FONDAZIONE CENTRO CARDIOLOGIA
E CARDIOCHIRURGIA A. DE GASPERIS
Niguarda Ca' Granda

Azienda Ospedaliera
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La Miocardite Acuta: dal sospetto clinico alla diagnosi

Fabrizio Oliva

IV Congresso Nazionale di Ecocardiochirurgia

Milano, 12 Marzo 2010

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**
  - Š **palpitation, atypical chest pain, SOB**
- **Minor ECG abnormalities**
  - Š **Conduction disturbance, ST-T changes**
- **Major arrhythmia**
  - Š **SVT, complete A-V block**
- **Syncope, sudden death**
- **Cardiogenic shock**
- **Heart failure resembling DCM**
  - Š **Recent onset**
  - Š **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

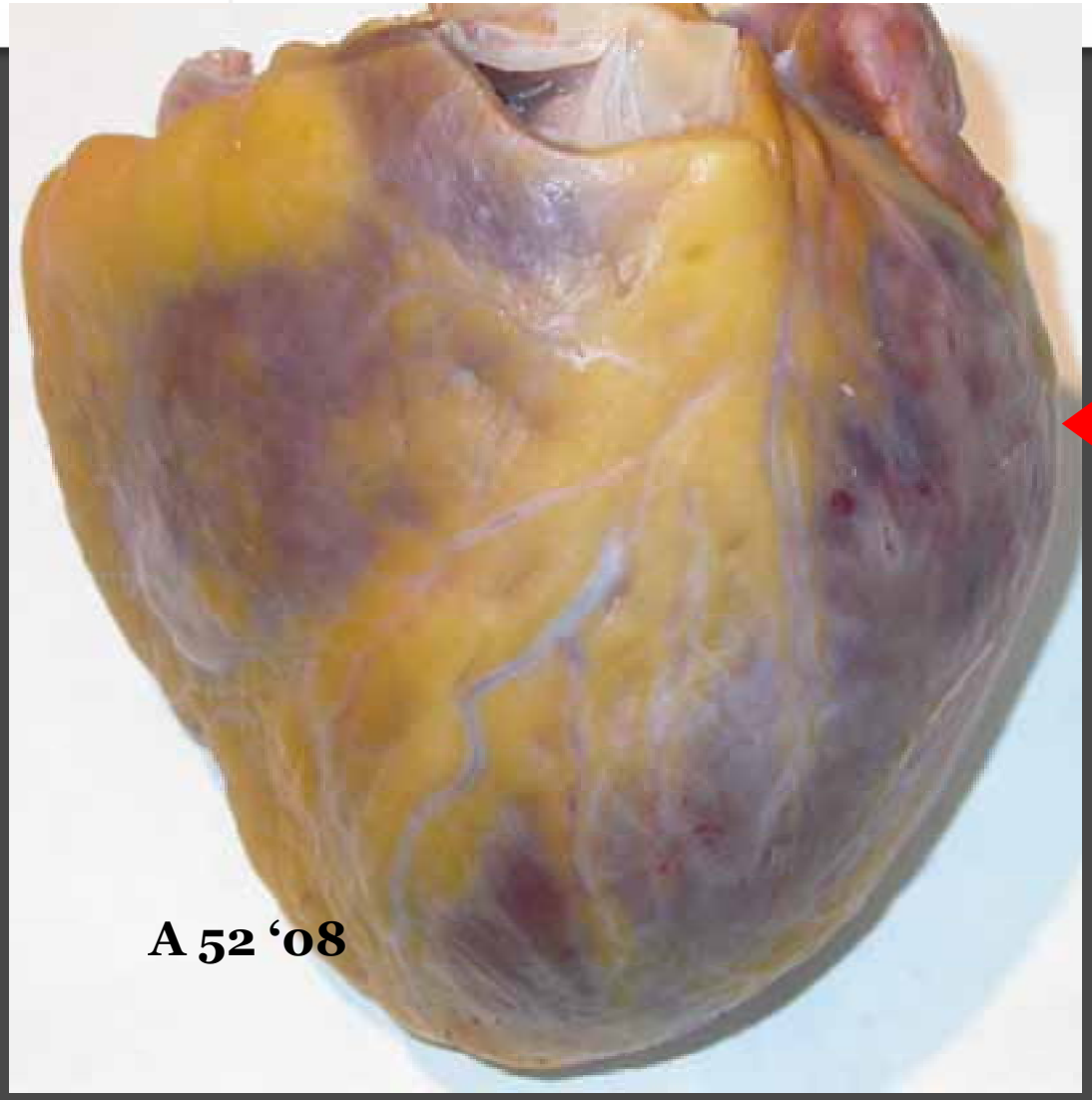
Clinical Presentation

- 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

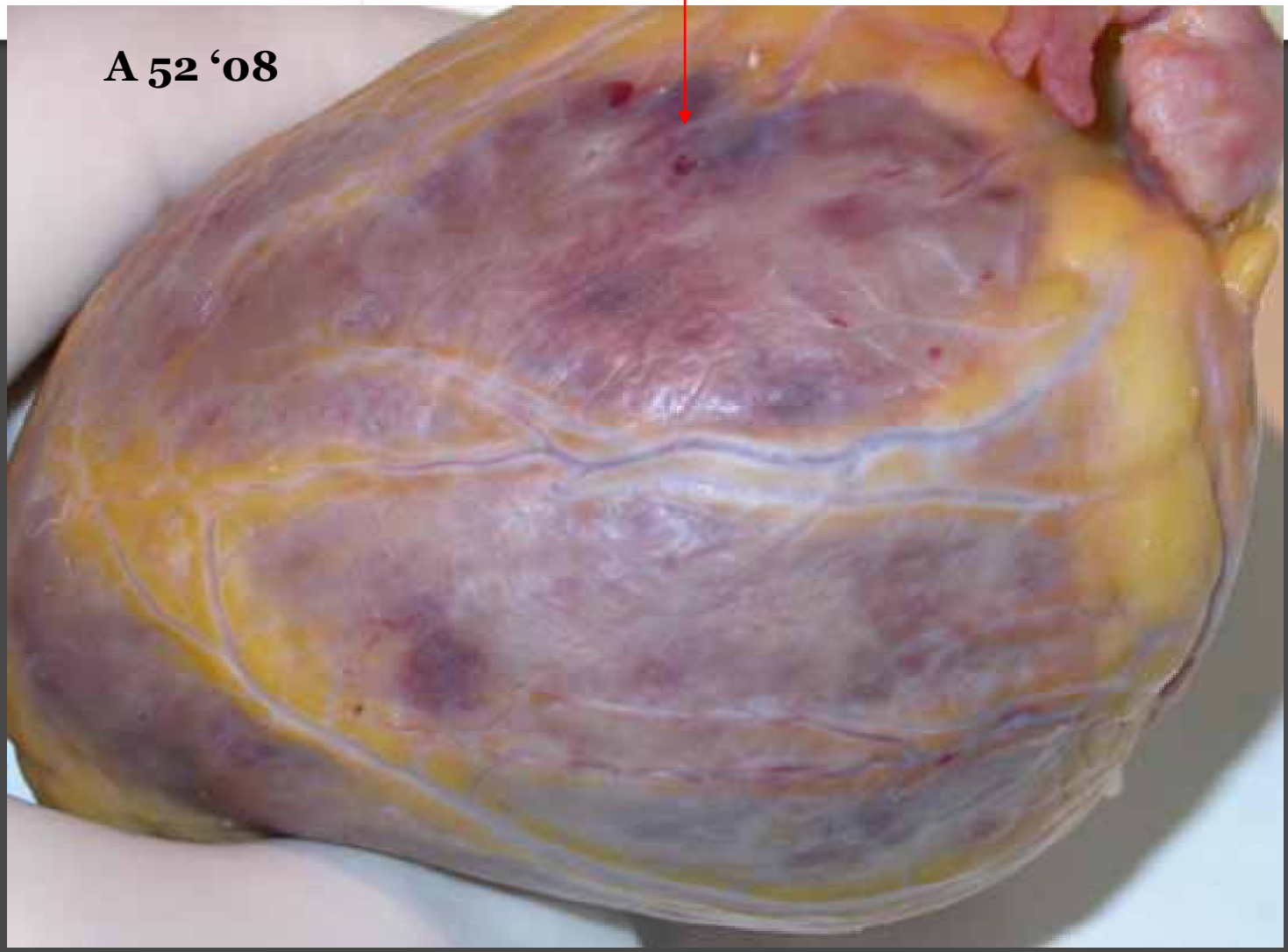
McCarthy *N Engl J Med 2000*

Miocardite acuta
Case Report

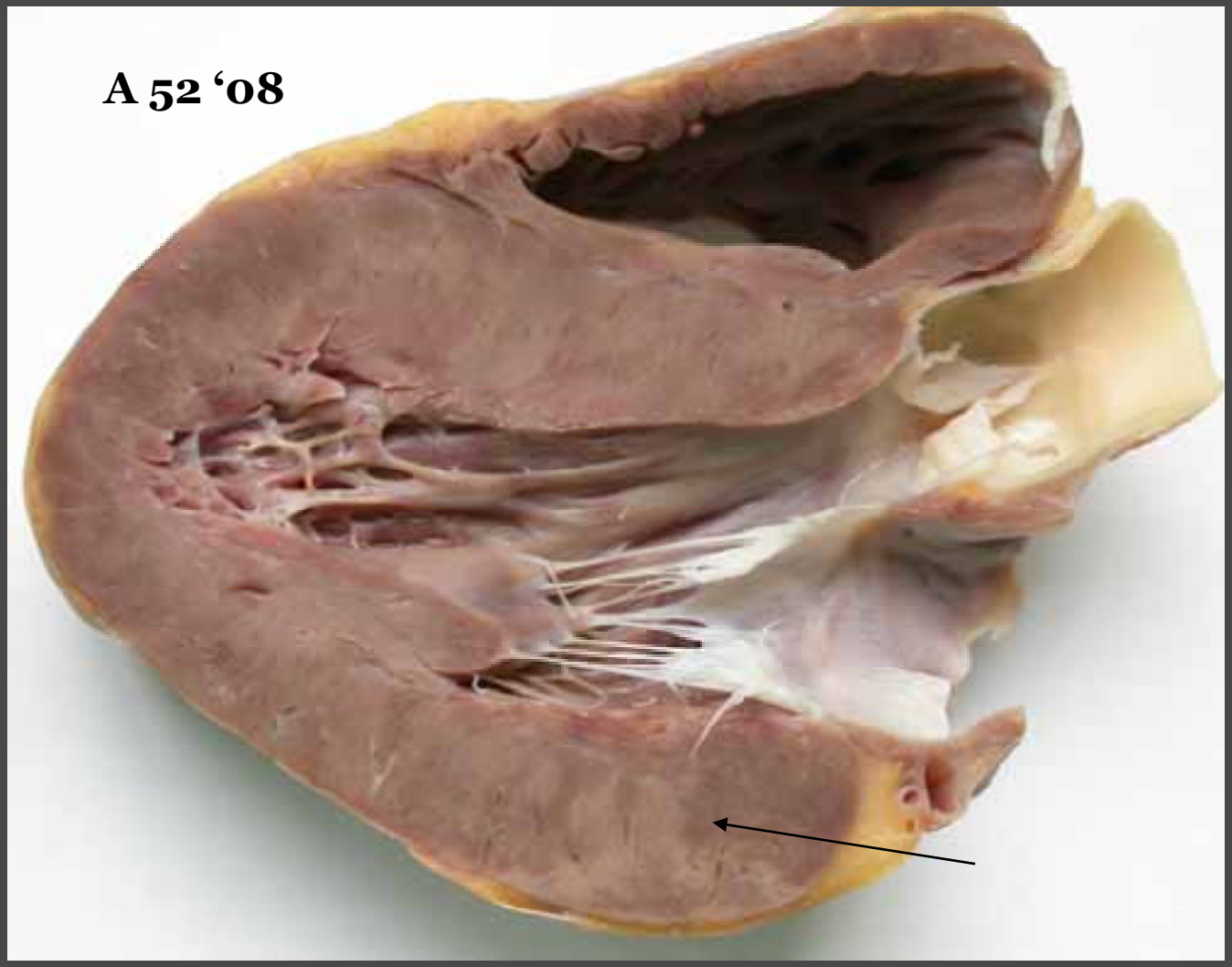
- Esordio acuto con dolore toracico in maschio di aa. 46
- Progressione di insufficienza cardiaca e respiratoria
- Sopraslivellamento ST diffuso all'ECG
- Aumento CPK e Troponina
- Exitus alla manovra di intubazione



