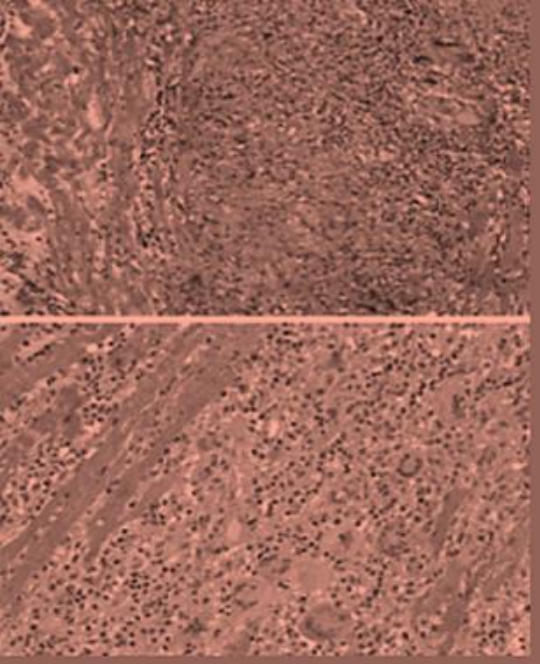
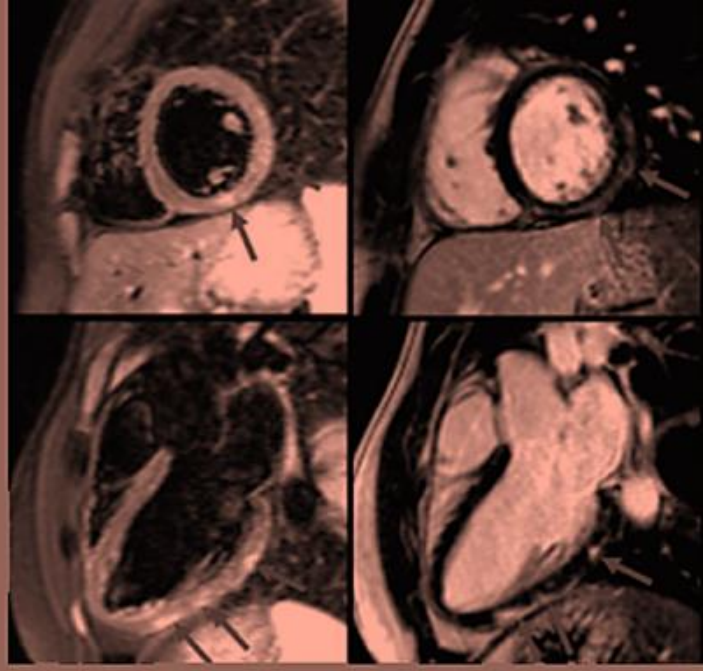




Miocarditi

Alla ricerca di certezze

Dr. Giuseppe Schembri
Tutor e Direttore: Prof.ssa Giuseppina Novo

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

ESC REPORT

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

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4],

*Myocarditis is a **challenging** diagnosis due to **heterogeneity** of clinical presentations. The actual **incidence** of myocarditis is also difficult to determine as **endomyocardial biopsy, the diagnostic gold standard**, is used infrequently…*

Definizione

Definitions

Myocarditis (WHO /ISFC[1]):

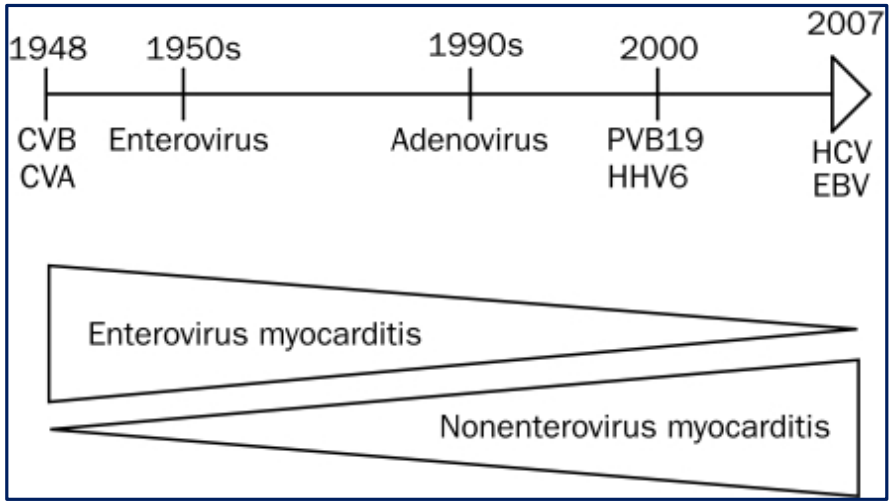
Inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria**.*

Eziologia

G Ital Cardiol 2013; 14: 504

Eziologia virale

Negli anni si è assistito ad una sorta di deriva epidemiologica delle specie virali associate più frequentemente a miocardite (Coxackievirus negli anni ‘50-’90, Adenovirus negli anni ‘90, Parvovirus B19 e HHV6 a partire dal 2000).



Eziologia non virale

Infettive: B. burgdorferi (malattia di Lyme), T. cruzi (malattia di Chagas)

Malattie autoimmuni (fino al 20% dei pazienti con miocardite gigantocellulare ha storia di malattie autoimmuni)

