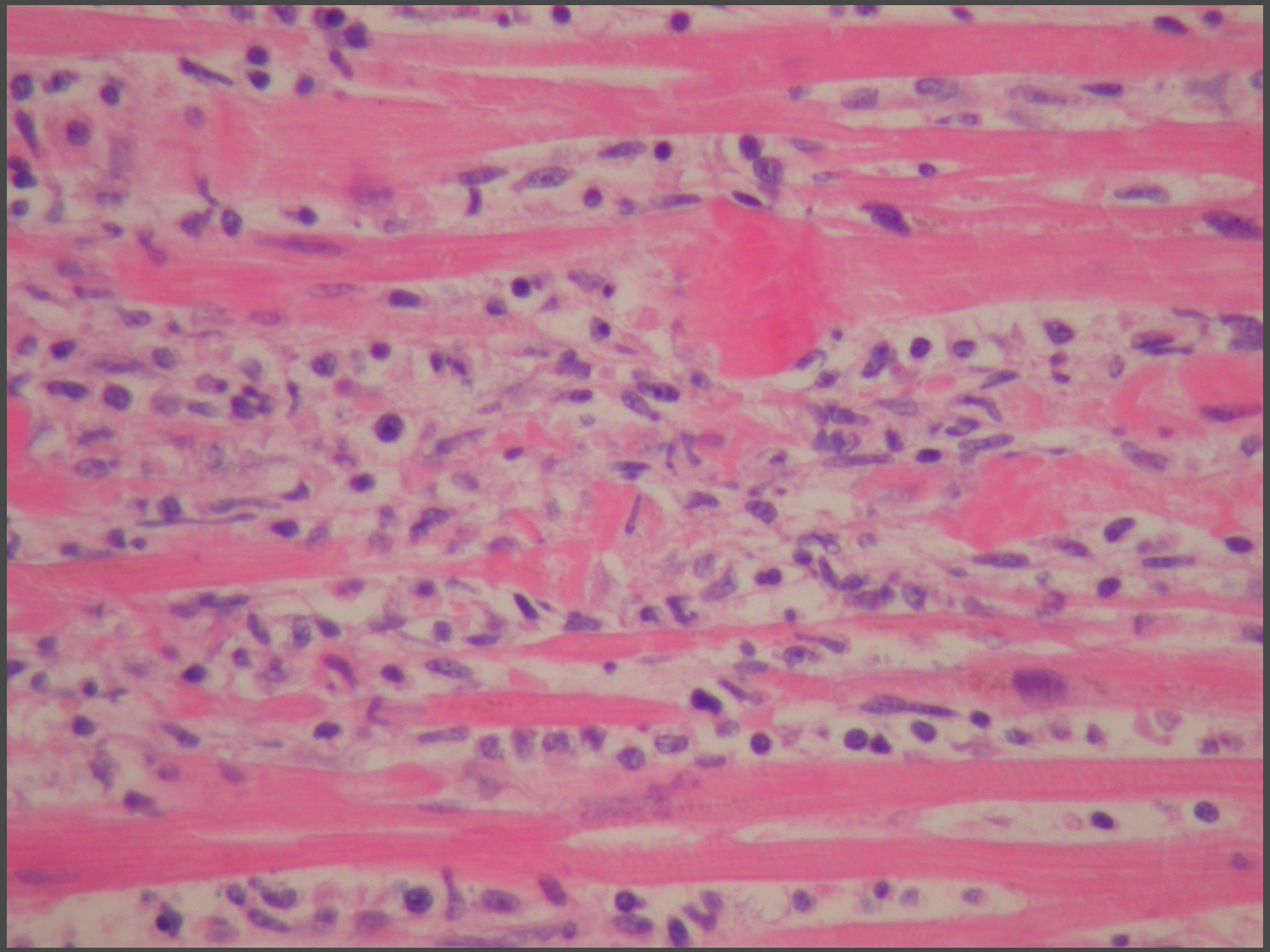
Sezione in asse lungo della massa ventricolare, che dimostra ispessimento della parete del ventricolo sinistro ed aspetto variegato del miocardio



Lieve dilatazione del VDX . Valvole e coronarie indenni.



Quadro istologico di Miocardite linfocitaria diffusa necrotizzante



Assenza di cellule giganti

Myocarditis
Clinical Presentation

- Myocarditis masquerading as an **acute coronary syndrome**
  - Elevated troponin levels more reliable predictor than levels of CK
  - ECG changes: ST elevation in ≥ contiguous leads (54%), T wave inversion (27%), ST depression (18%), pathological Q waves (20%)
  - Segmental or global ECHO wall motion abnormalities are frequent
  - Normal coronary anatomy

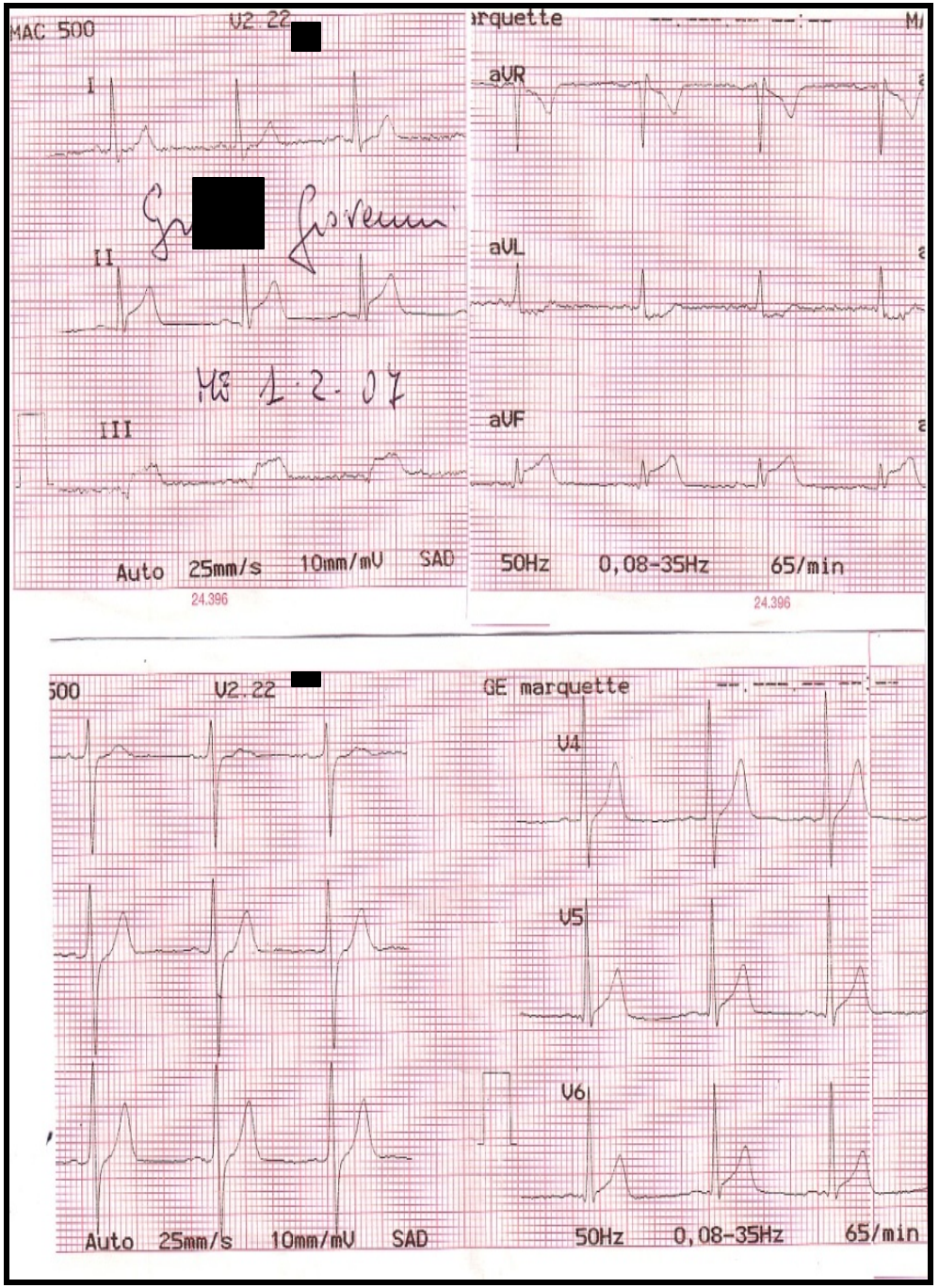
1.Dec *N Engl J Med 1985*
*2.*Angelini *Heart 2000*
*3.*Sarda *JACC 2001*

G. Giovanni, **Anni 24**

Fumatore;
Faringodinia da 1 settimana con febbricola intermittente;
Dolore toracico da circa 1 h.
Sera prima dolore addominale;
Trasferito per PTCA primaria da vicino PS.