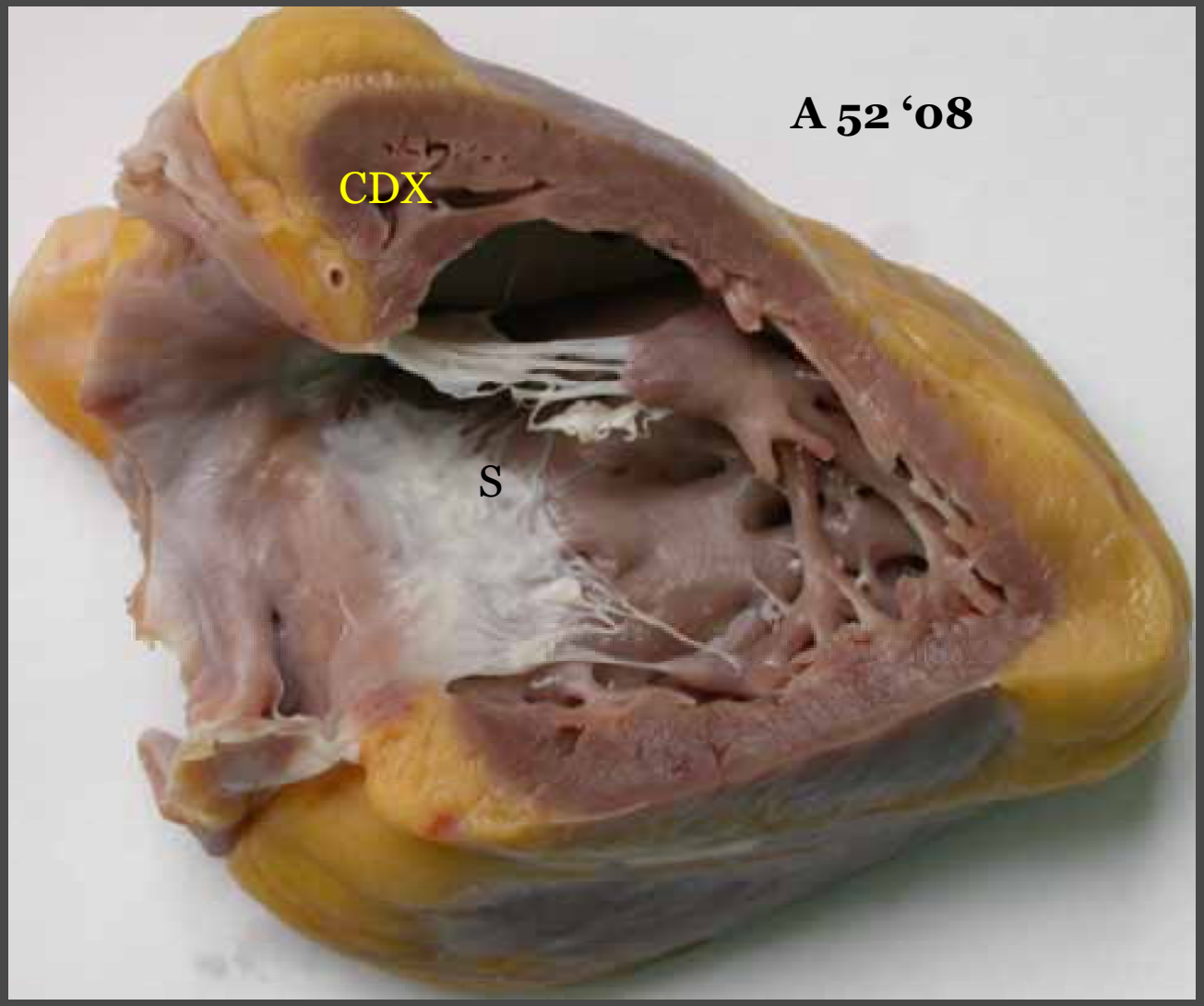
Cuore di dimensioni globalmente aumentate, con ispessimento parietale sinistro
Marezzatura emorragica epicardica con lieve opacamento fibrinoso



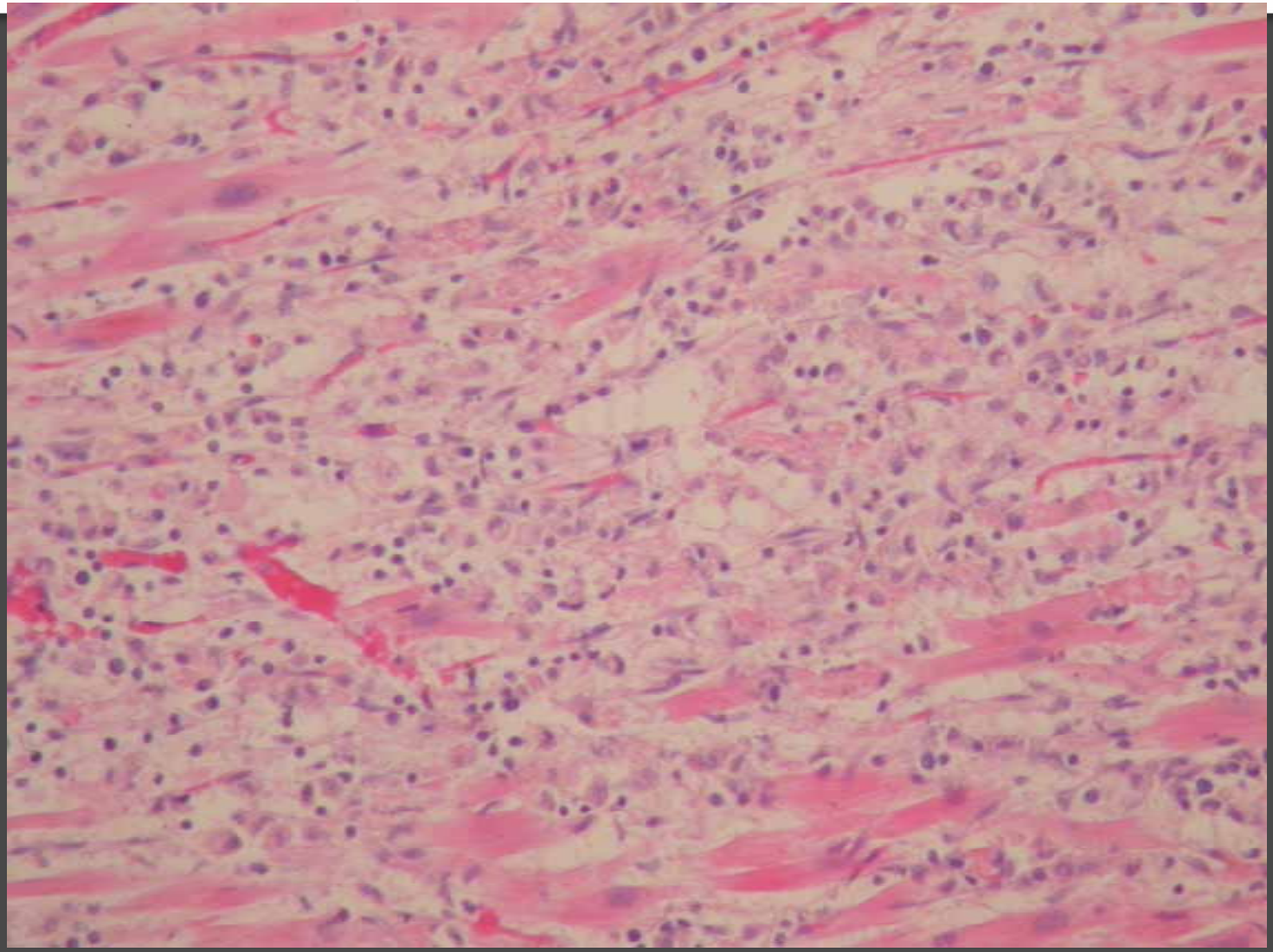
La fotografia laterale del VS dimostra una parete di spessore aumentato ed la variegatura emorra



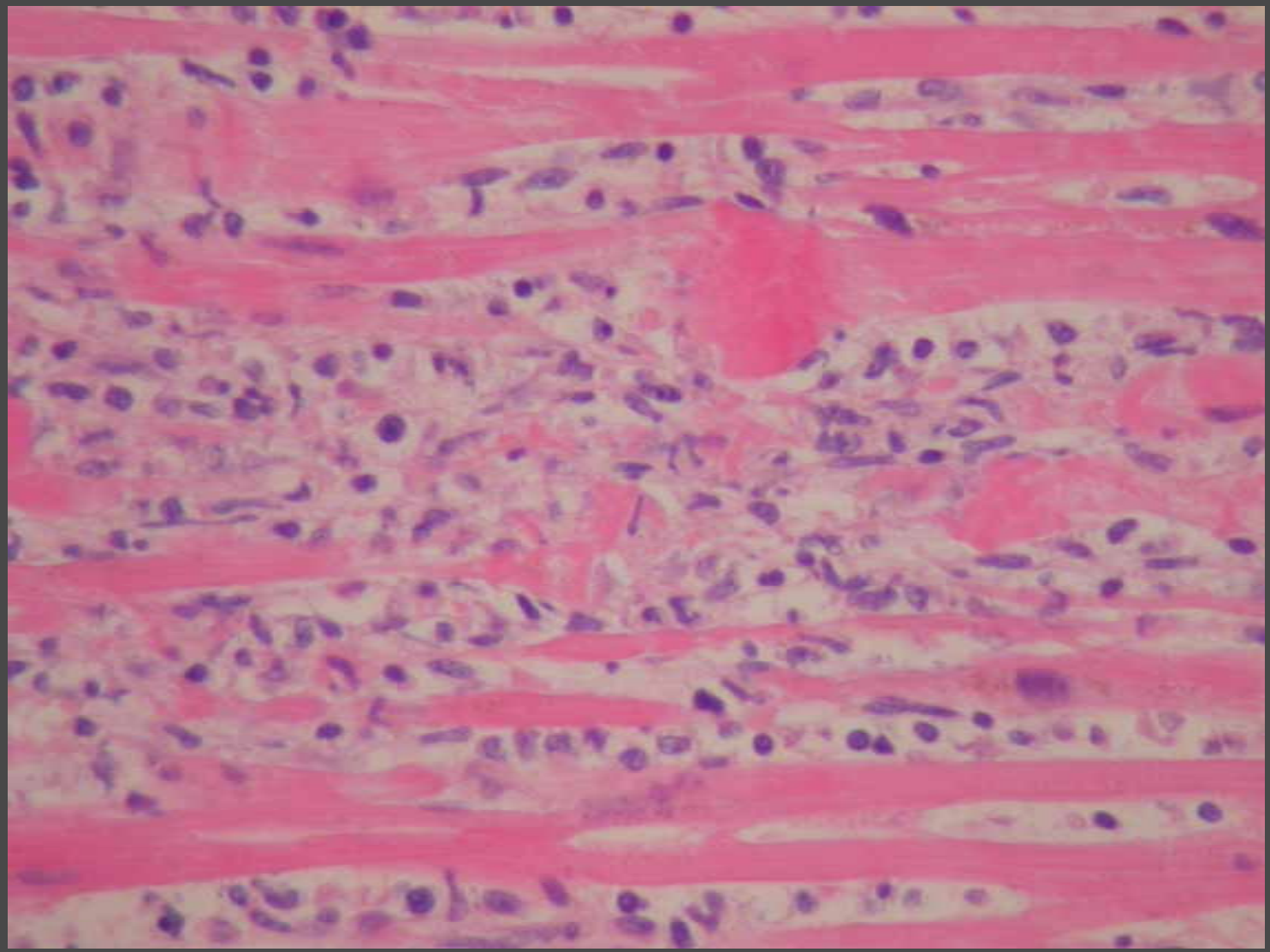
Sezione in asse lungo della massa ventricolare, che dimostra ispessimento della parete del ventricolo sinistro ed aspetto variegato del miocardio