Ipersensibilità a farmaci

Heymans S, JACC vol 68, no 21, 2016

Patogenesi

Nature Reviews Cardiol 2015; 108

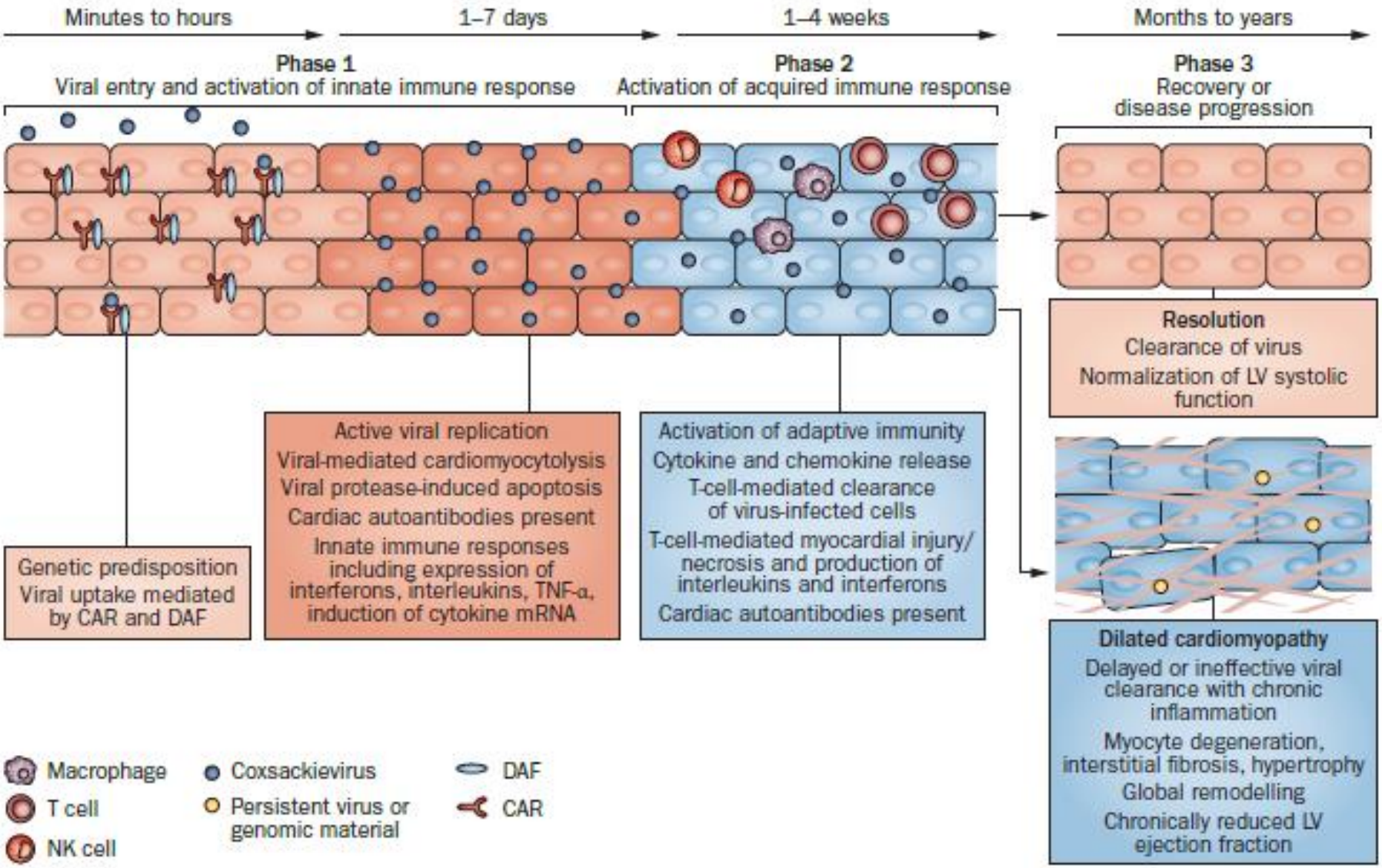
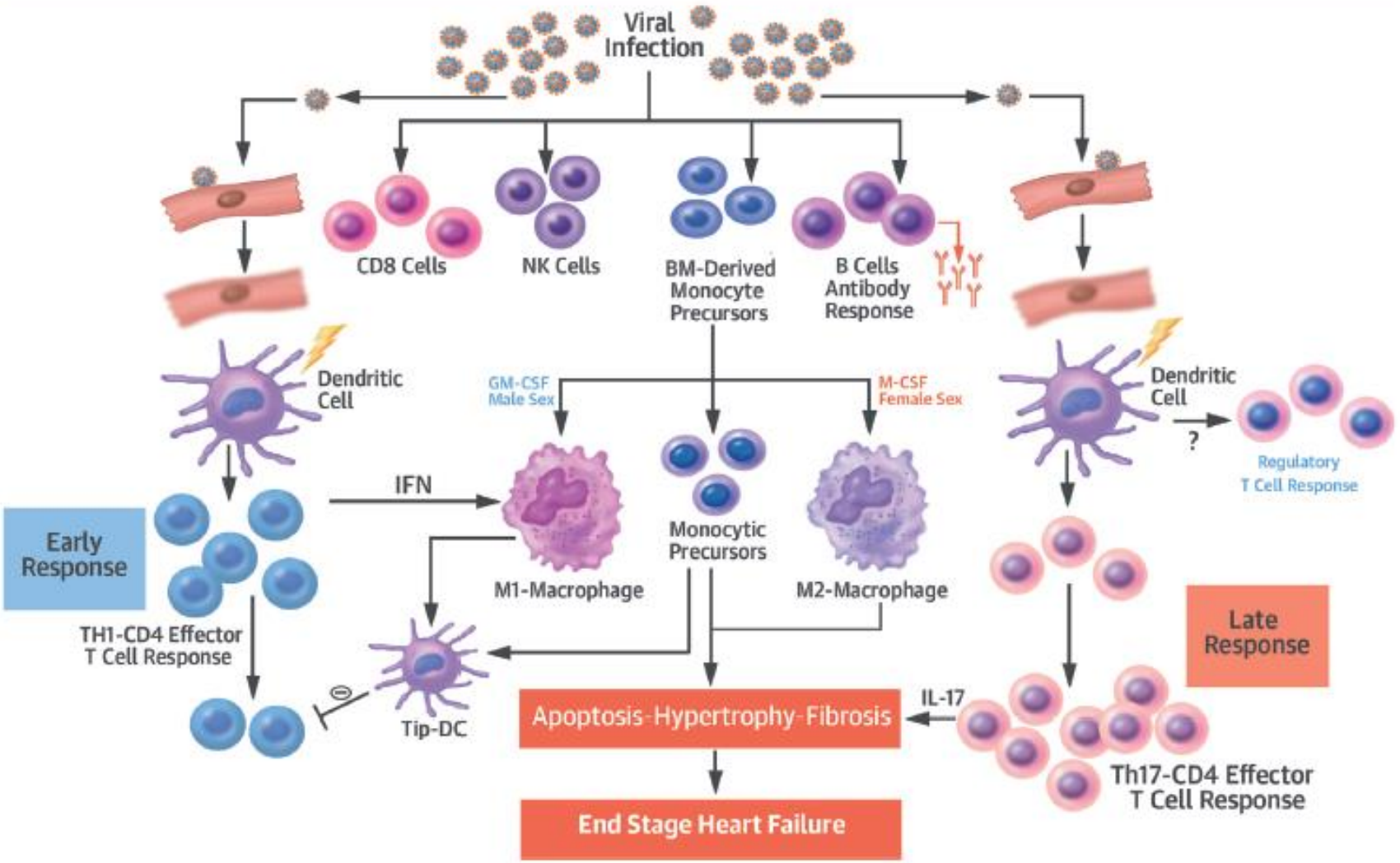