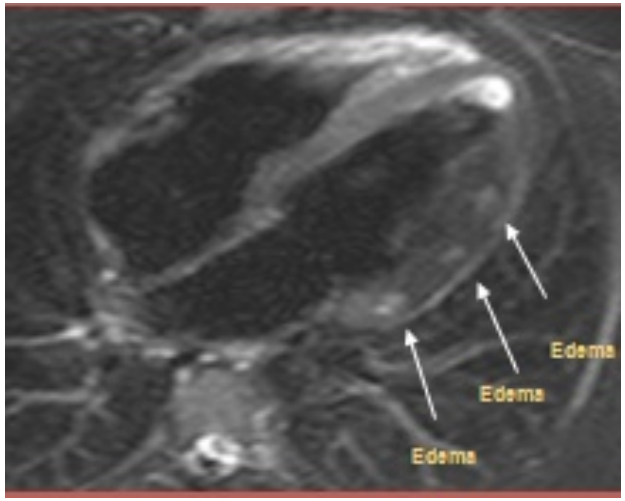
Troponina:
-I dosaggio:10,5 pg/ml.
-II dosaggio all'arrivo: 11 pg/ml
CPK: 708 U/l
CK-MB: 92
VES (IK): 24; Leucociti 11.200

ECO: diametria, FE e cinetica VS normali

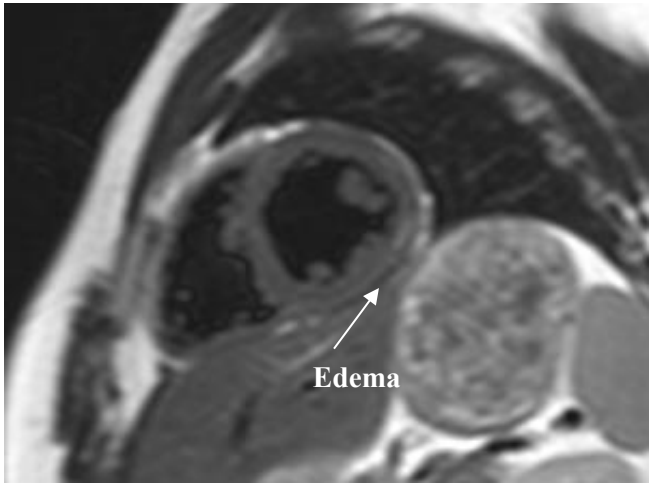


G. Giovanni, - RMC con gadolinio -

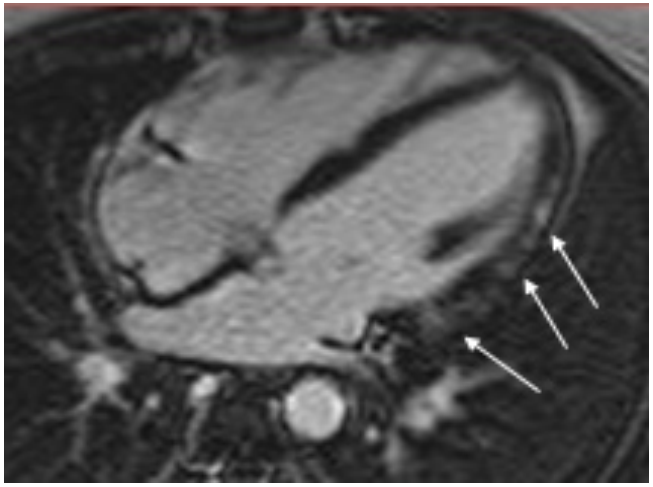
T2
STIR
4 cam

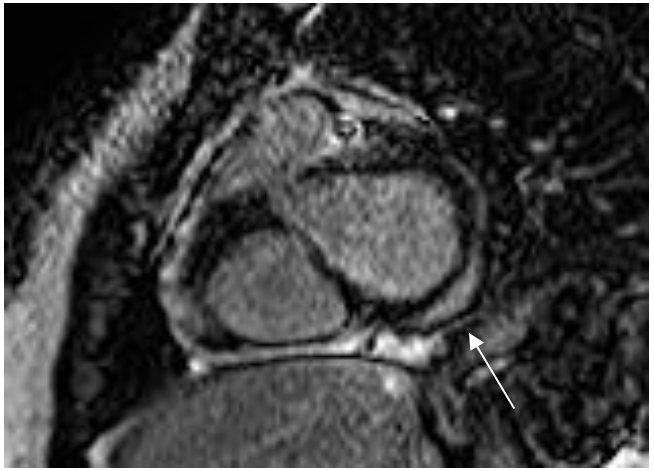


asse
corto



L-E
4 cam

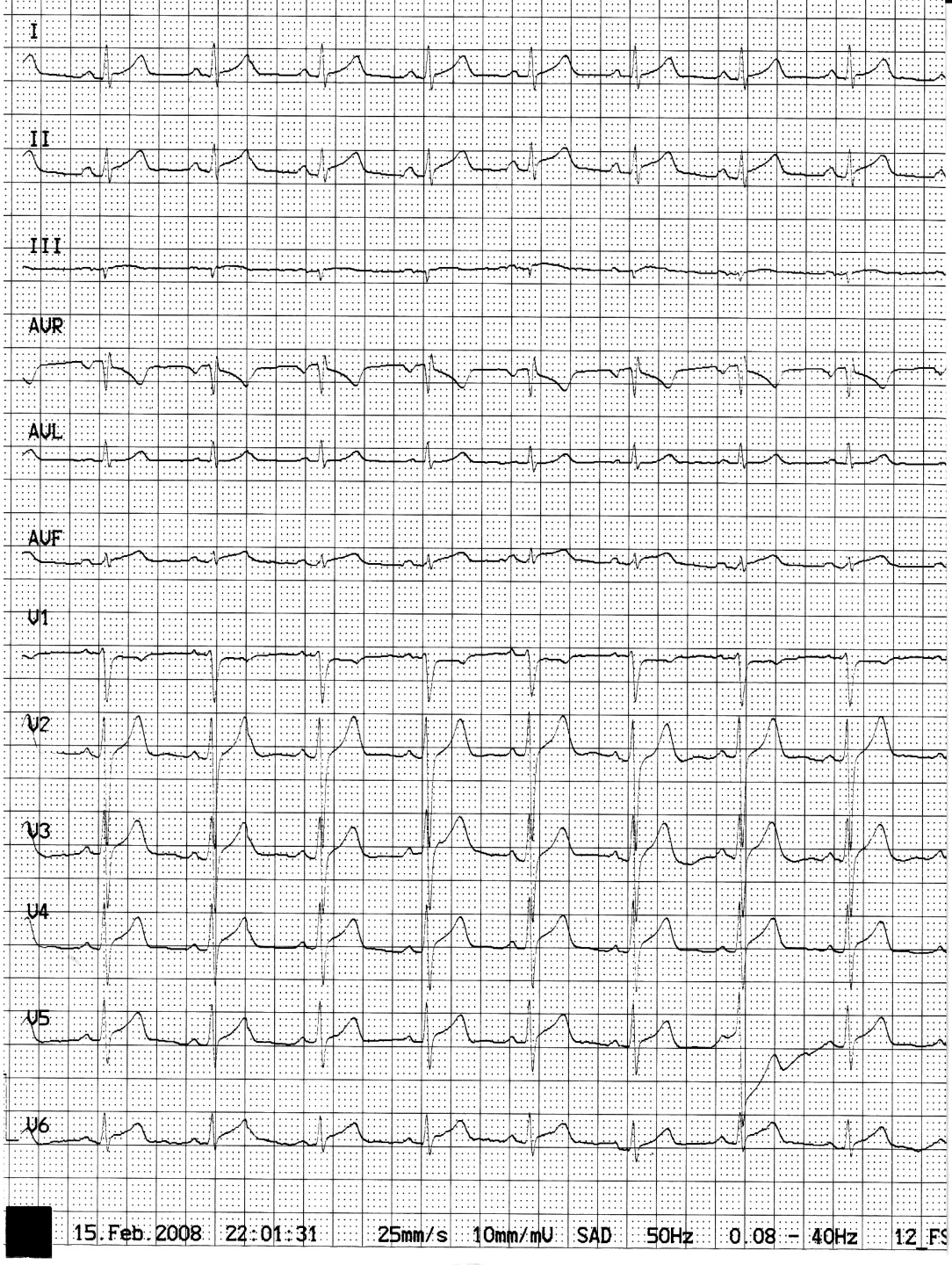




D. Biagio, a. 36

Fumatore;
Familiarità per CI;
Sindrome influenzale
1 mese prima;
Dolore tipico, remittente, da 2 giorni, ora + intenso.