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

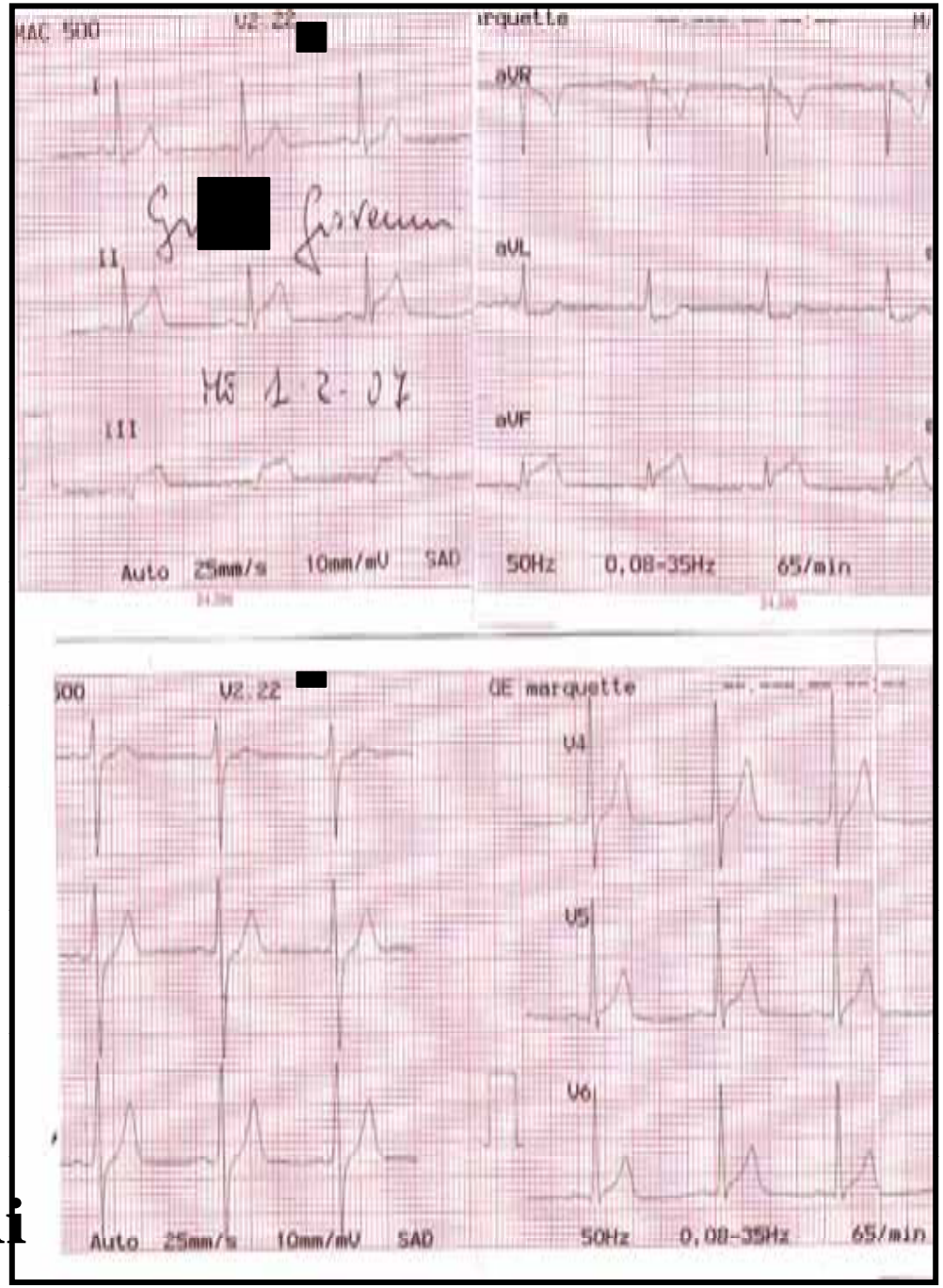
1.Dec *N Engl J Med 1985*
*2.*Angelini *Heart 2000*
*3.*Sarda *JACC 2001*

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

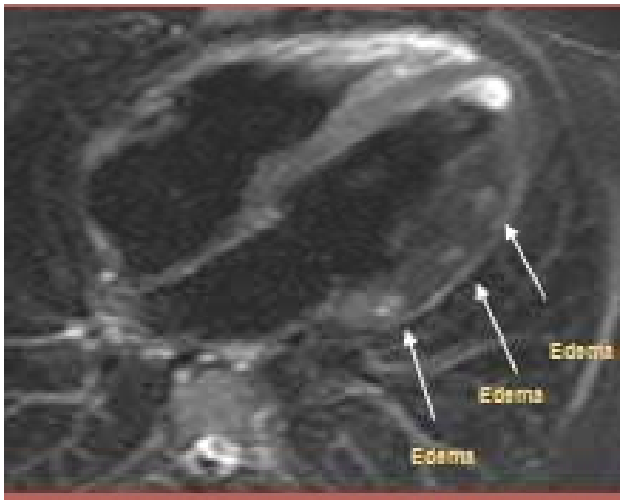
ECO: diametria, FE e cinetica VS normali



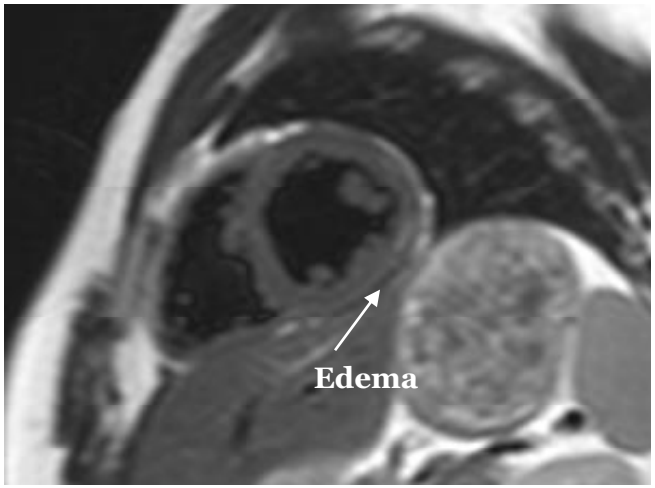
G. Giovanni, - RMC con gadolinio

-

T2
STIR
4 cam



asse
corto



L-E
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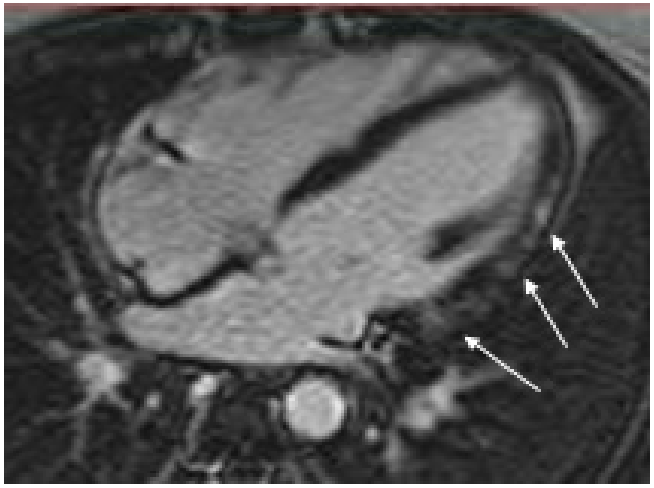
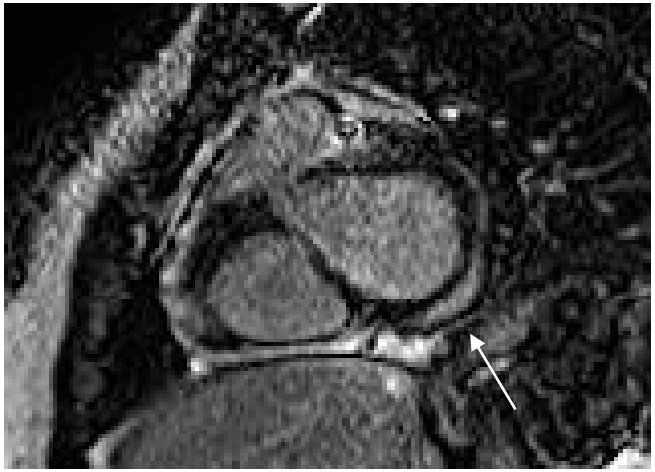
cam

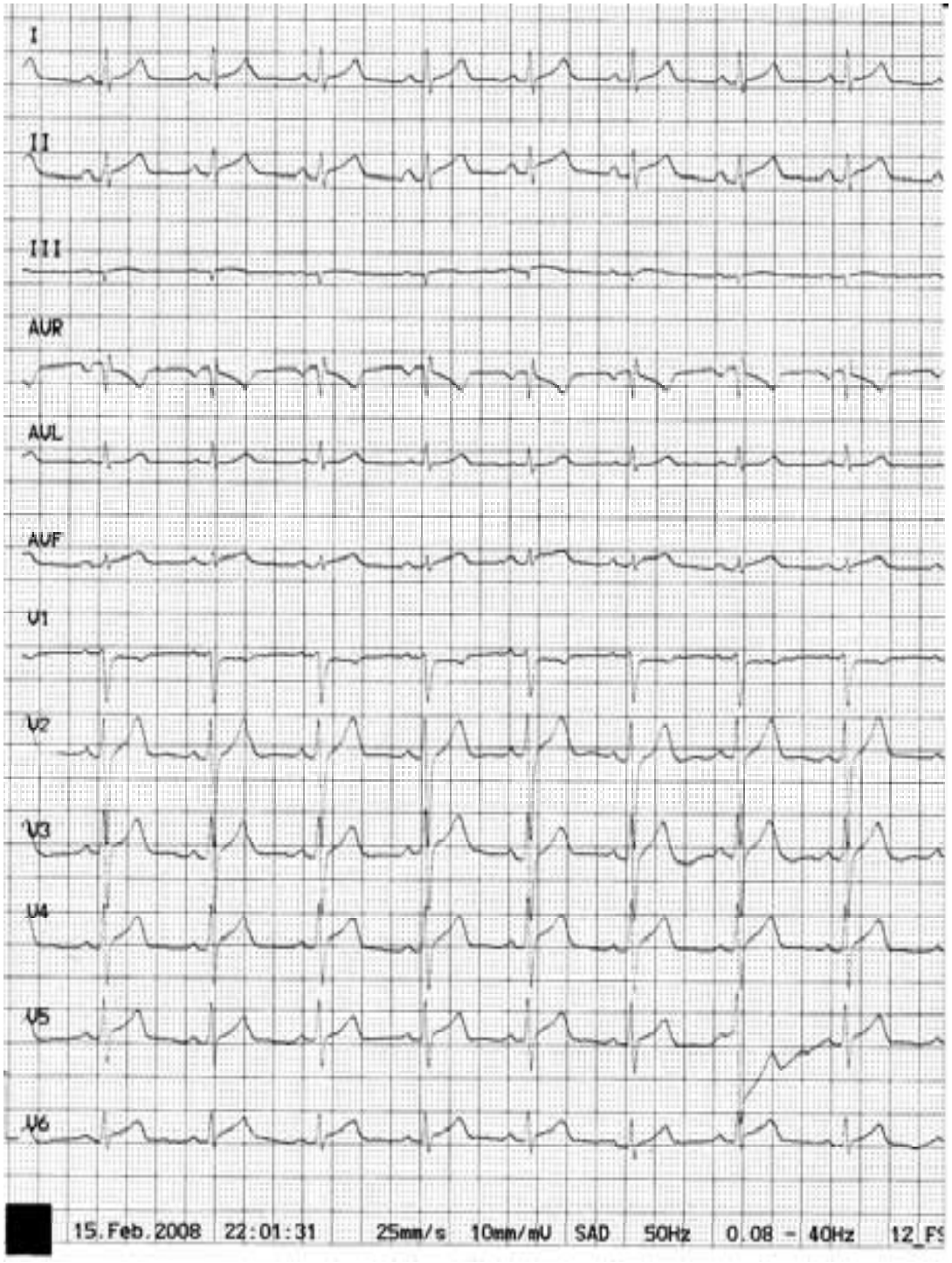




D. Biagio, a. 36

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 y

clinical AMI

-ECG:

STEMI (n=6), non STEMI (n

neg T wave (n=3), Q wave (n

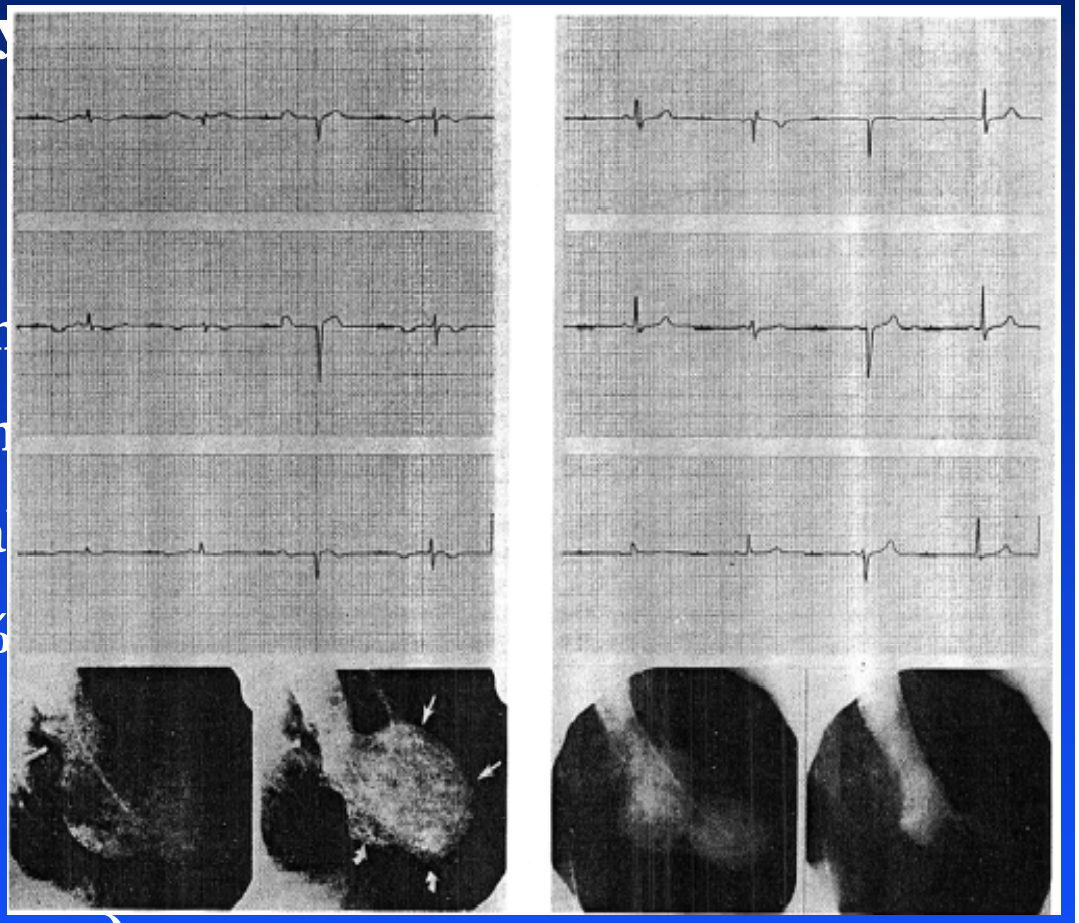
-LVEF: normal (n=6), globa

reduced (n=5, range 14-45%

- Normal coronary arteries

-BEM:

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



Dec WJ, JACC 1992

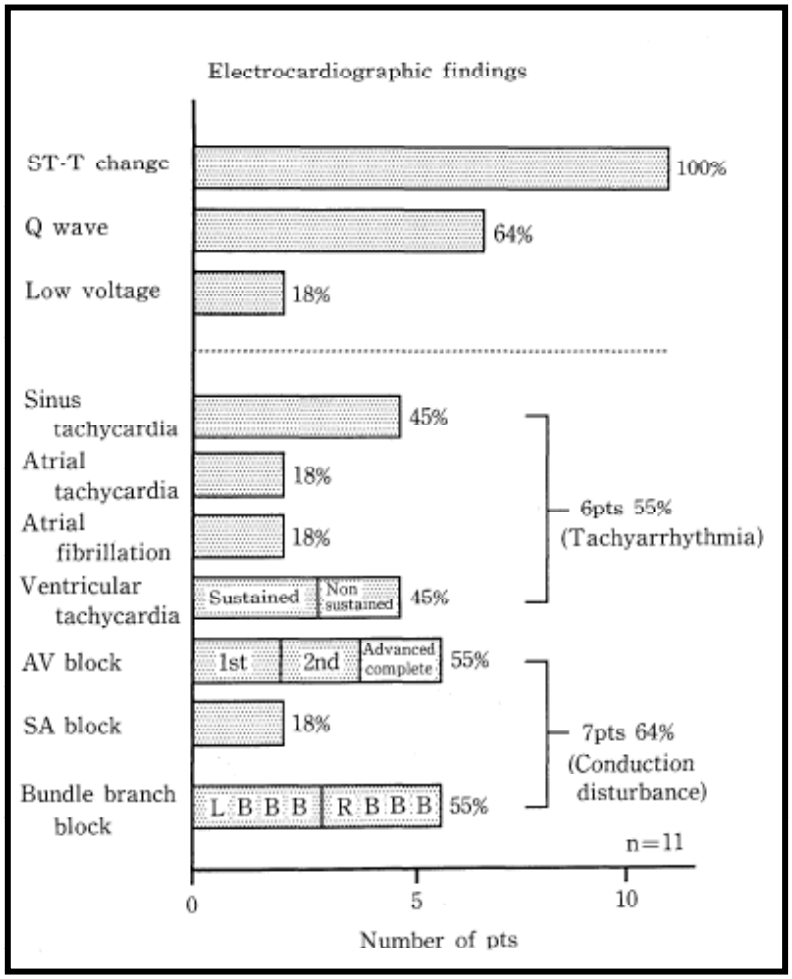
IMA ST-SOPRA

MIOCARDITE

Positività dei markers di danno ischemico
+
Dolore toracico tipico
Modificazioni ECG (ST sopra) suggestive

Serial Electrocardiographic Findings in Acute Myocarditis

Hiroshi NAKASHIMA, Yukiharu HONDA and Tomoyuki KATAYAMA



11 pz.

- **8 con ST sopra / 3 ST sotto**
- **Nessun caso di ST sotto reciproco**
- **Distribuzione delle onde Q non correlate alla sede dell'ST sopra.**

Internal Medicine 1994;33:659

BRIEF REPORT: RECOGNITION OF ACUTE MYOCARDITIS MASQUERADING AS ACUTE MYOCARDIAL INFARCTION

JAGAT NARULA, M.D., BAN AN KHAW, PH.D., G. WILLIAM DEC, JR., M.D., IGOR F. PALACIOS, M.D., JAMES F. SOUTHERN, M.D., PH.D., JOHN T. FALLON, M.D., PH.D., H. WILLIAM STRAUSS, M.D., EDGAR HABER, M.D., AND TSUNEHIRO YASUDA, M.D.

MYOCARDITIS occasionally masquerades as acute myocardial infarction because patients may present with severe chest pain, electrocardiographic changes, and elevated serum levels of creatine kinase. In patients with normal coronary arteries who presumably died of acute myocardial infarction, myocarditis has been reported as an incidental abnormality at autopsy.[1-4] Although there have been anecdotal clinical reports of myocarditis mimicking myocardial infarction in patients with normal coronary arteries, this association has almost always relied on a demonstration of diffuse electrocardiographic abnormalities or a preceding viral illness in young patients with few coronary risk factors.[5-7] In most cases no definitive diagnosis was sought after the patient was found to have normal coronary arteries, and the presence of myocarditis in this setting has only rarely been documented during life by endomyocardial biopsy.[8,9] The ability to recognize myocarditis in patients presumed to have myocardial infarction would be valuable because abnormal ventricular function generally resolves rapidly in such patients and their long-term outcome is usually good.[7,9]

making the diagnosis of myocarditis. The antimyosin scans in these patients were compared with images obtained from 45 patients with acute myocardial infarction and angiographic evidence of coronary artery occlusion.

CASE REPORTS

Patients with Myocarditis Mimicking Myocardial Infarction

Clinical Presentation

The study group comprised four men and four women (age, 26 to 70 years; mean ±SE, 51±6) (Table 1). Five patients had two or three coronary risk factors, two had one risk factor, and the remaining patient had none. No patient was febrile at the time of admission or during hospitalization, although two had an antecedent viral illness of the upper respiratory tract. Because a diagnosis of myocarditis was not considered initially by the patients' physicians, viral antibody titers were not serially evaluated.

All eight patients experienced severe, nonpleuritic precordial pain of sudden onset indistinguishable from that of acute myocardial infarction. One patient arrived at the hospital in cardiogenic shock, and cardiogenic shock developed in another in the hospital. The other six patients had no clinical features suggestive of left ventricular failure. Electrocardiographic changes in the ST segments and T waves were observed in the anterior leads in four patients and the inferior leads in one, with no evidence of reciprocal changes in the ST segments. The electrocardiographic abnormalities were diffuse (i.e., extended beyond a single vascular distribution) in two patients. One patient had left bundle-branch block. Peak serum creatine kinase levels were elevated in six of the eight patients (range, 150 to 1518 units per liter). The MB isoenzyme fractions ranged from 4 to 22 percent (normal values are given in Table 1).

After admission, five patients continued to have intractable or recurrent episodes of chest pain despite therapy directed at reversing ischemia. In all eight patients, the electrocardiographic changes failed to evolve in a pattern typical of acute myocardial infarction. Serum enzyme levels in one patient indicated mild but persistent release of creatine kinase. All eight patients underwent coronary angiography because of recurrent chest pain or doubts about the initial diagnosis of myocardial infarction due to coronary artery disease.

CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

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Case 8-2007: A 48-Year-Old Man with Chest Pain Followed by Cardiac Arrest

Gregory D. Lewis, M.D., Charles B. Holmes, M.D., M.P.H., Godtfred Holmvang, M.D., and Joan R. Butterton, M.D.

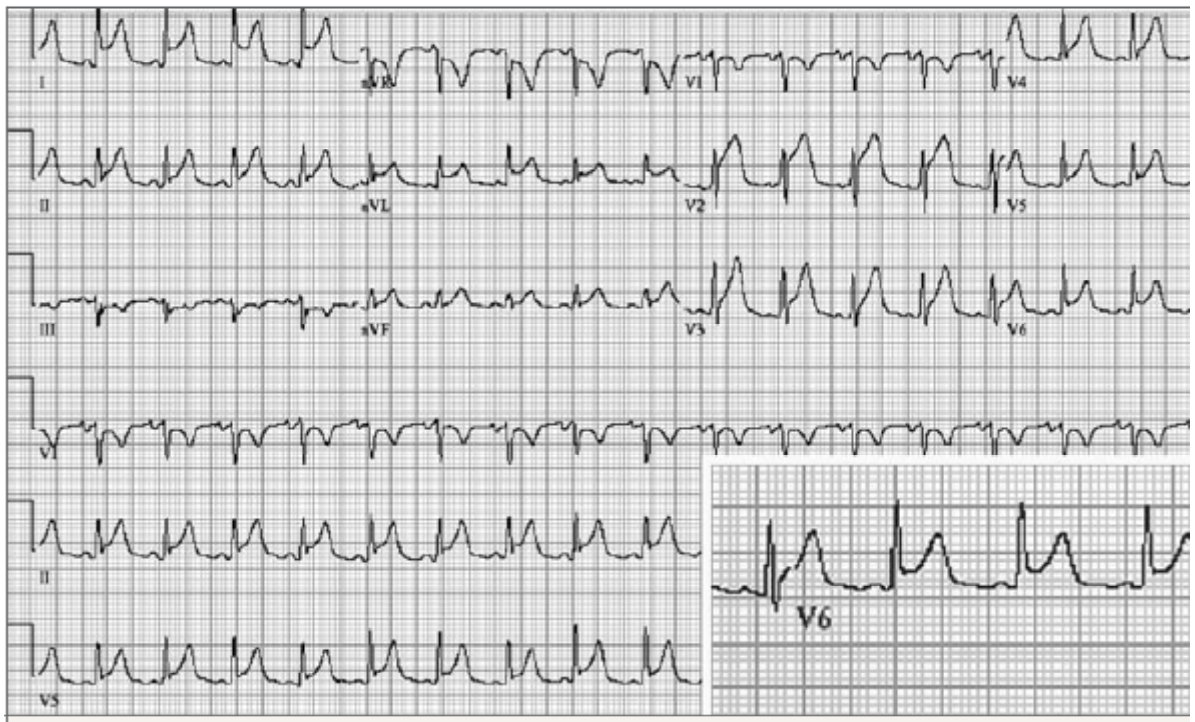


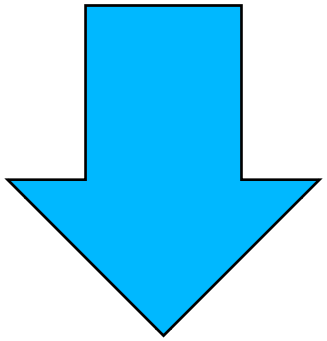
Figure 1. Electrocardiogram Obtained at Presentation.