FIGURE 2 Important Cellular Compartments Involved in Early Myocarditis and Progression to End-Stage Heart Failure

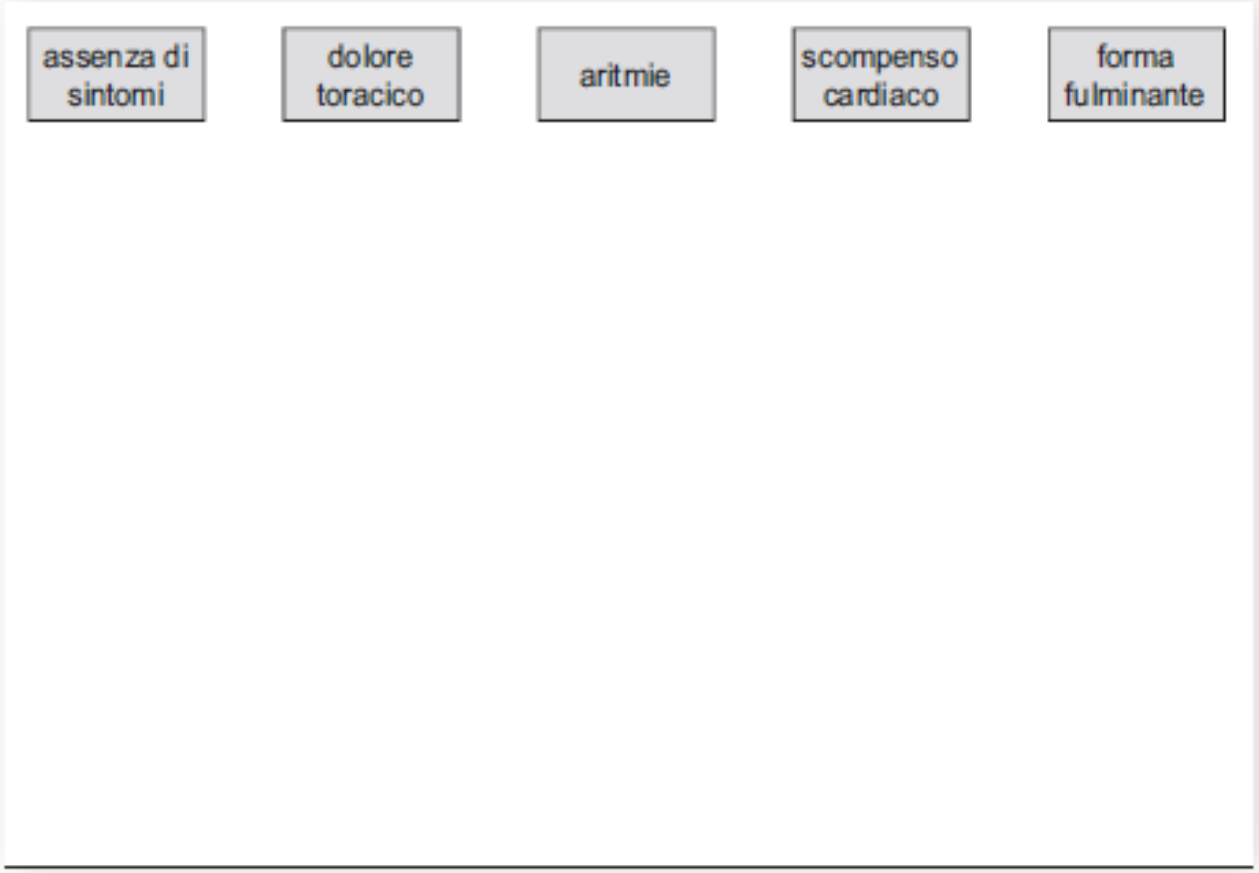


(Left) Early inflammation is a predominantly Th1-driven process, with an important role for M1 macrophages. In contrast, M2 macrophages and Th17 responses characterize late responses. IL-17 is a key cytokine in dilated cardiomyopathy progression. Tip-DCs are key elements of a negative, nitric oxide-dependent feedback loop limiting effector T-cell responses. **(Right)** Heart-infiltrating monocytic precursors are the cellular source of acute inflammation and tissue fibrosis, a hallmark of end-stage heart failure. BM = bone marrow; DC = dendritic cell; GM-CSF = granulocyte-macrophage colony stimulating factor; IFN = interferon; IL = interleukin; M-CSF = macrophage colony-stimulating factor; NK = natural killer; Tip-DC = tip-dendritic cell.

G Ital Cardiol 2013; 14: 504

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra



Diagnosi

European Heart Journal (2013) 34, 2636–2648
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ESC REPORT

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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)

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ESC REPORT

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Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4],

Recommendations

7. Troponins, erythrocyte sedimentation rate, reactive C protein levels should be assessed in all patients.
8. Routine viral serology testing is not recommended.
9. Serum samples should be assessed, if possible, for cardiac aabs, if one (or more) of the published tests is available (*Table 2*), according to specific centre expertise. Disease-specific aabs should preferably be tested.