Troponina:
-I dosaggio: 4.2pg/ml,
-II dosaggio: 11,53pg/ml.
CPK: 602 UI/l; 568 UI/l
CKMBmassa: 63 UI/l 58
VES (IK) 5 ; GB:10.000
ECO: lieve ipocinesia inferiore



Acute myocarditis mimicking Myocardial infarction

-Young age (n=11, mean 42 yrs), clinical AMI

-ECG:

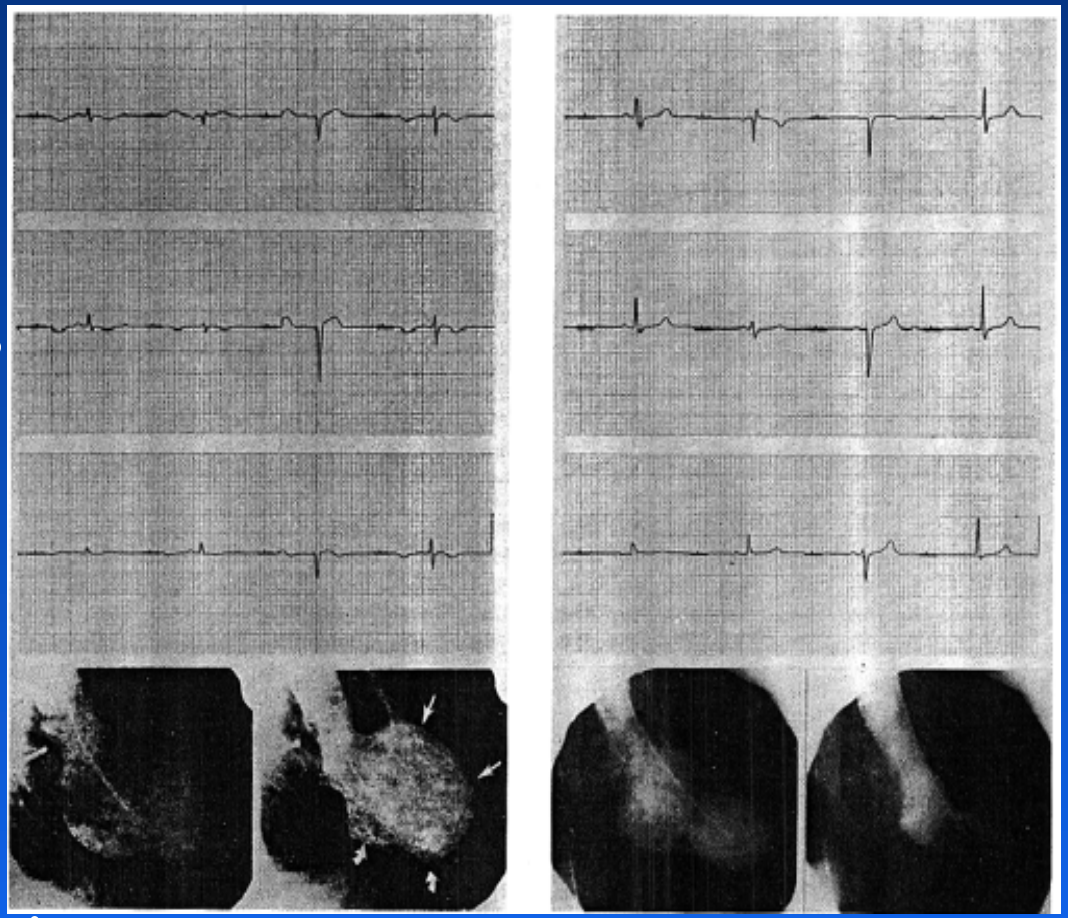
STEMI (n=6), non STEMI (n=2), neg T wave (n=3), Q wave (n=2)

-LVEF: normal (n=6), globally reduced (n=5, range 14-45%)

- Normal coronary arteries

-BEM:

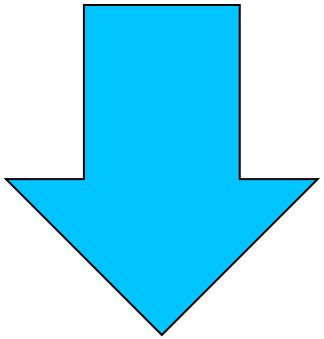
lymphocytic myocarditis (n=10), giant cell (n=1)



Dec WJ, JACC 1992

Esordio simil-infartuale / Esordio con SC

83 (64,8%) 45 (35.2%)



- Dolore toracico intenso
- Modificazioni ST-T
- VS non dilatato
- FE conservata
- Decorso benigno
- Completa guarigione

Mahrholdt H et al. *Circulation* 2006:114; 1581

Quando "pensare " ad una miocardite ?

- Giovane età, maschio
- Non preesistente cardiopatia e FR maggiori
- Episodi flogistici, mialgie, malessere, nausea-gastroenteriti, quadri simil-influenzali, concomitanti o precedenti (10-80% dei casi)
- Definito periodo stagionale (inverno-primavera)

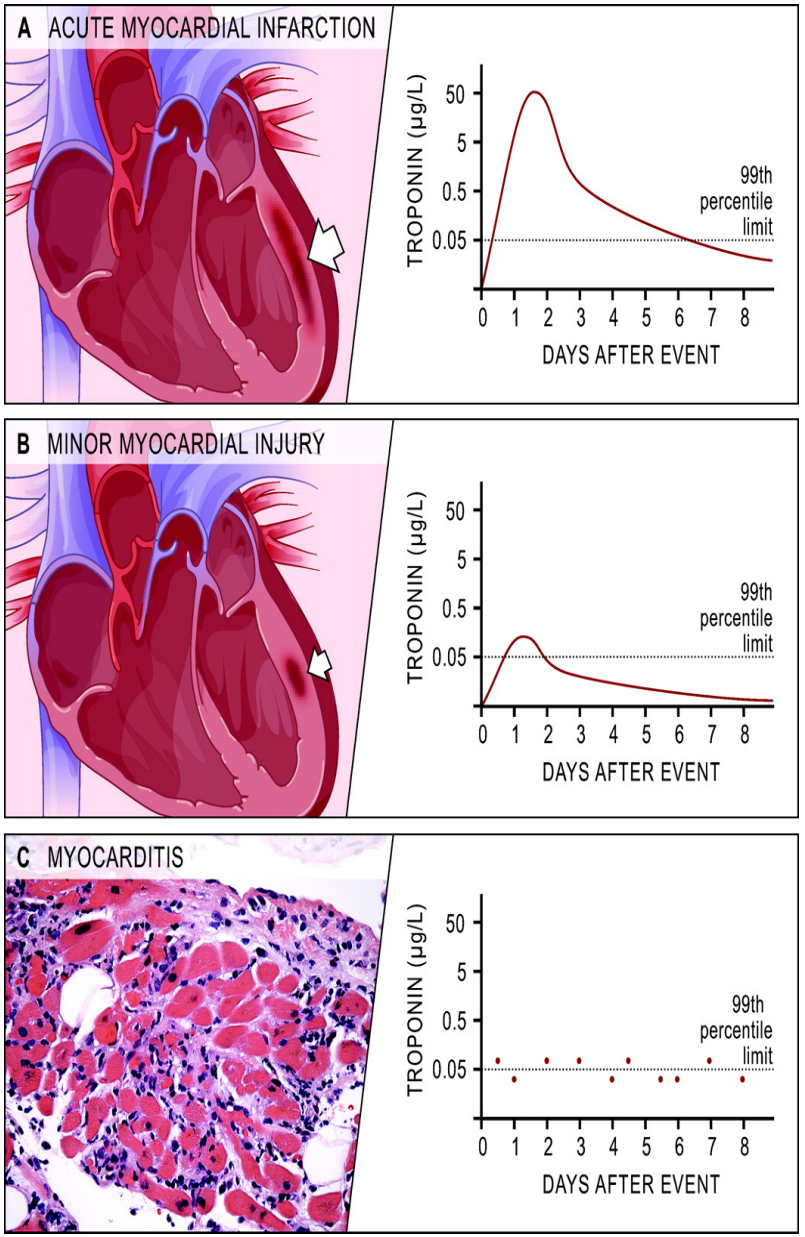
Myocarditis

Diagnostic Evaluation

- Cardiac Biomarkers and viral serology
- ECG
- Myocardial Imaging
  - Echocardiography
  - MRI
- Biopsy