Table 2. Differential Diagnosis of ST-Segment Elevations on the Electrocardiogram (ECG) in Patients Presenting with Chest Pain.*

Condition	Distribution of ST-Segment Elevations	Associated ECG Features	Associated Clinical Features
Myocardial infarction with occlusive thrombus	Typically confined to a single coronary vascular territory[1] Right coronary artery: Lead III>II, aVF Left circumflex artery: Leads I, aVL, V_5,V_6 Left anterior descending artery: Leads V_1–V_3	Convex ST segment, abnormal Q waves	Elevations in troponin I or T arising within 6–8 hr after the onset of chest pain
Acute pericarditis	Diffuse involvement of precordial and limb leads, associated ST-segment depression in aVR	PR-segment depression, diffuse concave ST segments, and ST:T ratio >0.24 in lead V_6	Clinical triad of chest pain, pericardial friction rub, and diffuse ST-segment elevations
Myocarditis	May mimic either myocardial infarction or pericarditis	May be associated with ventricular or atrial arrhythmias, heart block, or both	Clinical features vary, from asymptomatic abnormalities on ECG to fulminant heart failure and cardiogenic shock
Prinzmetal's angina	Typically confined to a single coronary distribution	Occurs within the distribution of the coronary artery affected by vasospasm[2]	
Pulmonary embolism	Acute right ventricular overload may produce a pattern mimicking right ventricular infarction Leads III, aVF, V_1	Sinus tachycardia, incomplete or complete right bundle-branch block, S1Q3T3 pattern	Often hypoxemia with elevated alveolar–arterial oxygen gradient, and acquired or inherited hypercoagulable state
Type A aortic dissection involving a coronary ostium or the pericardium	Right coronary artery ostium involvement is more common than left main coronary involvement[3] Lead III>II, aVF	If hemopericardium is present, low voltage with tachycardia	Abrupt onset of pain, widened mediastinum (63%),[4] pulse differential
Apical ballooning syndrome	Anteroapical distribution is most common[5] Leads V_2–V_6	Often associated with prolonged QT interval and deep T-wave inversions	Precipitated by profound emotional or physical stress, typically in women
Ventricular contusion	Right ventricular involvement Leads V_1, V_2		Follows blunt trauma; right ventricular involvement most common because of anterior location of the right ventricle[6]

Esordio simil-infartuale / Esordio con SC

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

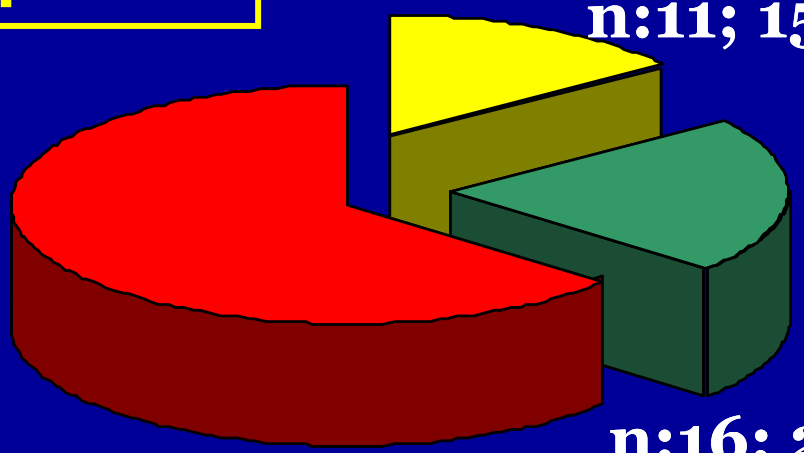


- Dolore toracico intenso
- Modificazioni ST-T
- VS non dilatato
- FE conservata
- Decorso benigno
- Completa guarigione

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

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

TOTALE PAZIENTI
n: 74



n:11; 15%, (M 73%; 38±14 aa

n:16; 22%, (M 81%; 35±14

n:47; 63%, (M 57%; 38±16 aa)

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

CRITERI DI CLASSIFICAZIONE:

✓ Sintomo clinicamente più rilevante all'esordio

Presentation, Patterns of Myocardial Damage, and Clinical Course of Viral Myocarditis

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

Protocollo diagnostico con CRM, EBM, CVG: 128 pz

TABLE 1. Baseline Patient Characteristics

Patient Group	n	Age, y	Sex, M/F	ChestPain	Dyspnea	Malaise	Edema	CK, U/L	Troponin I, μg/L	Symptoms to CMR, d
PVB19	49	42	35/14	49	16	12	2	298	0.75	8
HHV6	16	32	11/5	7	8	3	3	155	0.12	17
PVB+HHV	15	45	11/4	4	10	7	11	62	0.10	21
CBV	1	47	1/0	1	1	1	0	…	…	13
EBV	1	55	1/0	0	1	0	1	…	…	29
No virus	5	42	4/1	3	1	1	2	366	0.94	18
Healing	15	43	13/2	7	4	1	0	81	0.02	29

Age, creatine kinase (CK), troponin I, and symptoms to CMR are mean values. CBV indicates Coxsackie B virus; EBV, Epstein-Barr virus.

”False - Positive” Cardiac Catherization Laboratory Activation Among Patients With Suspected ST-Segment Elevation Myocardial Infarction. (*JAMA* 2007;298:2754)

- **1335 pz con sospetto STEMI**
- **14% (187) Falsi Positivi**

“ A major challenge for the ED physician is the patient who presents with nonspecific symptoms or subtle ST-elevation or QRS repolarization abnormalities that obscure or mimic ST segment elevation.
In these cases, **is it best to immediately activate the catheterization laboratory, considering the consequences of a false alarm, or take the time to obtain additional data, such as from serial ECGs, biomarkers, or an Echo ?”**

Table 2. Etiologies of False-Positive Cardiac Catheterization Laboratory Activation in Patients Without a Culprit Artery (n = 187)

Etiologies by Biomarker Results		No.
Negative biomarker results (n = 123)		
Early repolarization		25
Nondiagnostic electrocardiogram		21
Pericarditis		20
Previous myocardial infarction		20
Left bundle-branch block		11
Left-sided ventricular hypertrophy		8
Vasospasm		4
Tachycardia related		3
Right bundle-branch block		3
Pacemaker		3
Brugada syndrome		1
Aortic dissection		1
Unknown		3
Positive biomarker results (n = 64)		
Stress cardiomyopathy		17
Myocarditis	31%	15
Previous myocardial infarction		9
ST-elevation myocardial infarction–embolic/spasm		9
Left bundle-branch block		4
Non–ST-elevation myocardial infarction		2
Pulmonary embolus		2
Aortic neoplasm		1
Severe aortic stenosis		1
Drug overdose		1
Unknown		3

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)**

- **Alterazioni tratto ST dubbie… (concavità in alto, diffuse, o infero-laterali, non ST-sotto reciproco).**
- **Troponina positiva, anche precocemente…**
- **CK-MB massa di poco/non elevato.**

Myocarditis

Diagnostic Evaluation

- Biopsy
- Cardiac Biomarkers
- Immunologic Approaches
- Myocardial Imaging
  - Echocardiography
  - MRI

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

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

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

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

Indications for Endomyocardial Biopsy

Exclusion of potential common etiologies of dilated cardiomyopathy (familial; ischemic; alcohol; postpartum; cardiotoxic exposures) and the following:

- Subacute or acute symptoms of heart failure refractory to standard management
- Substantial worsening of EF despite optimized pharmacological therapy
- Development of hemodynamically significant arrhythmias, particularly progressive heart block and ventricular tachycardia
- Heart failure with concurrent rash, fever, or peripheral eosinophilia
- History of collagen vascular disease such as systemic lupus erythematosus, scleroderma, or polyarteritis nodosum
- New-onset cardiomyopathy in the presence of known amyloidosis, sarcoidosis, or hemachromatosis
- Suspicion for giant cell myocarditis (young age, new subacute heart failure, or progressive arrhythmia without apparent etiology)

Adapted with permission from Wu et al.[78]

Indications for Endomyocardial Biopsy

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Adapted with permission from Wu et al.[78]

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

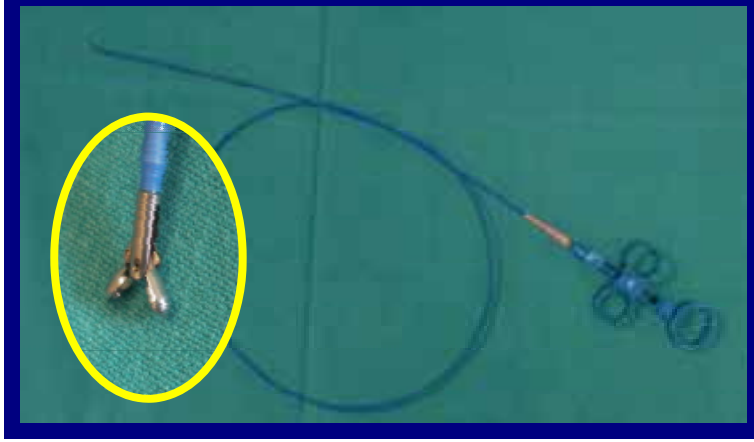
Condizione patologica sospettata	Potenzialità diagnostiche della BEM	Annotazioni tecniche	Standards diagnostici della malattia
Miocarditi	**Diagnosi di certezza** **Altre informazioni:** -grading ed attività della malattia	**Importante** -timing della BEM -numero/ Rappresentatività BEM **Necessarie** -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

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)*



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"

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

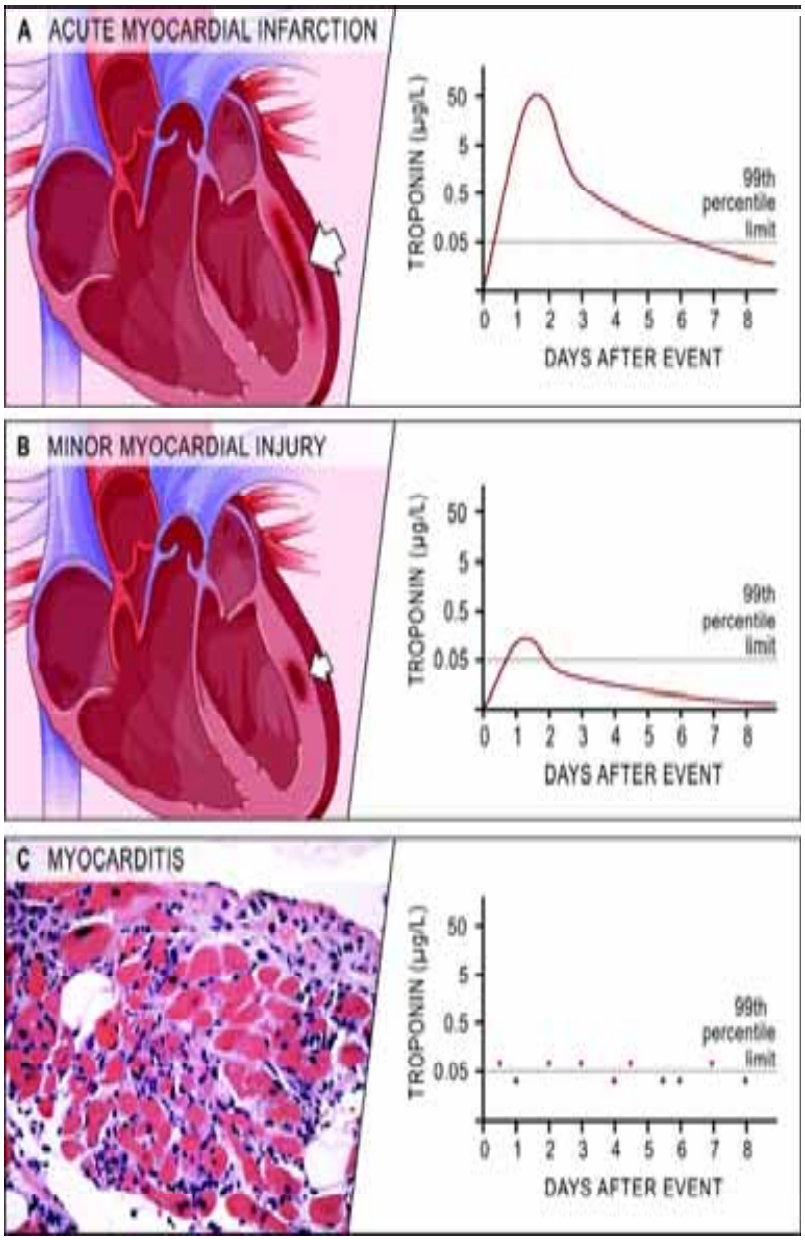
Cardiac Biomarkers

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

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

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

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

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)