European Heart Journal (2013) 34, 2636–2648
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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

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4],

Troponin and BNP levels

While cardiac troponins are more sensitive of myocyte injury in patients with clinically suspected myocarditis than creatine kinase levels,[140,141] they are non-specific and when normal do not exclude myocarditis.[142] This also applies to cardiac hormones such as brain natriuretic peptides,[143] circulating cytokines,[144] markers related to extracellular matrix degradation,[145] and new biomarkers such as pentraxin 3, galectin 3, and growth differentiation factor 15.[146]

ELSEVIER

International Journal of Cardiology 127 (2008) 17–26

International Journal of Cardiology

www.elsevier.com/locate/ijcard

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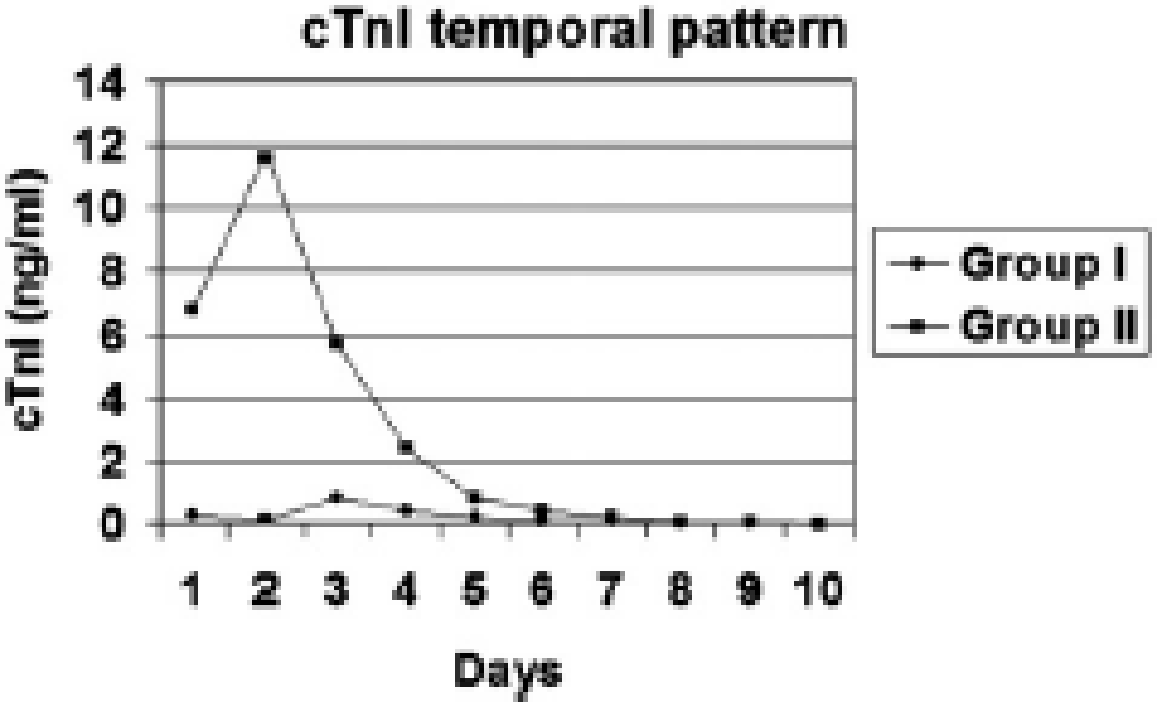

Fig. 3. Different temporal patterns of troponin release in pericarditis: fast clearance for elevations below the threshold for acute myocardial infarction (group I), acute coronary syndrome-like pattern when troponin is above the threshold for acute myocardial infarction (group II).

Transplantation Proceedings 2009; 41: 2234

Low Troponin-I Levels on Admission Are Associated With Worse Prognosis in Patients With Fulminant Myocarditis

X. Freixa, A. Sionis, Á. Castel, E. Guasch, P. Loma-Osorio, D. Arzamendi, E. Roig, and F. Perez-Villa

ABSTRACT

Background. The clinical outcomes of patients with fulminant acute myocarditis (FAM) range from death to complete recovery. We sought to identify clinical, biological, and echocardiographic characteristics of prognostic value for this population.

Methods and Results. We prospectively included 185 patients with the diagnosis of acute myocarditis who were admitted to our institution between 2000 and 2007, selecting 15 who displayed FAM, namely, severe congestive heart failure or cardiogenic shock, requiring inotropic and/or mechanical circulatory support. Their mean age was 27.9 ± 12.4 years (range, 12–52) and mean left ventricular ejection fraction (LVEF) was 22 ± 8.4% (range, 10–35). Seven subjects had poor outcomes, defined as death ($n = 4$), urgent transplantation ($x = 2$), or persistent left ventricular dysfunction ($n = 3$). The other 6 individuals experienced complete recovery of ventricular function. Troponin-I values below 1 ng/mL on admission were significantly associated with greater in-hospital ($P = .05$) and mid-term poor outcomes ($P = .001$). Additionally, patients with poor outcomes showed significantly lower LVEF (17.6 ± 6.2% vs 28.8 ± 6.9%; $P = .006$).

Conclusion. Among patients with FAM, normal or minimal elevation of troponin-I and low LVEF on admission were associated with worse in-hospital and mid-term prognosis.

J Card Fail 2016; 22: 583

Johns Hopkins Hospital database EMB (2000 → 2014)

6 GCM – 36 non-GCM

GCM : TnI picco = <0.06 – 0.09 – 0.3 – 1.8 – 15.4 – 26.6 (quelli con valori più bassi: estesa necrosi alla BEM) (5 paz MCS e/o Tx, 4 dei quali morti)

Non-GCM : TnI picco da 0.0… a 192 ng/ml (mediana 0.6)

Conclusioni: data l'ampia variabilità, TnI non può essere usata come marker prognostico per GCM. Inoltre un livello basso non esclude la miocardite, per cui non può essere un motivo per decidere di non fare la biopsia endomiocardica

European Heart Journal (2013) 34, 2636–2648
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ESC REPORT

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Recommendations

7. Troponins, erythrocyte sedimentation rate, reactive C protein levels should be assessed in all patients.
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European Heart Journal (2011) 32, 897–903
doi:10.1093/eurheartj/ehq493

CLINICAL RESEARCH
Myocardial disease

Virus serology in patients with suspected myocarditis: utility or futility?