Table 2. Elevations of Troponin in the Absence of Overt Ischemic Heart Disease

Trauma (including contusion, ablation, pacing, implantable cardioverter-defibrillator firings including atrial defibrillators, cardioversion, endomyocardial biopsy, cardiac surgery, after interventional closure of atrial septal defects)
Congestive heart failure—acute and chronic
Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy
Hypertension
Hypotension, often with arrhythmias
Postoperative noncardiac surgery patients who seem to do well
Renal failure
Critically ill patients, especially with diabetes, respiratory failure
Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms
Hypothyroidism
Apical ballooning syndrome
Coronary vasospasm
Inflammatory diseases, e.g., myocarditis, e.g., Parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of bacterial endocarditis
Post-percutaneous coronary intervention patients who seem to have no complications
Pulmonary embolism, severe pulmonary hypertension
Sepsis
Burns, especially if total body surface area is >30%
Infiltrative diseases including amyloidosis, hemachromatosis, sarcoidosis, and scleroderma
Acute neurological disease, including cerebrovascular accident, subarachnoid bleeds
Rhabdomyolysis with cardiac injury
Transplant vasculopathy
Vital exhaustion



Melanson S. E.F. et al. Circulation 2007;116:e501

Myocarditis
Diagnostic Evaluation

ECG

- A QTc prolongation > 440 ms, an abnormal QRS axis and ventricular ectopic beats were associated with poor clinical outcome

- QRS > 120 ms is a independent predictor for cardiac death or heart transplantation

Morgera *Am Heart J 1992*
Nakashima *Jpn Heart J 1998*
Ukena *Eur J Heart Fail 2011*

Echocardiography

- Reccomended in the initial evaluation
- LV dysfunction 69%
- LV cavity enlargement minimal or absent
- RV dysfunction 23%
- Segmental wall motion abnormalities 64% (hypokinetic, akinetic, dyskinetic)
- Reversible LV hypertrophy 15%
- More recent techniques are promising (TDI)

Felker *JACC 200*

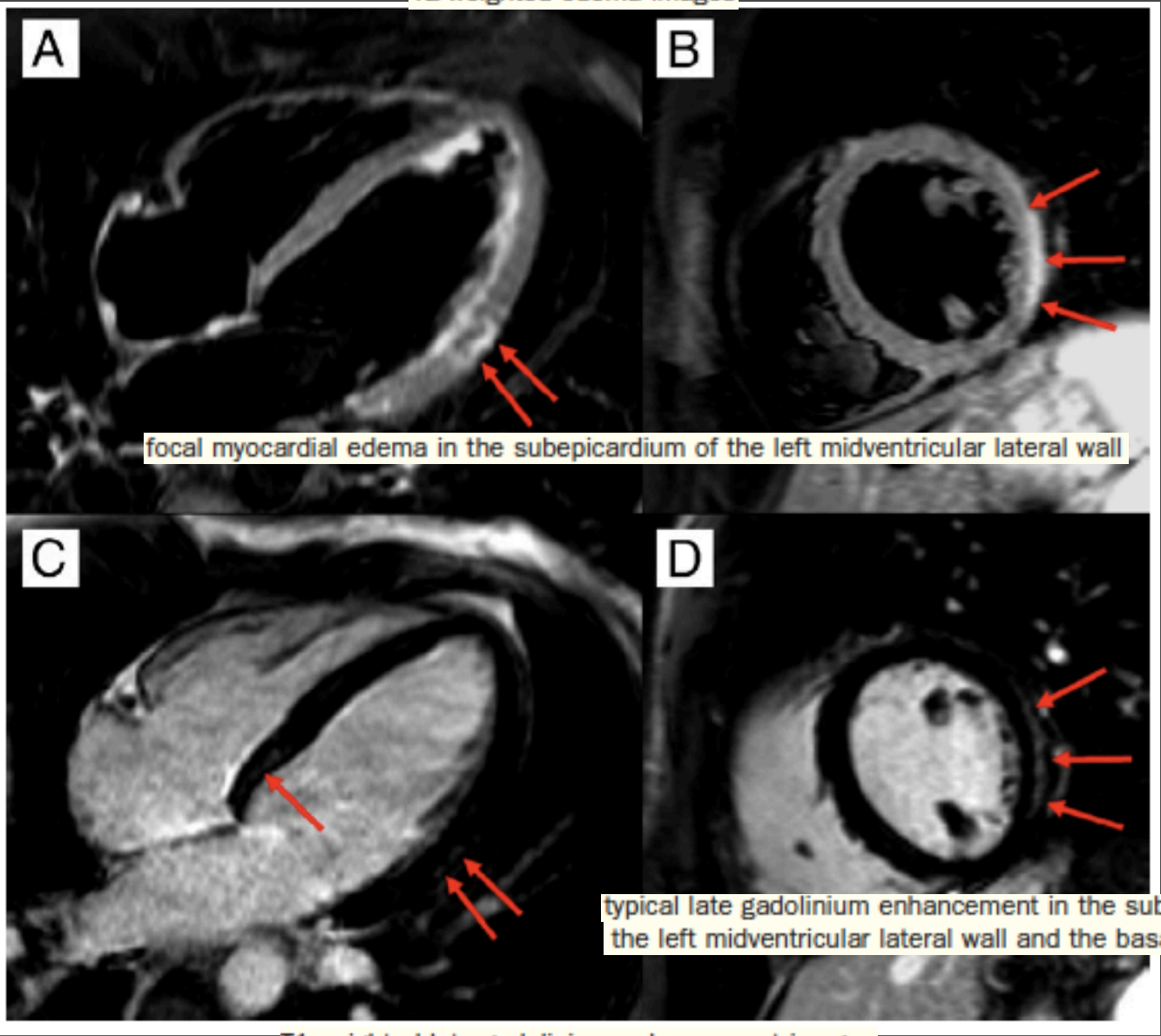
Myocarditis
Diagnostic Evaluation

MRI

- Appears to be the most promising technique for diagnosing myocardial inflammation and myocardial injury
- Focal myocardial enhancement combined with regional wall motion abnormalities
- Biopsy of these specific myocardial regions resulted in positive predictive value of 71% and negative predictive value 100% (guided approach)
- Serial MRI for tracking the natural hystory of the disease

Abdel-Ary *JACC 2005*

T2-weighted edema images



focal myocardial edema in the subepicardium of the left midventricular lateral wall

typical late gadolinium enhancement in the subepicardium of the left midventricular lateral wall and the basal septum

T1-weighted late gadolinium enhancement images

Biopsy (EMB)

- Diagnostic information in only 10-20% of cases but EBM findings remain the gold standard for unequivocally establish the diagnosis
- Multiple investigators have described strong clinical and laboratory evidence of myocarditis among pts with negative biopsies
- EMB performed within weeks of symptom onset have a higher yield than those undertaken when symptoms have been more longstanding