Myocarditis

Diagnostic Evaluation

MRI

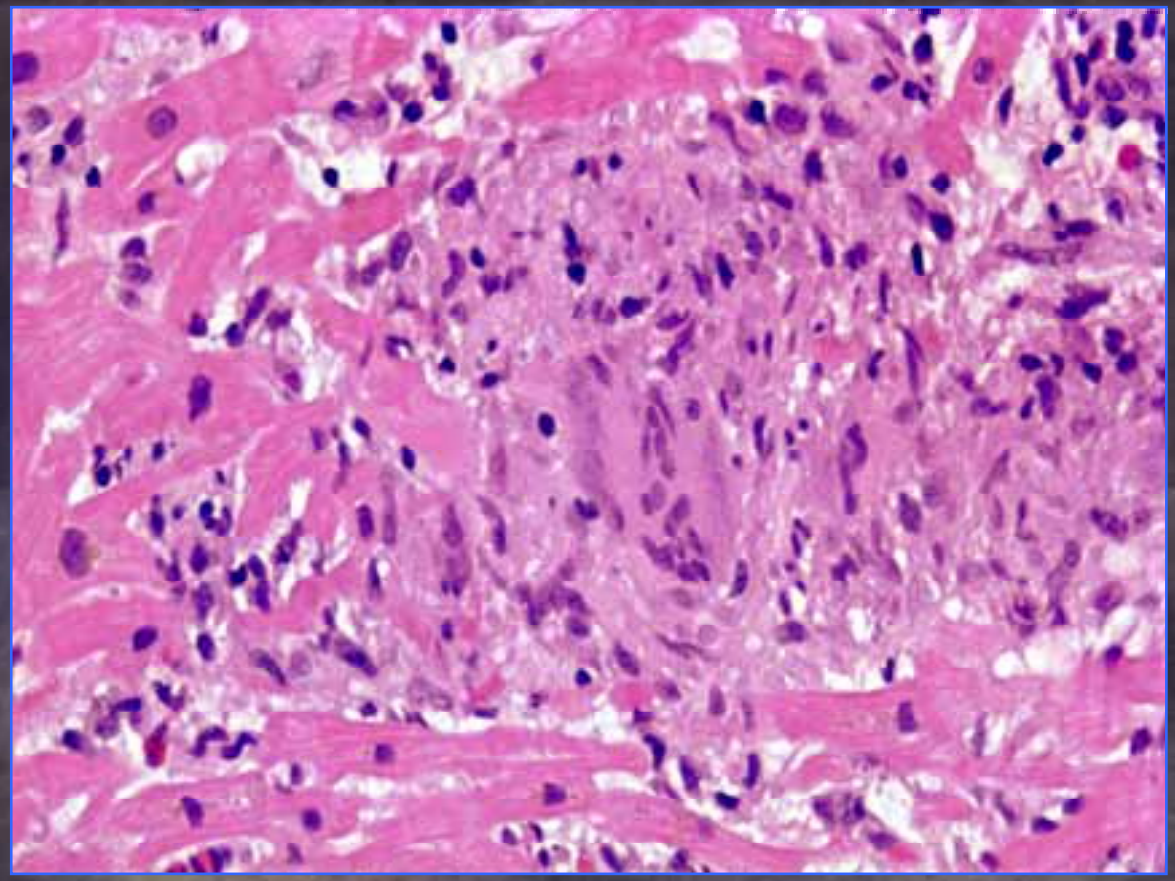
- Appears to be the most promising technique for diagnosing myocardial inflammation and myocardial injury
- Focal myocardial enhancement combined with regional wall motion abnormalities
- Biopsy of these specific myocardial regions resulted in positive predictive value of 71% and negative predictive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

Myocarditis

Natural History

- **Myocarditis masquerading infarction**: full recovery
- **Smallpox vaccine-associated myocarditis:** rapid resolution
- **Giant cell myocarditis:** poorest outcomes (median survival 5.5 months) (<20% surviving 5 years)

Giant Cell Myocarditis



Microscopy (H&E, High Power)

Giant Cell vs Lymphocytic Myocarditis

Transplant-Free Survival from Presentation

Cooper LT: NEJM, 1997

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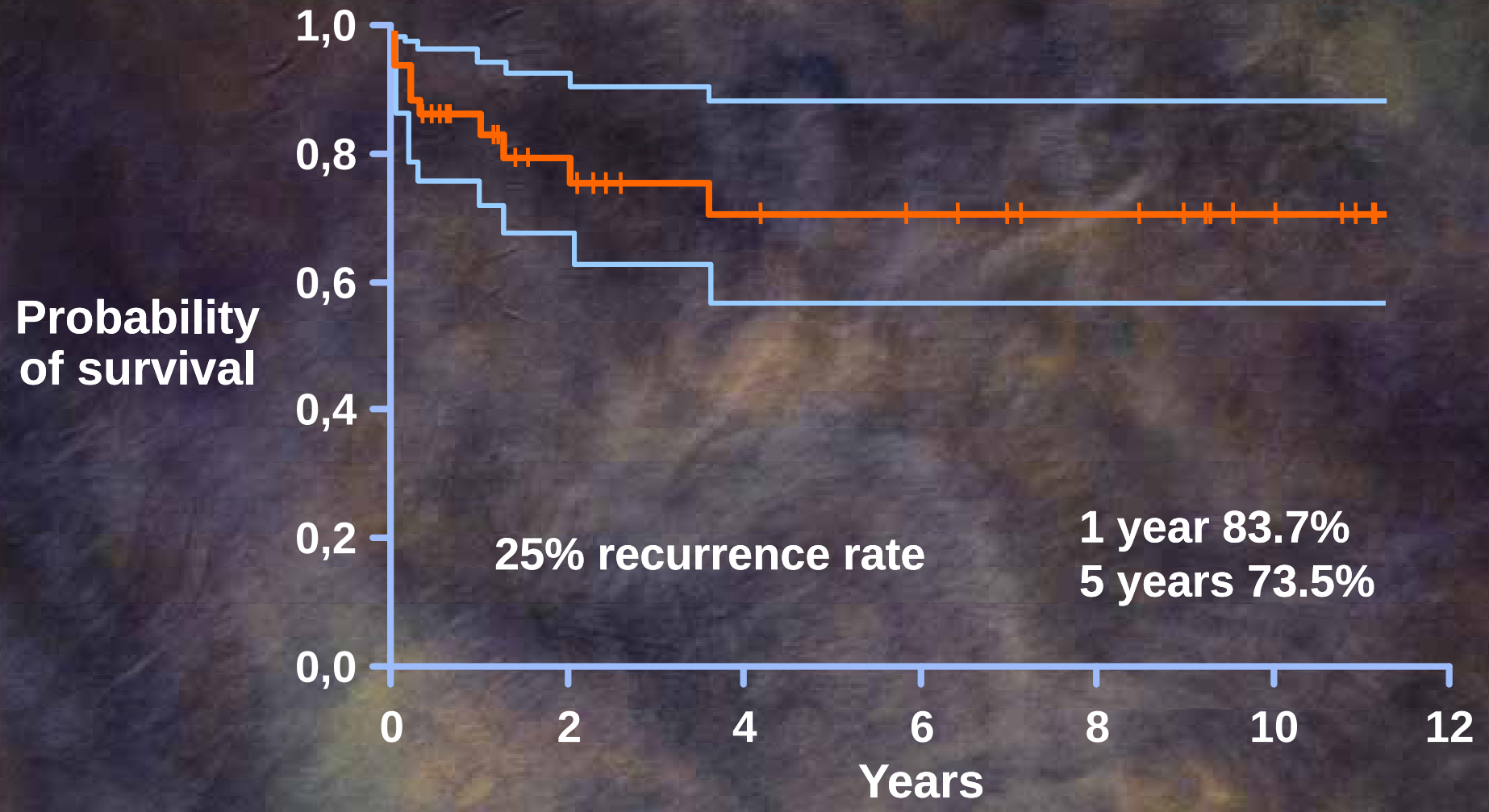
Immunosuppressive Treatment for GCM

	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



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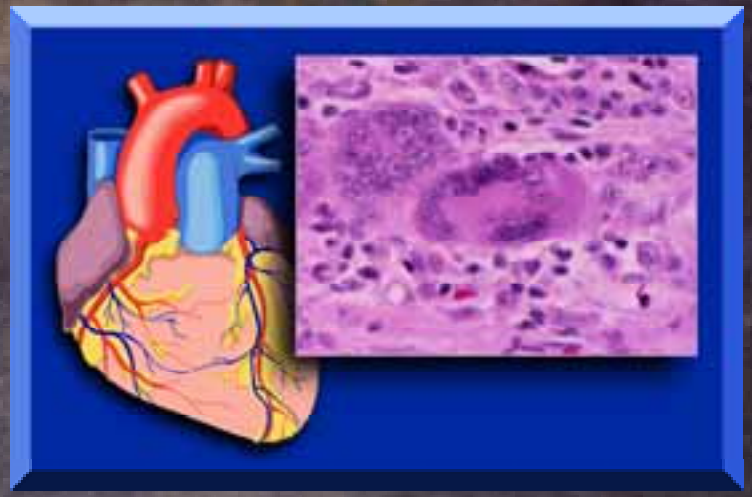
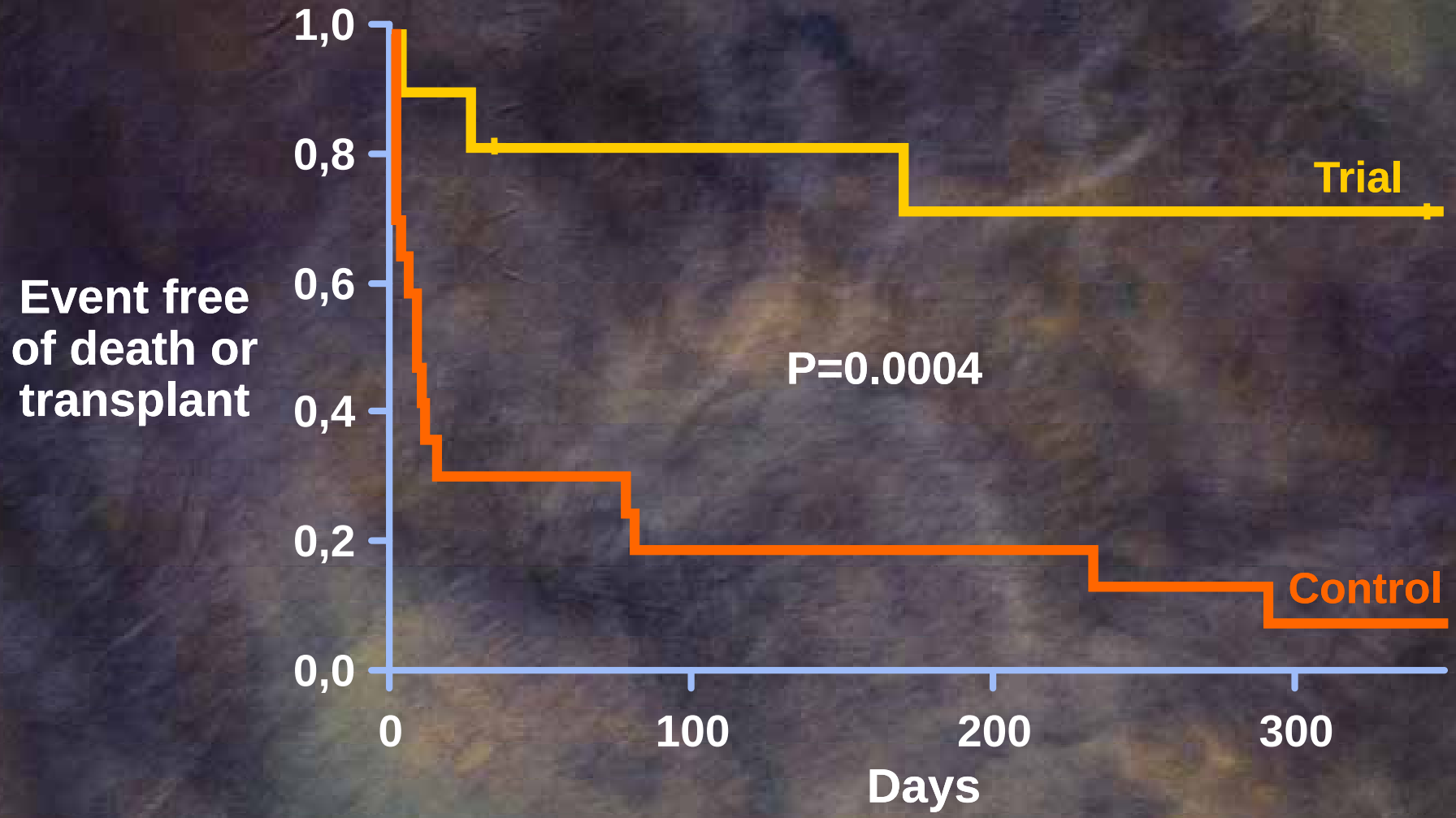
The Giant Cell Myocarditis Treatment Trial and Registry