Felix Mahfoud[1]*, Barbara Gärtner[2], Michael Kindermann[1], Christian Ukena[1], Katharina Gadomski[1], Karin Klingel[3], Reinhard Kandolf[3], Michael Böhm[1], and Ingrid Kindermann[1]

Aims Serological analyses of viral infection in suspected myocarditis are still widely used, although convincing evidence for their value is lacking. We determined prospectively the diagnostic value of virus serology in comparison with endomyocardial biopsy (EMB) including viral genome detection and immunohistochemistry in patients with clinically suspected myocarditis.

Methods and results Virus serology and state-of-the-art evaluation of EMB were performed in 124 patients (age 40 ± 15 years) with suspected myocarditis. Endomyocardial biopsy was studied for inflammation with histological and immunohistological criteria. The viral genome was detected in the myocardium by polymerase chain reaction. Acute viral infection

*…for patients with suspected myocarditis virus serology has **NO** relevance for the diagnosis of myocardial infection…*

Conclusions For patients with suspected myocarditis, virus serology has no relevance for the diagnosis of myocardial infection. Endomyocardial biopsy remains the gold standard in the diagnostic of viral myocarditis.

European Heart Journal (2011) 32, 897–903
doi:10.1093/eurheartj/ehq493

CLINICAL RESEARCH
Myocardial disease

Virus serology in patients with suspected myocarditis: utility or futility?

**Felix Mahfoud[1]*, Barbara Gärtner[2], Michael
Katharina Gadomski[1], Karin Klingel[3], Reinha
Ingrid Kindermann[1]**

Ricerca di anticorpi **specifici** utile nel contesto di quadri clinici particolari:
- BAV avanzati
- lesioni cutanee
- manifestazioni articolari

(Diagnosi di miocardite **batterica** da Borrelia, Rickettsia, Corynebacterium Diphtheriae)

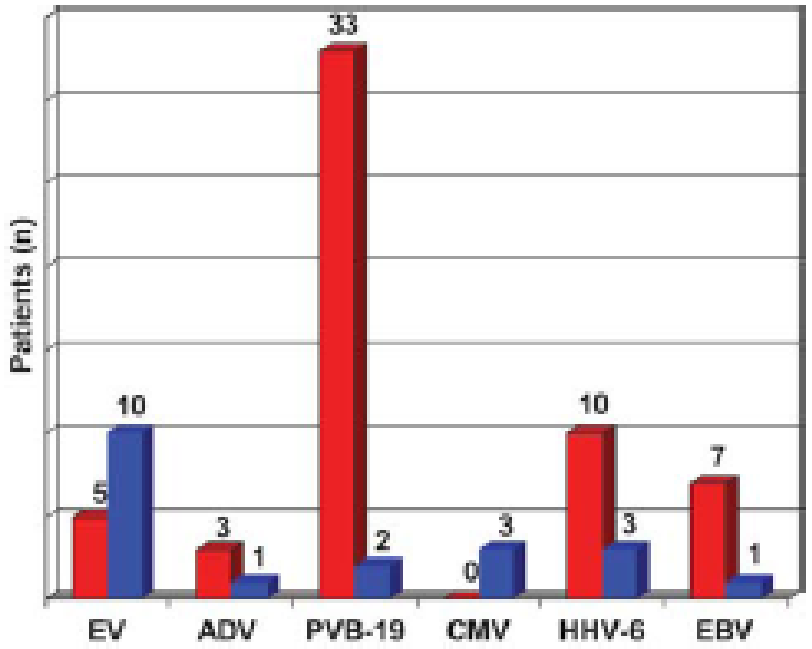

Figure 2 Prevalence of RNA- and DNA viral infection in cardiac tissue (red) and serology (blue) in patients with suspected myocarditis. EV, enterovirus (RNA); ADV, adenovirus (DNA); PVB-19, parvovirus B19 (DNA); CMV, cytomegalovirus (DNA); HHV-6, human herpesvirus (DNA) 6; EBV, Epstein-Barr virus (DNA).

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

Table 5 Diagnostic cardiac magnetic resonance criteria for myocarditis

In the setting of clinically suspected myocarditis (*Tables 3–4*), CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

(1) Regional or global myocardial signal intensity increase in T2-weighted oedema images[a]
(2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images[b]
(3) There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)[c]

A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present

A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if

- None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation
- One of the criteria is present

The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis

Table reprinted with permission from (20).
[a]Global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥2.0. If the edema is more subendocardial or transmural in combination with a colocalized ischaemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.
[b]A global SI enhancement ratio of myocardium over skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45% is consistent with myocarditis.
[c]Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

6. Cardiovascular magnetic resonance may be considered in clinically stable patients prior to EMB. Cardiovascular magnetic resonance does not replace EMB in the diagnosis of myocarditis and should not delay EMB in life-threatening presentations.

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

…CMR imaging can be useful in making the diagnosis of myocarditis and for monitoring disease progression, but ***we strongly endorse the concept that EMB should be the gold standard for the diagnosis****…this implies that* ***all patients with suspected myocarditis should undergo an EMB****…which is not routine practice; moreover, current guidelines recommended EMB only in a limited number of clinical scenarios that not include some common presentations of myocarditis, g.e. pseudo-infarction…*

Recommendation

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

ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Col *ythm Society and*

Endorsed *abilitation*

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.[318] Routine endomyocardial biopsy is not recommended in all cases of HF, given limited diagnostic yield and the risk of procedure-related complications.

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis which can be confirmed only in myocardial samples and specific therapy is available and effective.	IIa	C	93

93. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. 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 Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2007;**28**:3076–3093.