Baughman *Circulation 2006*
Yilmaz *Circulation 2010*

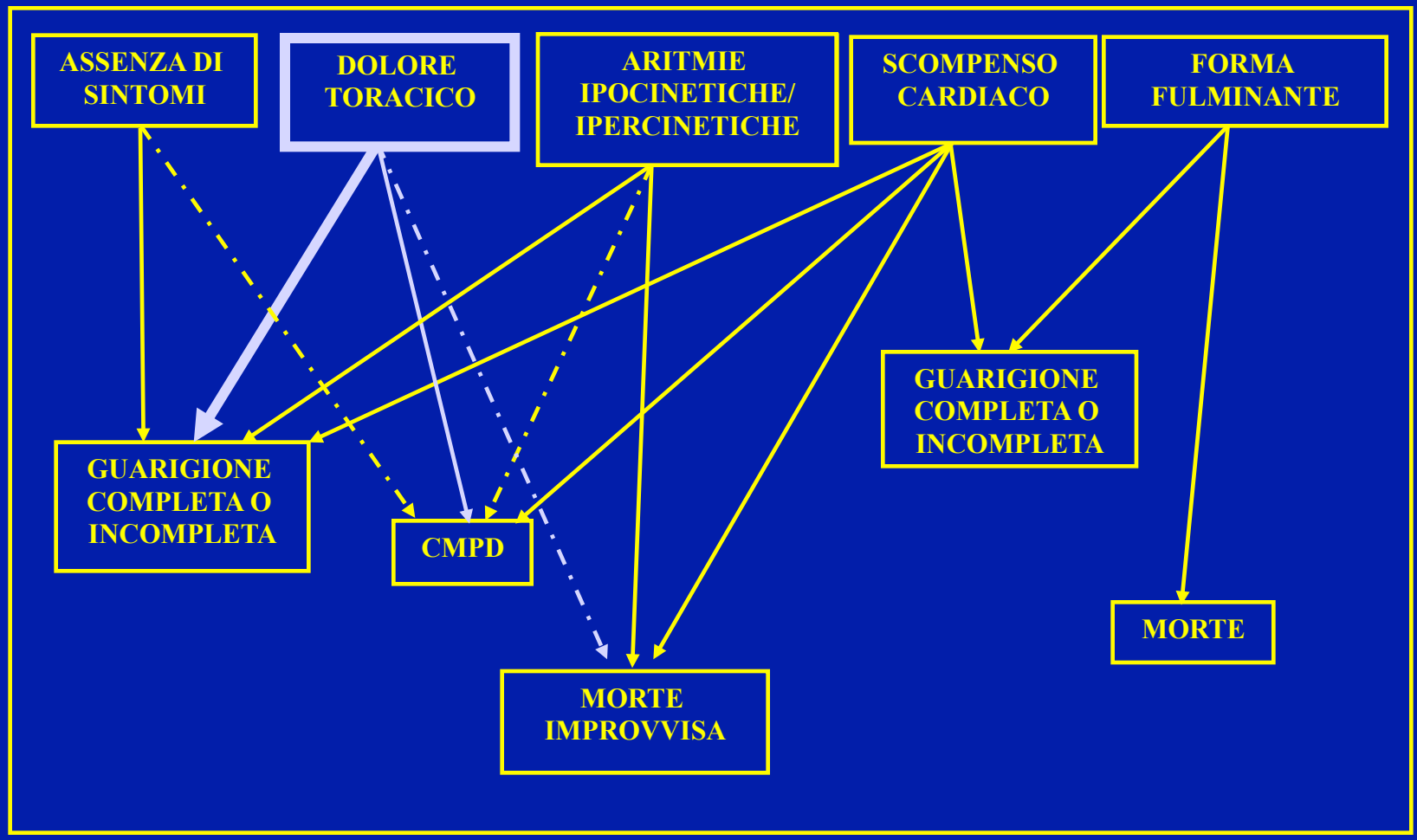
Dallas classification of myocarditis

Aretz TH , Hum Pathol 1987

- **First biopsy**
  - Myocarditis (inflammation +necrosis/degenerative changes) with/without fibrosis
  - Borderline myocarditis (sparse inflammation, no necrosis/ degenerative changes, no unequivocal diagnosis)
  - No myocarditis

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

MIOCARDITI: Polimorfismo di Presentazione ed Evoluzione



Myocarditis
Natural History

- Predicting prognosis remains problematic

- Prognosis depends on:
  - Clinical presentation
  - Different clinical parameters
  - EMB findings

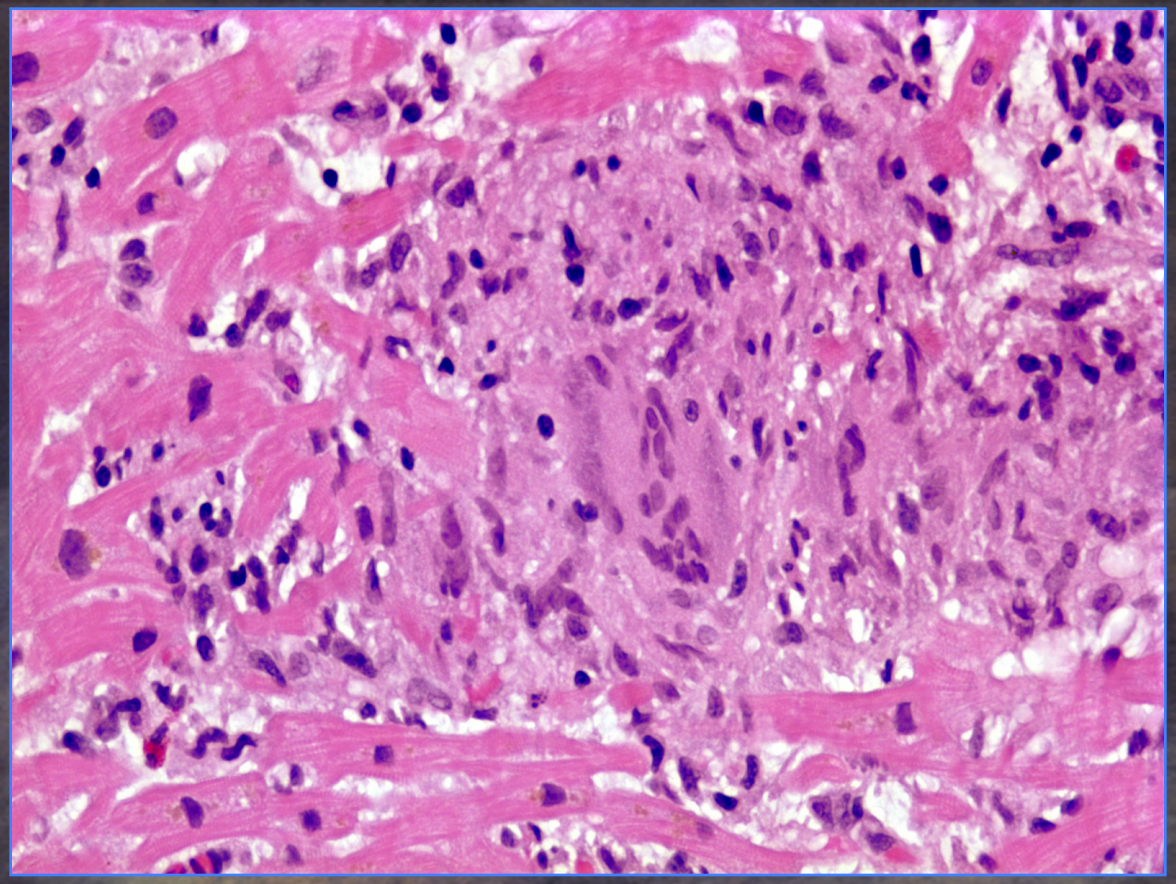
Kindermann et al 2012

Myocarditis
Natural History

- Acute myocarditis with preserved LVEF have a good prognosis.
- Fulminant myocarditis and hemodynamic compromise at presentation have an excellent long term prognosis if aggressive pharmacological and/or mechanical support is initiated early.
- In sarcoidosis and giant cell myocarditis prognosis depends on an early initiated treatment (immunosoppressive therapy or Htx).