- 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



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Patients who present with HF

Myocarditis: Evolution

- Substantial recovery in LVEF% in about 50% of p
- 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 increased immunosuppression

Myocarditis

Natural History

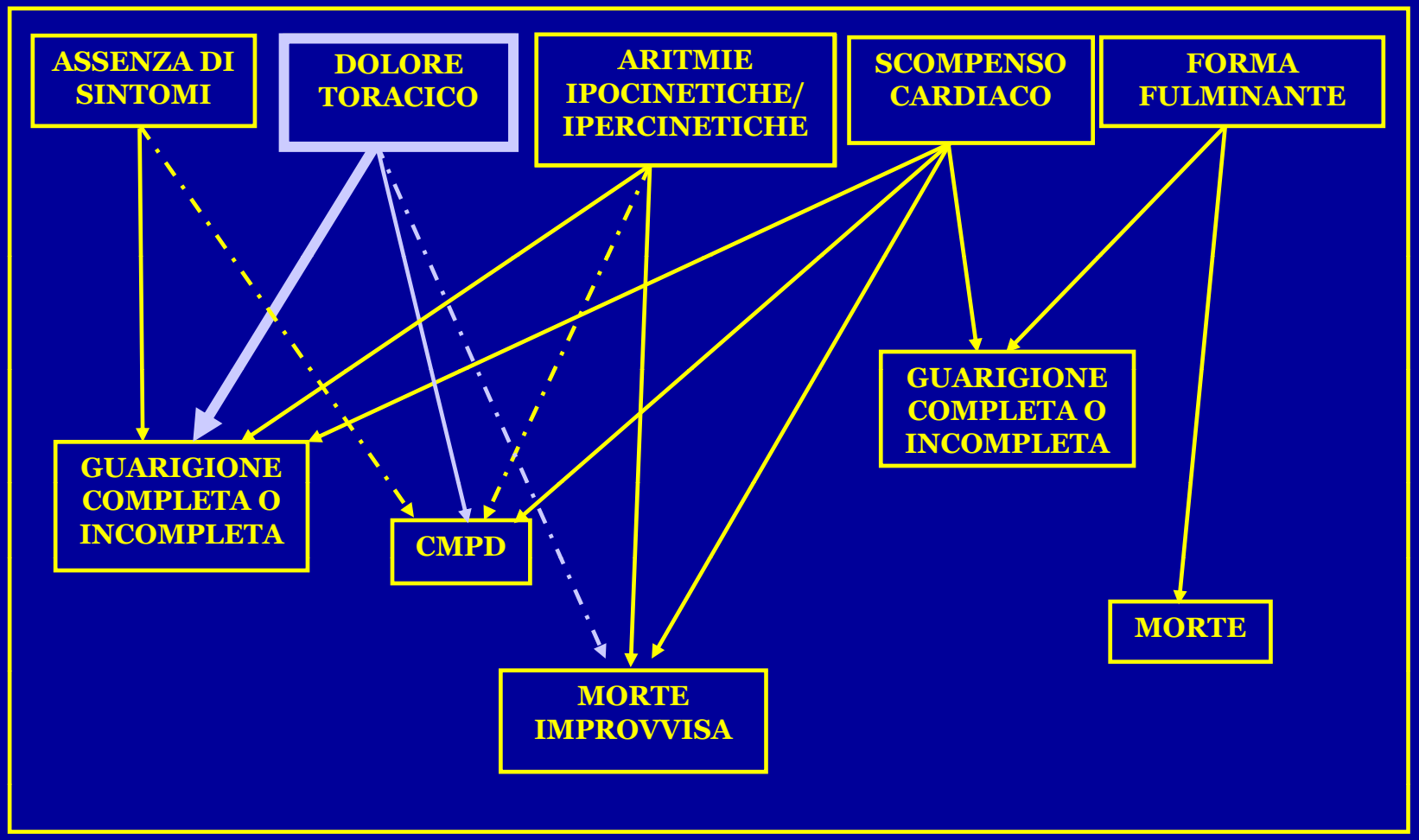
- Predicting prognosis remains problematic

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

  - Genomic analysis of biopsy: conflicting results

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

OCARDITI: Polimorfismo di Presentazione ed Evoluzione



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.

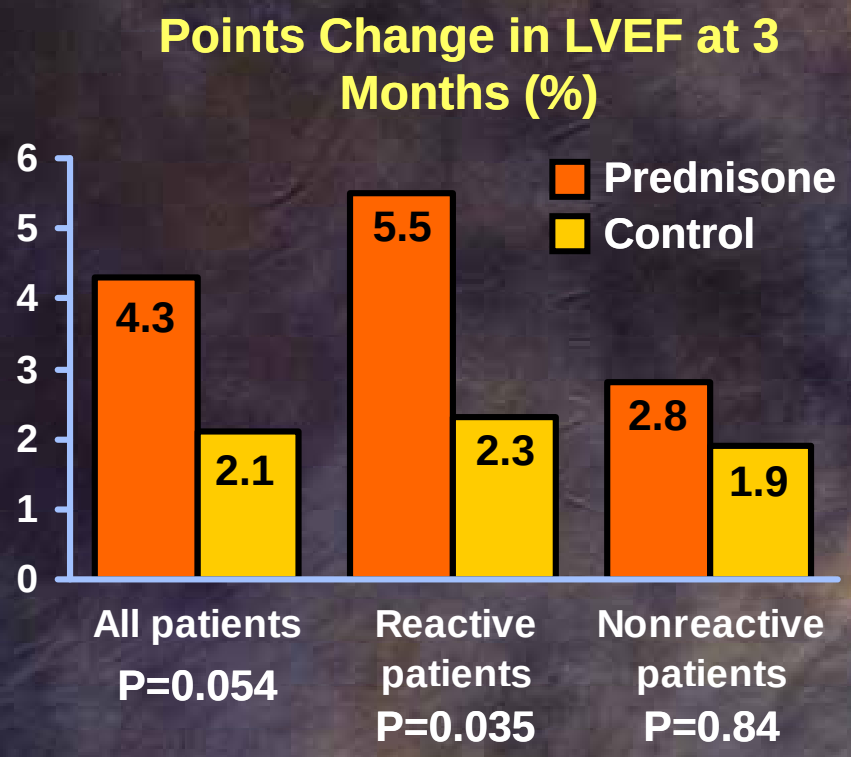
Immunosoppression ?

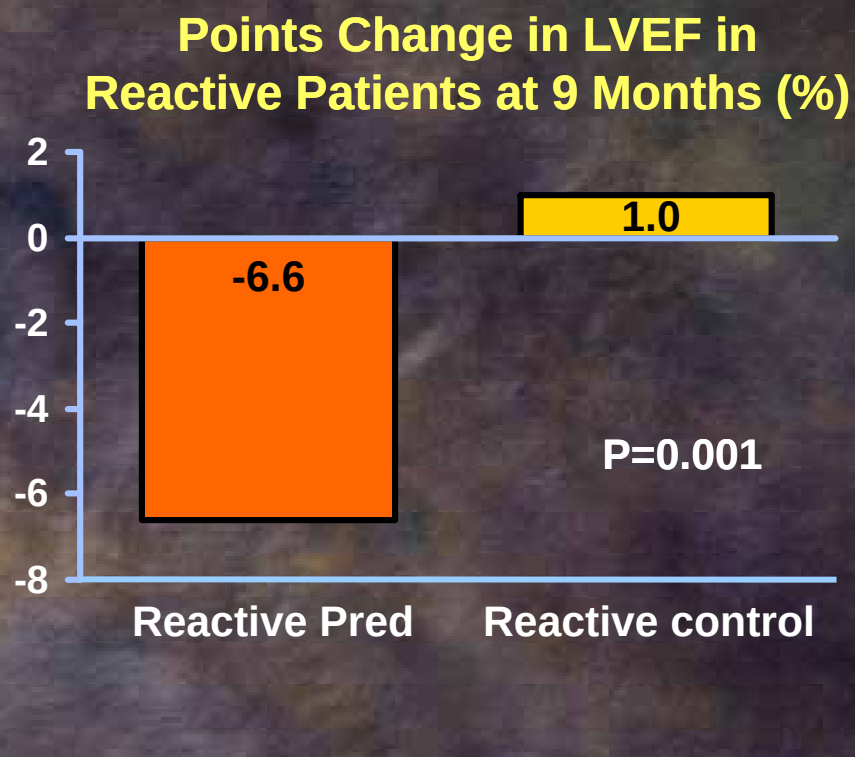
- Long-term sequelae appear to be related to abnormal cellular and humoral immunity
- > 20 uncontrolled observational studies reported successs with a variety of immunosoppressive agents
- BUT several caveats……..
  - Histological resolution of inflammation does not correlate with improvement in ventricular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

Previous controlled trials of immunosuppression in myocarditis/DCM: *Parrillo et al, NEJM 1989*

- 102 pts with IDC with inflammation (n=60, reactive) or without (n=42, non reactive) randomised to daily PDN (60 mg/day) or no PDN for 3 mo, then alternate day PDN for 6 mo
  - Reactive if one or > of the following criteria: fibroblastic or lymphocytic infiltration or Ig deposition on EMB, a positive Gallium scan or high ESR
  - Endpoint: increase in LVEF ≥5%; not statistically powered for survival
- daily PDN produced improved LVEF overall and in reactive pts with IDC at 3 mo, no longer present at 9 mo
- This study suggested that a subset of IDC pts might respond to PDN, but the "reactive" group was too heterogeneous to produce a substantial response to therapy.

Prednisone in DCM





Reactive patients with chronic DCM may respond to Immunosuppressive therapy

Parillo JE: NEJM, 1989

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Previous controlled trials of immunosuppression in myocarditis/DCM: Mason et al, NEJM 1995

- 111 pts with myocarditis (Dallas Criteria) randomised to 6 mo immunosuppression (PDN and CsA or azathioprine) vs control
  - Endpoint: LVEF at 6 and 12 mo; not statistically powered for survival
- Results: in both treatment and control groups LVEF increased at 6 and 12 mo, with no difference between the groups. Treatment was well tolerated.
- If one uses the 5% increase in LVEF as definition of improvement, significantly more pts in the immunosuppression group improved compared to controls.

Limitations of the MTT (Mason et al, NEJM 1995)

- Only 78 of 111 pts with myocarditis (Dallas Criteria) randomised to 6 mo immunosuppression vs control were followed up for 12 mo, so 30% of pts were lost to follow-up
- Poor reproducibility of Dallas criteria:
  - Pathology review panel disagreed with the original diagnosis of myocarditis in 39% of the 111 pts
- Lack of characterization of pts in relation to viral and/or immune-mediated pathogenesis.