AHA/ACCF/ESC Scientific Statement

Circulation 2007; 116: 2216

The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

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

AHA/ACCF/ESC Scientific Statement

Circulation 2007; 116: 2216

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

Leslie T. Cooper, MD, FAHA, FACC; Kenneth L. Baughman, MD, FAHA, FACC; Arthur M. Feldman, MD, PhD, FAHA, FACC; Andrea Frustaci, MD; Mariell Jessup, MD, FAHA, FACC; Uwe Kuhl, MD; Glenn N. Levine, MD, FAHA, FACC; Jagat Narula, MD, PhD, FAHA; Randall C. Starling, MD, MPH; Jeffrey Towbin, MD, FAHA, FACC; Renu Virmani, MD, FACC

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

Clinical Scenario 1

EMB should be performed in the setting of unexplained, new-onset heart failure of ≤*2 weeks'* duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise. *Class of Recommendation I, Level of Evidence B.*

Clinical Scenario 2

EMB should be performed in the setting of unexplained new-onset heart failure of *2 weeks' to 3 months'* duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular (AV) heart block, or failure to respond to usual care within 1 to 2 weeks. *Class of Recommendation I, Level of Evidence B.*

Hum Pathol 1987; 18: 619

Myocarditis:

The Dallas Criteria

Myocarditis

By definition,[1] the diagnosis of myocarditis can be made only if myocyte necrosis or degeneration or both associated with an inflammatory infiltrate adjacent to the degenerating or necrotic myocytes can be demonstrated (fig. 1).

TABLE 1. Classification of Myocarditis

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

Heart 1996;75:295–300

Immunohistological evidence for a chronic intramyocardial inflammatory process in dilated cardiomyopathy

U Kühl, M Noutsias, B Seeberg, H-P Schultheiss

Special Report

Circulation 2006; 113: 593

Diagnosis of Myocarditis

Death of Dallas Criteria

Kenneth L. Baughman, MD

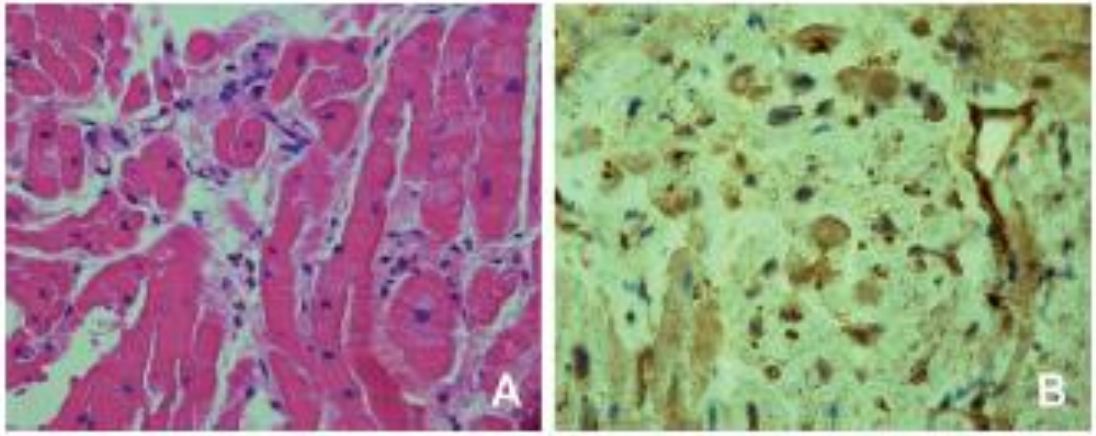

Figura 2. Biopsia endomiocardica. *A:* miocardite con infiltrati linfocitari attivi (colorazione ematossilina-eosina, 20x). *B:* miocardite con evidenza di immunoattivazione. Immunoistochimica (marcatore LN3) per espressività antigeni HLA a livello delle miocellule, interstizio e vasi (colorazione bruna sul fondo miocellulare azzurro, ingrandimento 63x). Gentile concessione della prof.ssa R. Bussani, Istituto di Anatomia Patologica, Università degli Studi di Trieste.

Immunoistochimica

Figura 3. Reazione polimerasica a catena. Corsa elettroforetica su gel di Agarosio del prodotto di amplificazione del gene NS1 di Parvovirus B19 da tre campioni di biopsia endomiocardica.
Gentile concessione della dr.ssa S. Moimas, International Centre for Genetic Engineering and Biotechnology (ICGEB) di Trieste.

Ricerca genoma virale (PCR = Polymerase Chain Reaction)

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ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.09.074

STATE-OF-THE-ART PAPER

Update on Myocarditis

Ingrid Kindermann, MD,* Christine Barth,* Felix Mahfoud, M
Matthias Lenski, MD,* Ali Yilmaz, MD,† Karin Klingel, MD,
Udo Sechtem, MD,† Leslie T. Cooper, MD,§ Michael Böhm,

Homburg/Saar, Stuttgart, and Tübingen, Germany; and Rochester,

Ruolo prognostico dell'immunoistochimica

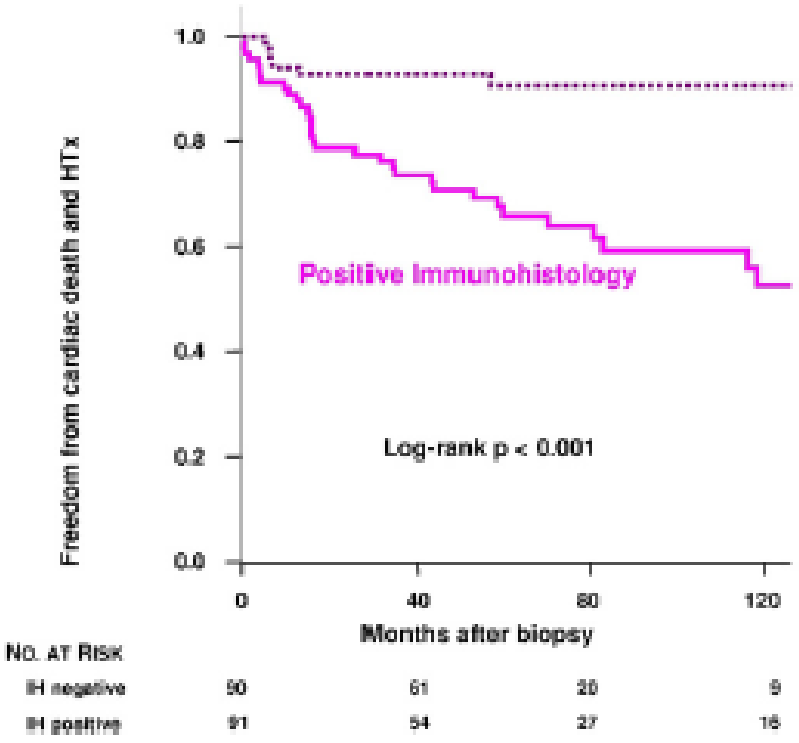


Figura 6 **Freedom From Cardiac Death and HTx by Endomyocardial Biopsy Findings, IH Results**