Kindermann *JACC 2012*

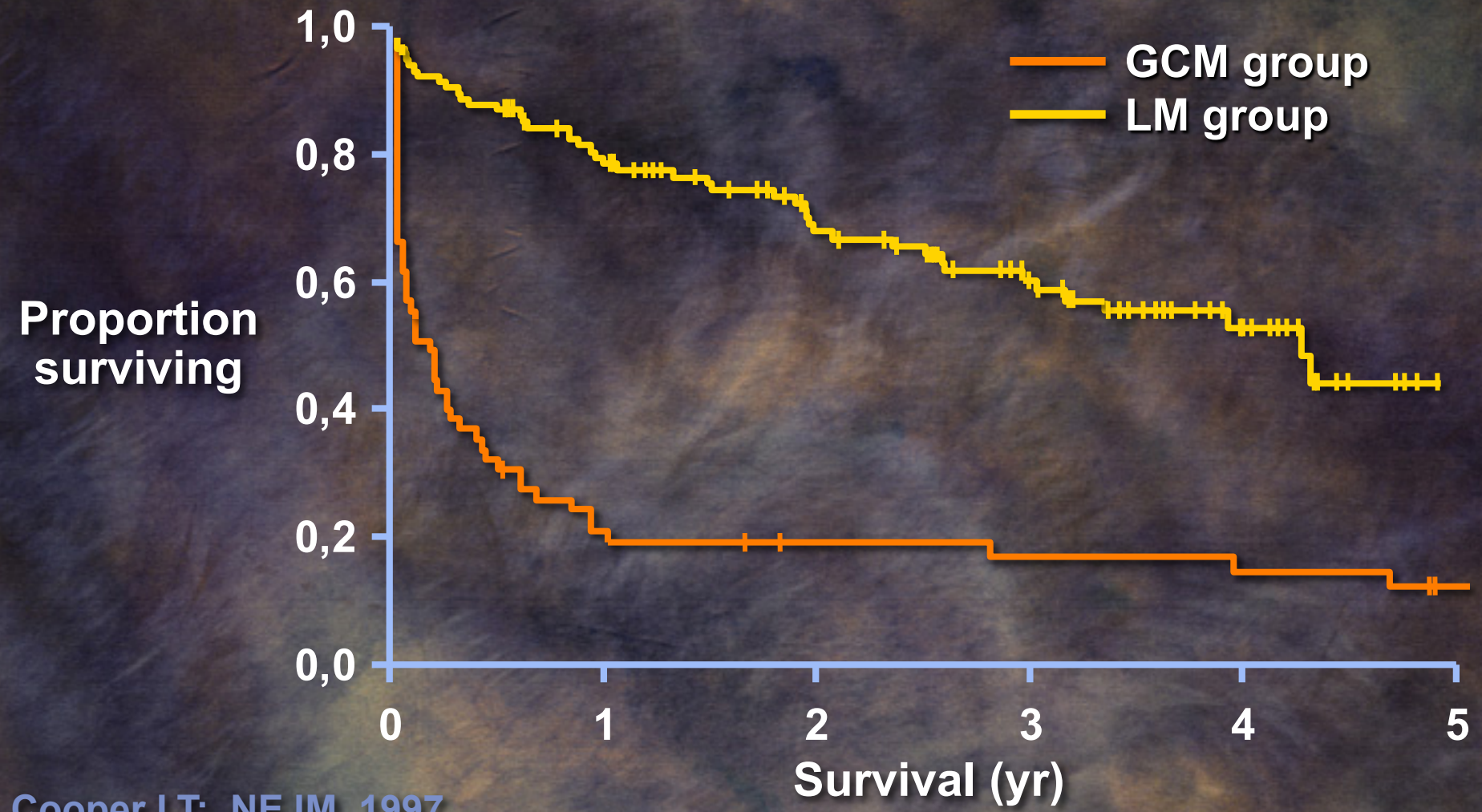
Giant Cell Myocarditis



Microscopy (H&E, High Power)

Giant Cell vs Lymphocytic Myocarditis

Transplant-Free Survival from Presentation



Cooper LT: NEJM, 1997

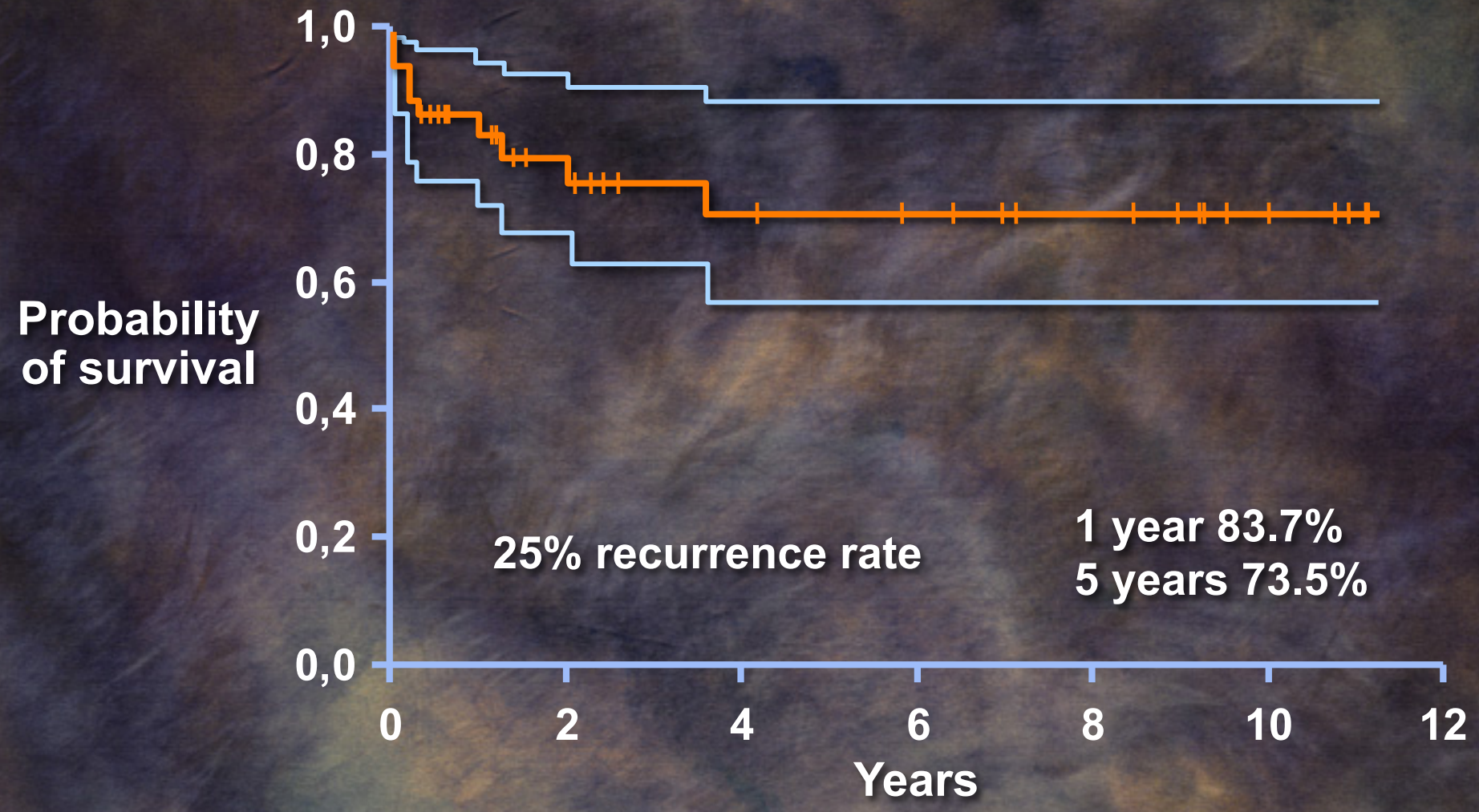
Immunosuppressive Treatment for GCM

	No.	Median survival	P
No immuno-suppression	24	3.00	–
Steroid only	13	3.75	0.68
Azathioprine and steroids	13	11.50	0.025
Cyclosporine and steroids	12	12.63	0.003