Immunosuppressive Treatment of Inflammatory DCM

Objective

Determine if immunosuppressive therapy improves mortality & outcomes in patients with HLA upregulation on EMB

Eligibility

- EF < 40%
- Onset of CHF > 6 mo
- HLA expression on EMB

n = 202

Randomization

- Pred/AZA
- Placebo

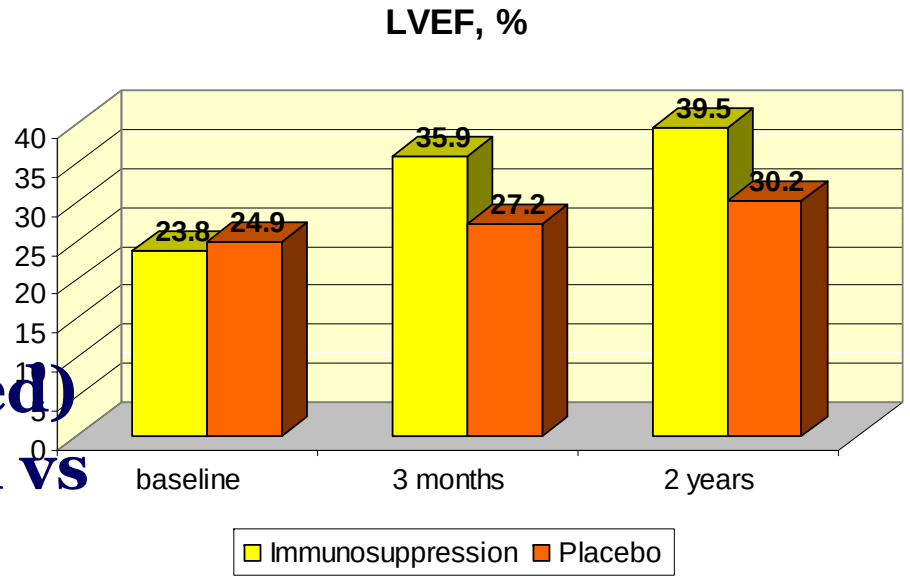
Wojnicz R. Circulation, 2001

'ABLE 2. Continued

	1-Year Follow-Up			2-Year Follow-Up			
	Mean±SD	95% CI	*P*	n	Mean±SD	95% CI	*P*
0	31.5±12.9	5.48–17.73	0.001	30	30.9±13.6	6.94–19.04	<0.001
8	43.1±10.0			28	43.9±9.1		
0	204.7±72.6	19.44–88.09	0.003	30	205.2±78.4	29.35–98.68	<0.001
8	150.9±57.9			28	141.2±48.8		
0	148.4±67.0	17.42–77.37	0.002	30	152.5±74.8	25.85–89.71	0.001
8	101.0±45.5			28	94.7±40.2		
0	62.9±9.9	2.57–12.94	0.004	30	62.4±11.5	3.73–15.07	0.0
8	55.2±9.9			28	52.9±10.0		
0	2.0	1.0, 2.0	0.165	30	2.0	1.0, 3.0	0.0
8							

IT i

Immunosuppressive ther is beneficial in patients w DCM & HLA upregulation on EMB



Limitations:
NS for survival (not powered)
No characterization of viral vs autoimmune DCM

jnicz et al. Circulation 2001; 104: 39-45

Immunomodulation therapy of myocarditis with intravenous immune globulin

- Effective in murine viral myocarditis
- Associated with increased LV function in:
  - pediatric pts with "presumed" acute myocarditis of unspecified etiology (Viral? Autoimmune?) vs historical controls

    Drucker et al, Circulation 1994
  -
  - adult pts with recent onset CHF with "presumed" acute myocarditis of unspecified etiology and in women with peri-partum cardiomyopathy

    McNamara et al, Circulation 1997
    Bozkurt, J Am Coll Cardiol 1999
- No significant effect in the randomized placebo-controlled IMAC trial of recent-onset DCM of unspecified etiology

  McNamara et al, Circulation 2001

IMAC Trial

Objective

Determine if IVIG improves LVEF in patients with recent onset DCM or myocarditis

Eligibility

- CHF
- EF <40%
- Onset of symptoms <6 months

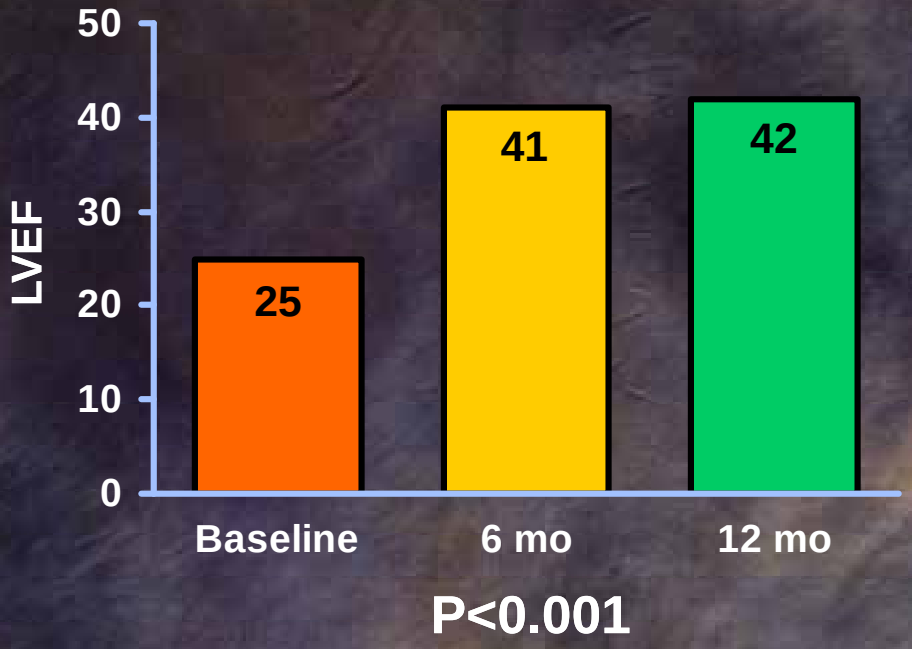
n=62, 37 males, mean age 43
EMB+ 16%

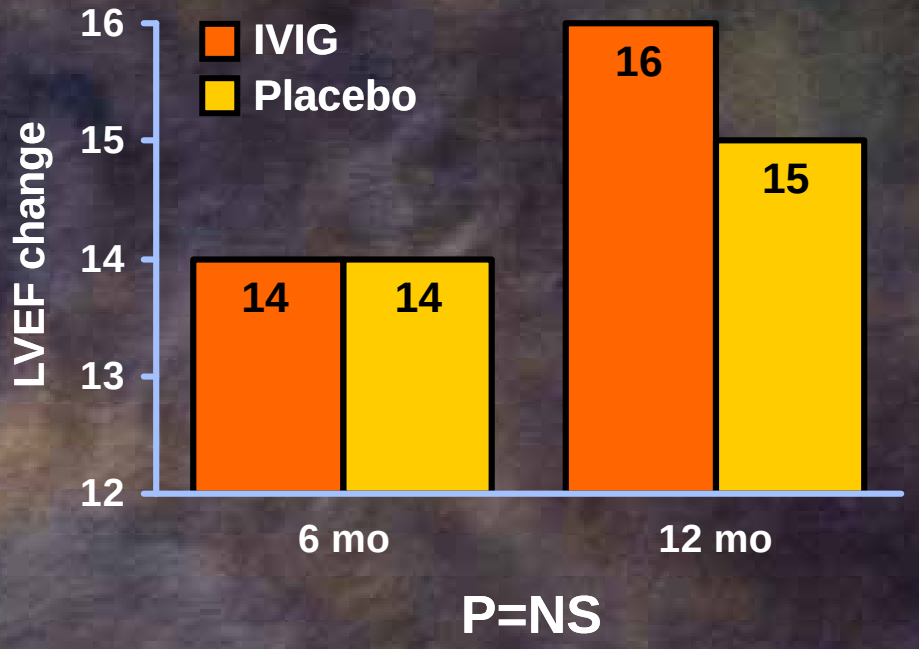
Randomization

- IVIG
- Placebo

McNamara DM: Circ, 2001

IMAC Trial





No improvement in LVEF at 6 or 12 months

McNamara DM: Circ, 2001

MAYO CLINIC

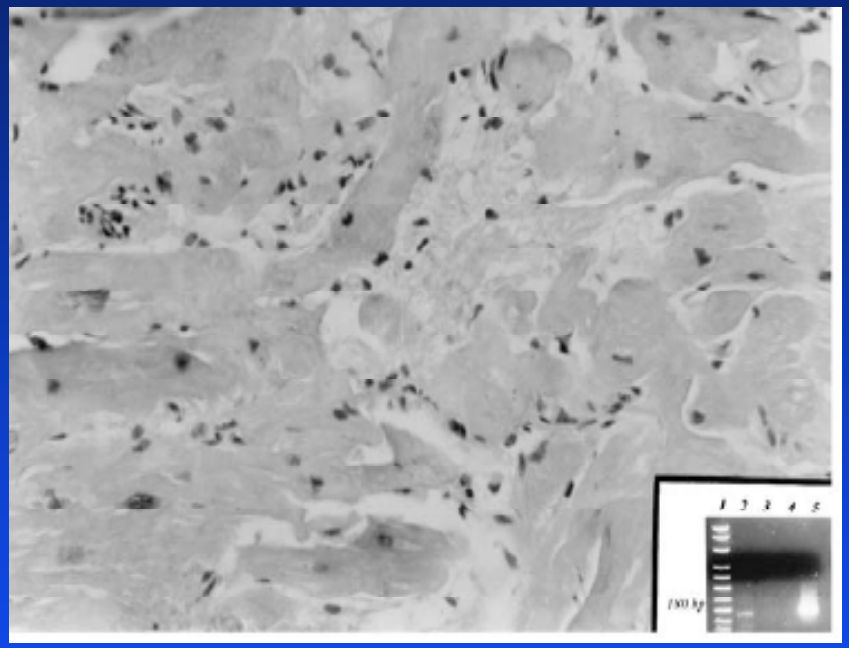
CP1184266-13

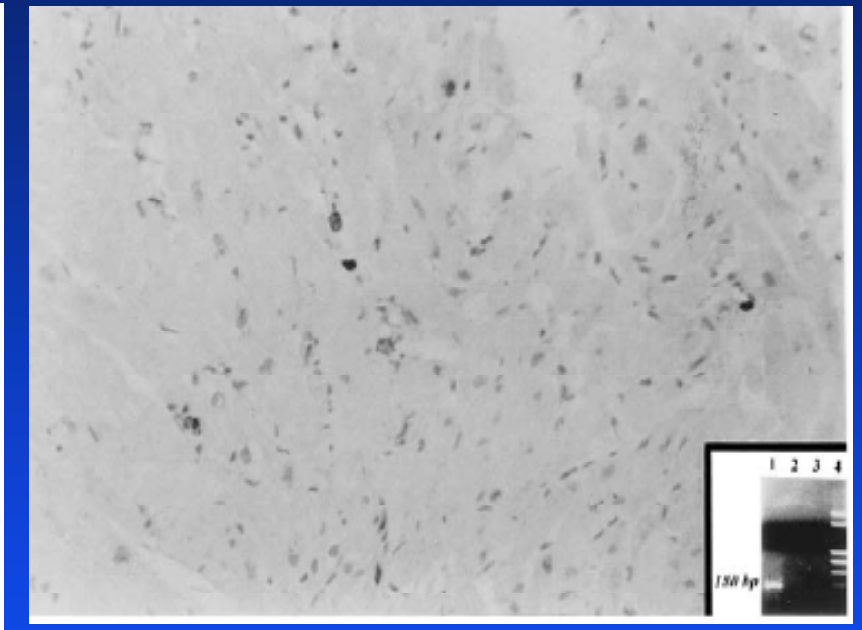
Anti-viral therapy of myocarditis with interferon

- Effective in murine viral myocarditis
- Associated with improved LV function and/or NYHA in:
  - Small uncontrolled studies in pts with "biopsy-proven" myocarditis of enteroviral etiology (diagnosis based on PCR) Stille-Siegener et al, Eur Heart J 1995
  - Small randomised, open label, study of adult pts with "biopsy-proven" myocarditis or dilated cardiomyopathy of "presumed" enteroviral etiology (diagnosis based on viral serology) Miric et al, Heart 1996
- No randomized placebo-controlled trials (ESETCID ongoing) Maisch et al, Eur Heart J 1995

Successful Treatment of Enterovirus-induced Myocarditis With Interferon-α

Daliento et al,





No randomized, placebo-controlled studies have investigated interferon-α therapy in enterovirus-proven myocarditis. This report describes 2 patients with enterovirus-induced myocarditis (1 with associated Churg-Strauss syndrome) who at follow-up endomyocardial biopsy showed clinical and hemodynamic improvement and viral clearance (using polymerase chain reaction) after interferon-α therapy. J Heart Lung Transplant 2003;22:214–217.

Interferon-β Treatment Eliminates Cardiotropic Viruses and Improves Left Ventricular Function in Patients With Myocardial Persistence of Viral Genomes and Left Ventricular Dysfunction

n = 22 EMB+ viral genome
n = 14 enteroviruses persistence
n = 8 adenoviral persistence

IFN-beta x 6 months

Viral genome on EMB
Complete elimination in all pts

EMB
Cessation of inflammatio & CAM expression

12-mo clinical follow-up
LVEF improved
•HF symptoms improved

Kuhl U. Circulation, 2003

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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