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

RASSEGNA

G Ital Cardiol 2013; 14: 504

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra

Dipartimento Cardiovascolare, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste

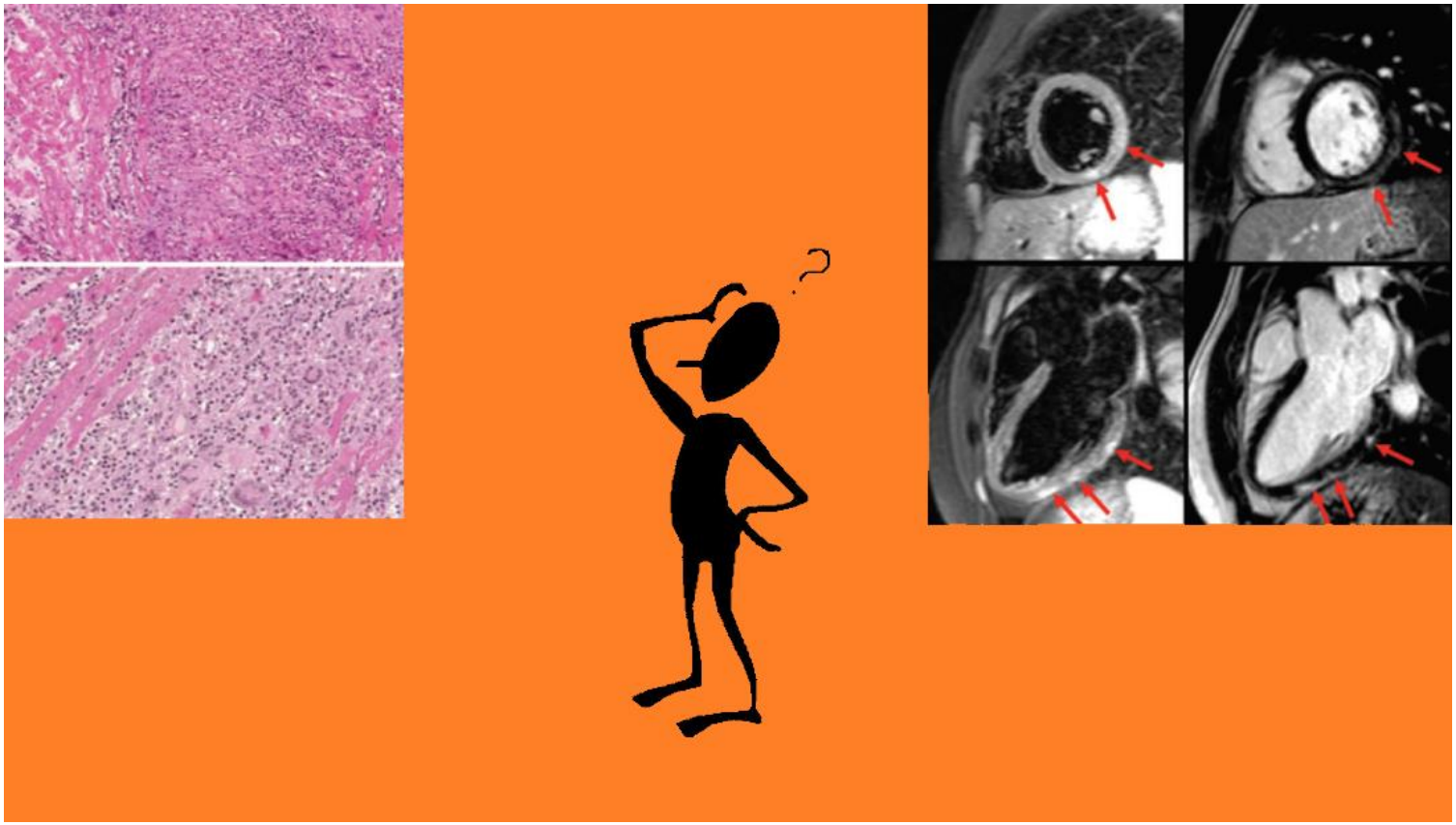
Persistenza del genoma virale nei cardiomiociti (PCR)

Rilevanza patogenetica (?)

Impatto prognostico e ricaduta terapeutica: **controversia** (Kuhl Circ 2005 e Caforio EHJ 2007 **vs** Kindermann Circ 2008)

Nella pratica (buon senso clinico): la presenza di genoma virale sconsiglia la t. immunosoppressiva (Frustaci Circ 2003)

Se si associa la valutazione dell'attività infiammatoria per mezzo dell'immunoistochimica, si possono selezionare accuratamente i *responders* alla immunosoppressione



La risonanza magnetica cardiaca integra o sostituisce la biopsia endomiocardica nella diagnosi di miocardite?

La biopsia endomiocardica è insostituibile

Andrea Frustaci

Dipartimento di Scienze Cardiovascolari, Nefrologiche, Respiratorie e Geriatriche, Università La Sapienza, Roma

G Ital Cardiol 2011;12(12):851-853

CONTROVERSIE IN MEDICINA CARDIOVASCOLARE

La risonanza magnetica cardiaca integra o sostituisce la biopsia endomiocardica nella diagnosi di miocardite?

Nell'era della risonanza magnetica cardiaca, le indicazioni alla biopsia endomiocardica sono limitate

Massimo Lombardi

U.O.C. di Risonanza Magnetica, Fondazione CNR/Regione Toscana "G. Monasterio", Pisa

G Ital Cardiol 2011;12(12):846-850

CONTROVERSIE IN MEDICINA CARDIOVASCOLARE

La risonanza magnetica cardiaca integra o sostituisce la biopsia endomiocardica nella diagnosi di miocardite?