Cooper et al: N Engl J Med, 1997

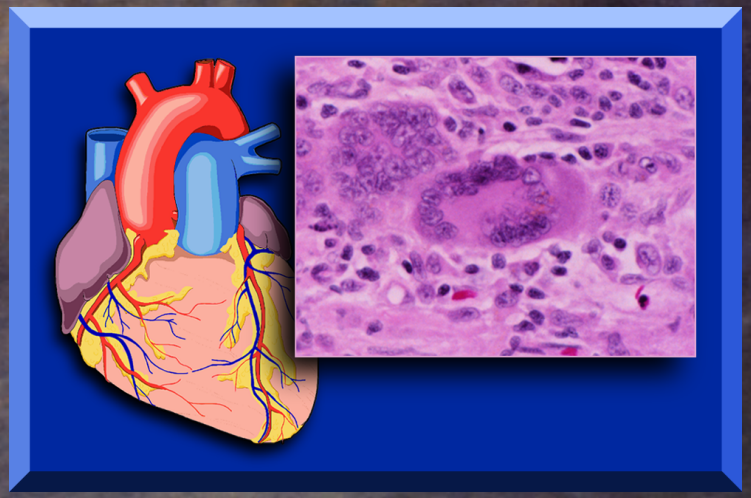
Survival of Giant Cell Myocarditis

Patients Post-Transplantation



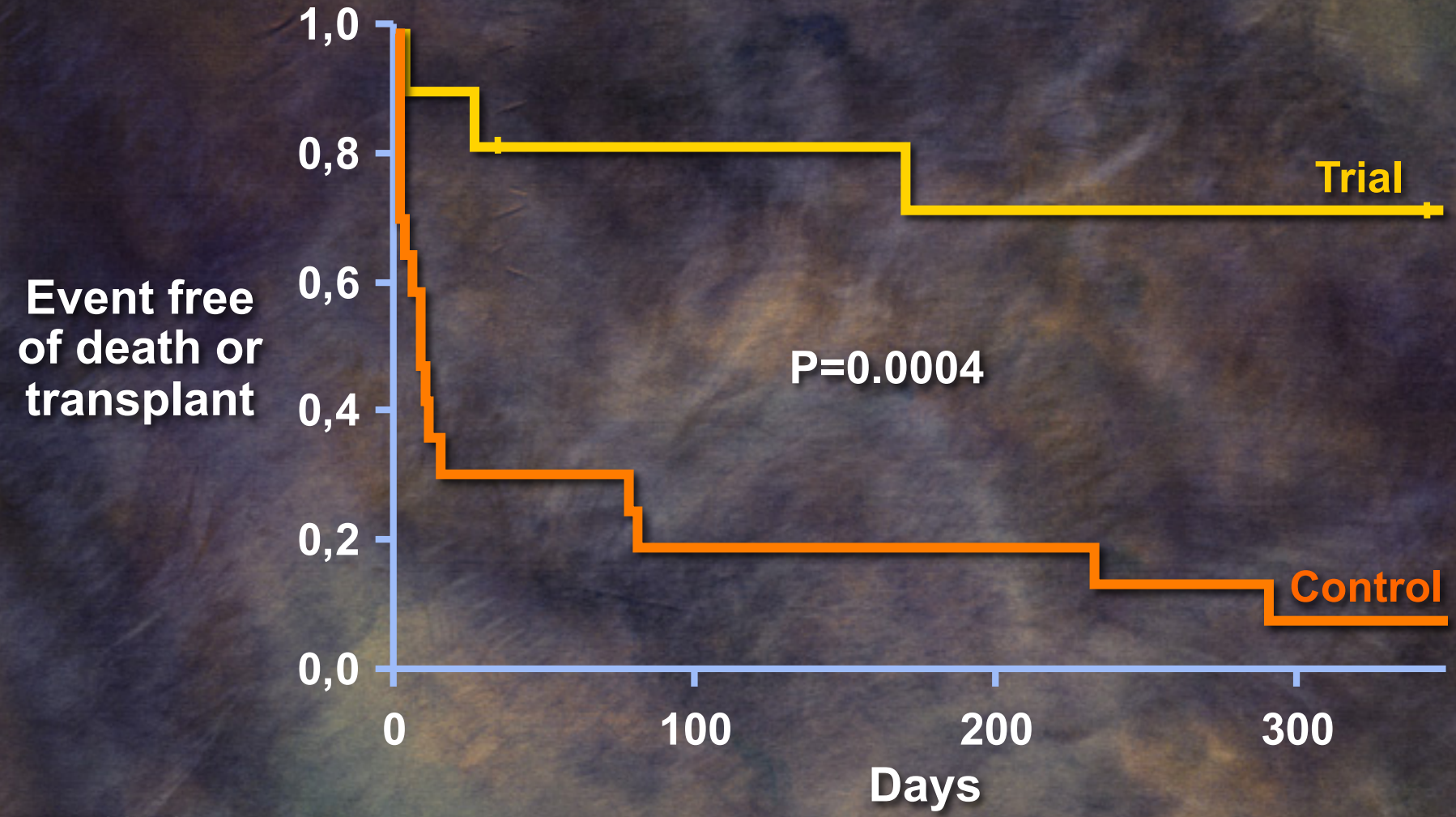
The Giant Cell Myocarditis Treatment Trial and Registry

- Randomized trial of muromonab-CD3, CSA steroids vs CSA and steroids
- Less than 3 months of symptoms
- Endomyocardial biopsy with GCM



GCM Trial: Pooled Treatment Groups vs Historical Controls

Death or Transplant at 1 Year



Patients who present with HF

Myocarditis: Evolution

- Substantial recovery in LVEF% in about 50% of pts
- Clinically stable but low LVEF% in about 25% of pts
- Deterioration and need for heart transplantation (HTx) in the remainder
  - Defer HTx acutely (potential for recovery)
  - HTx may be life-saving
  - Myocarditis pts do not have worse outcome following HTx
  - Recurrence of GCM following HTx (up to 9 yrs) generally responds to increased immunosuppression

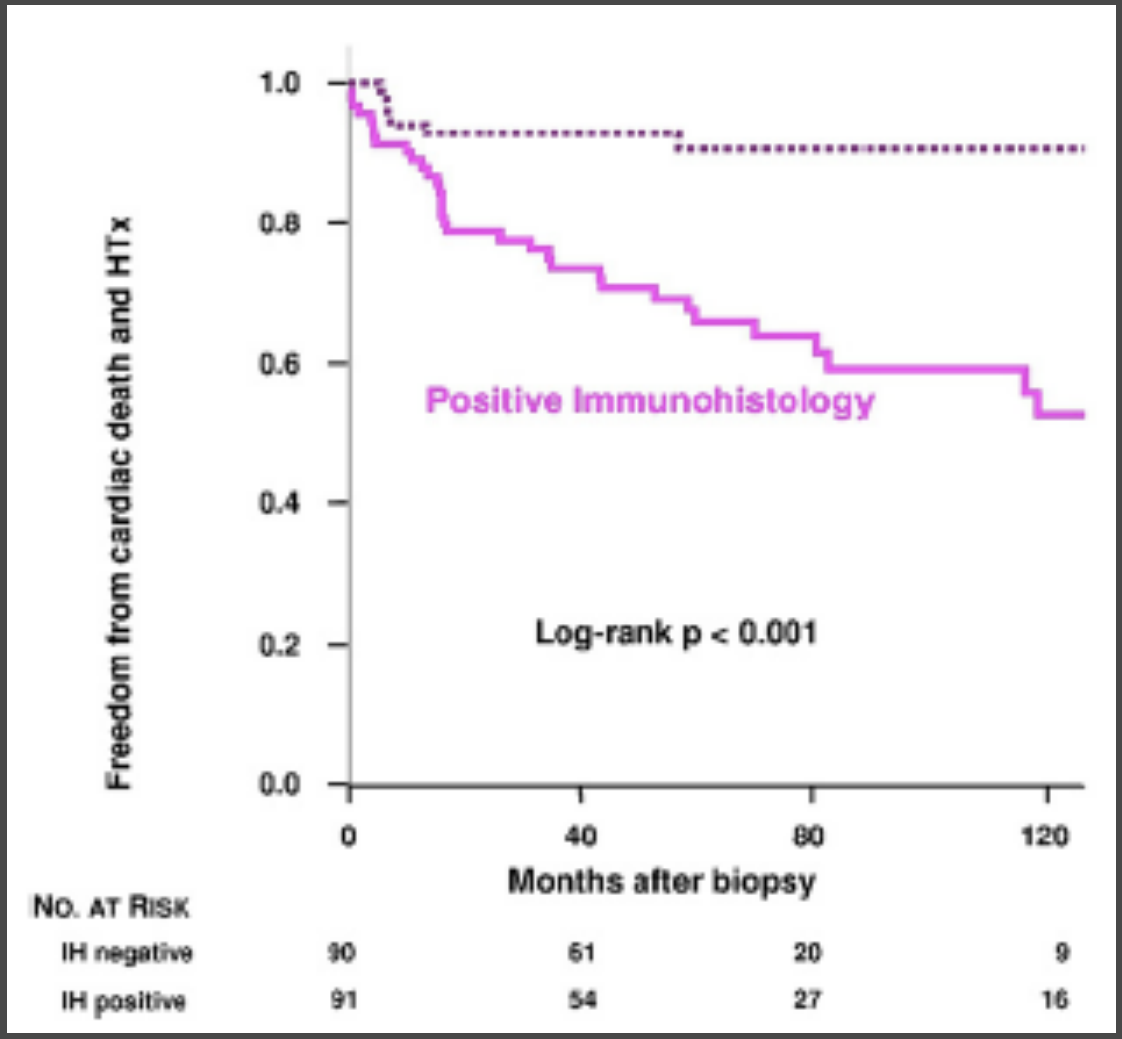
Myocarditis
Natural History

- Significant predictors:
  - Presentation with syncope
  - Bundle brunch block
  - EF < 40%
  - NYHA III-IV
  - Elevated LV filling pressures
  - Right ventricular dysfunction
  - Pulmonary hypertension

  - Neither hystopathological Dallas criteria nor detection of viral genome was a predictor of poor outcome

1.Magnani *Am Heart J 2006*
*2.*Why *Circulation 1994*

Freedom From Cardiac Death and HTx by Endomyocardial Biopsy Findings, IH Results



Immunohistology (IH) evidence of inflammatory infiltrates in the myocardium (IH positive) predicts cardiovascular death and the need for heart transplantation (HTx).

Kindermann et al *Circulation 2008*

Myocarditis
Treatment

- Effects of a specific causative therapy (immunosoppressants) has only been confirmed in inflammatory heart disease:

  - SARCOIDOSIS
  - GIANT CELL MYIOCARDITIS

Myocarditis
Treatment

- First line: supportive care
- In a minority of pts (fulminant or acute myocarditis): vasopressors, inotropes, VAD, ECMO)
- After stabilization: treatment should follow reccomendations for LV systolic dysfunction

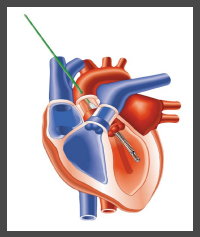
VAD

Miocardite fulminante

N. Pazienti	Svezzati	Svezzati dimessi	Txc	Txc dimessi	Sopravvivenza
7	29%	100%	43%	100%	71%

Età media : **35.8 aa (range 22-45)**

Sesso: **4 M**



Device utilizzati: Thoratec 1, Abiomed 1, Medos 3, Impella Recover 2.

Immunosoppression ?

- Long-term sequelae appear to be related to abnormal cellular and humoral immunity
- > 20 uncontrolled observational studies reported successs with a variety of immunosoppressive agents
- BUT several caveats……..
  - Histological resolution of inflammation does not correlate with improvement in ventricular function
  - High incidence of spontaneous improvement
  - The specific viral agent and the immunologic state of the host may results in different response to immunosoppression

Mason *N Engl J Med 1995*
Hufnagel *Herz 2000*
McNamara *Circulation 2001*

Myocarditis
Treatment

Immunoglobuline ?

- Antiviral and immunomodulating effects
- In recent onset myocarditis or DCM no difference
- Children with acute myiocarditis had a improvement of LV function and survival at 1 year

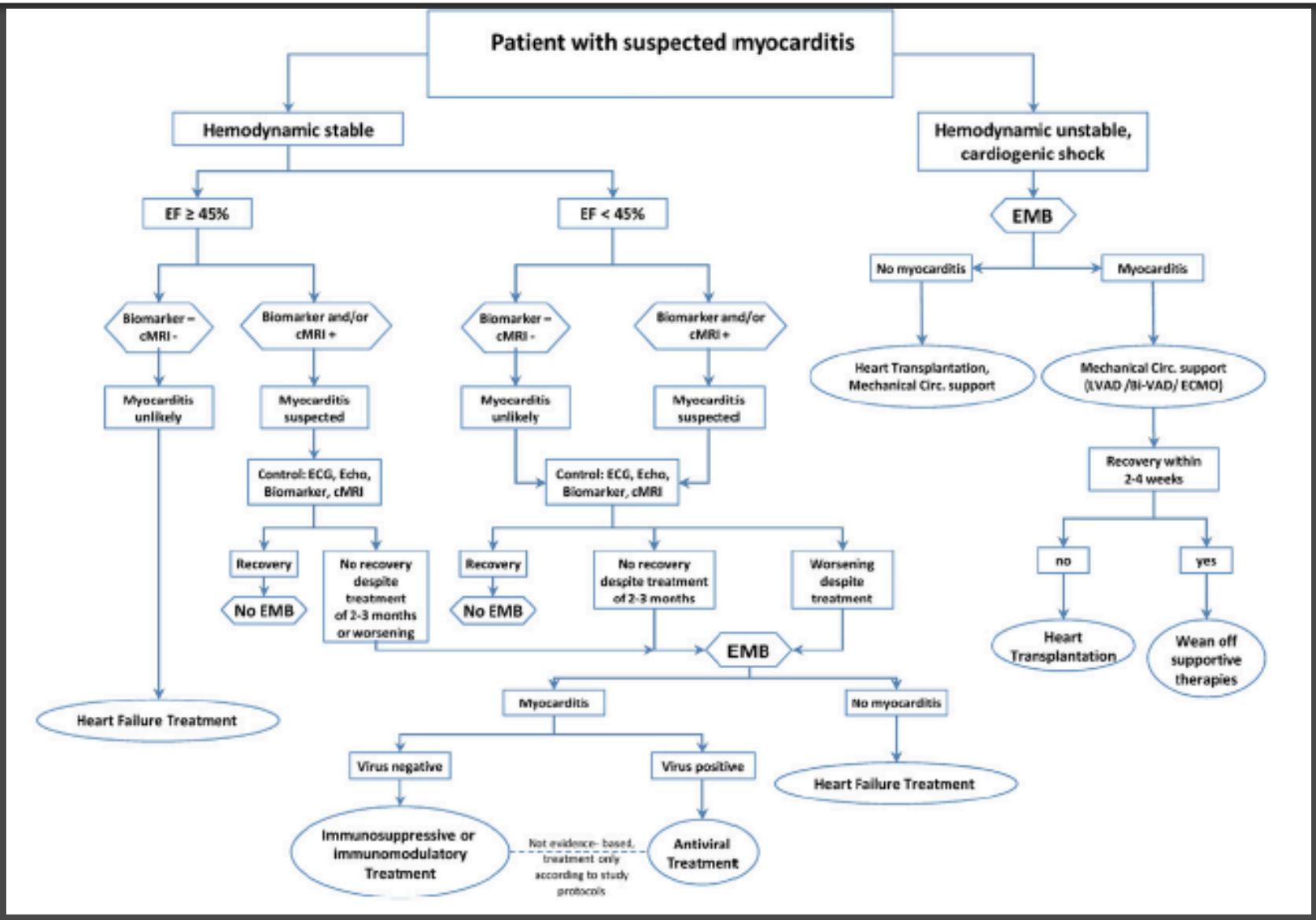
Immunoadsorption ?

- Target: elimination of anticardiac antibodies against various cardiac cell protein
- Multicenter, randomized, double-blind study is ongoing

Antiviral treatment ?

- Most common cases of myocarditis are induced by viral infections
- BICC Trial (Betaferon in patients with chronic viral cardiomyopathies):
  - significant reduction in viral load
  - Improvement only in NYHA functional class and patient global assessment

Shultheiss *Circulation 2008*



Kindermann et al JACC 2012

Myocarditis

Inferences (I)

- Precise characterization and natural history have been limited by variability of clinical presentation and laboratory findings and the diversity of etiologies
- Low incidence and difficulties in diagnosis > no large scale randomized trials

- ECG, ECHOCARDIOGRAPHY, serum troponin and MRI are warranted for initial diagnosis evaluation
- EBM should be considered for selected group

Myocarditis

Inferences (I)

- Treatment remains largely supportive
- Immunosoppression has not been shown to be effective as routine therapy

- Although a high rate of spontaneous improvement, patients who progress to chronic dilated cardiomyopathy experience 5-year survival rates < 50%.

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