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Andrea Frustaci

Dipartimento di Scienze Cardiovascolari, Nefrologiche, Respiratorie e Geriatriche, Università La Sapienza, Roma

G Ital Cardiol 2011;12(12):851-853

Pro

- È il *gold standard*
- Identifica il meccanismo
- Consente una terapia mirata

➢**NB**: se include IC e PCR

Contro

- Costo e invasività
- Complicazioni (*expertise*)
- Errore di campionamento

➢**NB**: ridotti in Centri *hub*

Pro

- Valore diagnostico = o +
- Valore prognostico = o +
- BEM *RM-guided*

➢**NB**: *timing* e ripetizione

Contro

- Scarsa disponibilità
- Tempi di risposta lenti
- Competenza specifica

➢**NB**: graduale crescita

CONTROVERSIE IN MEDICINA CARDIOVASCOLARE

La risonanza magnetica cardiaca integra o sostituisce la biopsia endomiocardica nella diagnosi di miocardite?

Nell'era della risonanza magnetica cardiaca, le indicazioni alla biopsia endomiocardica sono limitate

Massimo Lombardi

U.O.C. di Risonanza Magnetica, Fondazione CNR/Regione Toscana "G. Monasterio", Pisa

G Ital Cardiol 2011;12(12):846-850

POINT BREAK G Ital Cardiol 2015;16(10):533-538

La biopsia endomiocardica nella miocardite acuta: per tutti i pazienti

anche nelle forme con presentazione *pseudo-infartuale*

Alida L.P. Caforio[1], Martina Testolina[1], Alessandro Schiavo[1], Renzo Marcolongo[2], Sabino Iliceto[1]

[1]Dipartimento di Scienze Cardiologiche Toraciche e Vascolari, [2]Immunologia Clinica, Dipartimento di Medicina, Azienda Ospedaliera e Università degli Studi di Padova

POINT BREAK G Ital Cardiol 2015;16(10):539-543

La biopsia endomiocardica nella miocardite acuta: per alcuni ma non per tutti i pazienti

se la FE è conservata, basta una diagnosi di probabilità

Enrico Ammirati[1], Manlio Cipriani[1], Edgardo Bonacina[2], Andrea Garascia[1], Fabrizio Oliva[3]

[1]Cardiologia 2 - Insufficienza Cardiaca e Trapianto, [2]Servizio di Anatomia Patologica, [3]Unità di Cure Intensive Cardiologiche, Dipartimento Cardiotoracovascolare "A. De Gasperis", A.O. Ospedale Niguarda Ca' Granda, Milano

Neth Heart J (2014) 22:80–84
DOI 10.1007/s12471-013-0499-3

ICIN

ICIN Netherlands Heart Institute

Diagnostic approach of myocarditis: strike the golden mean

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

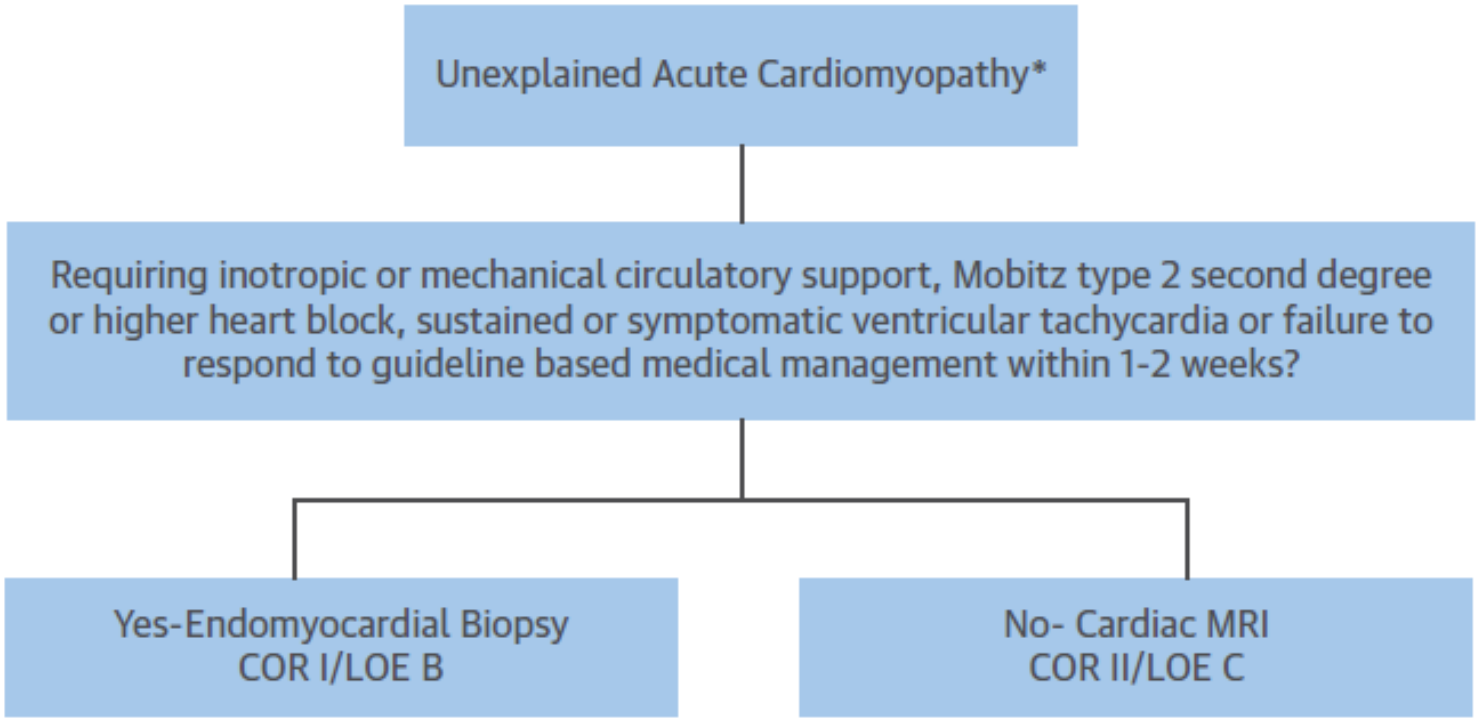
Referral for EMB in acute suspected myocarditis is recommended in the case of:

- 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

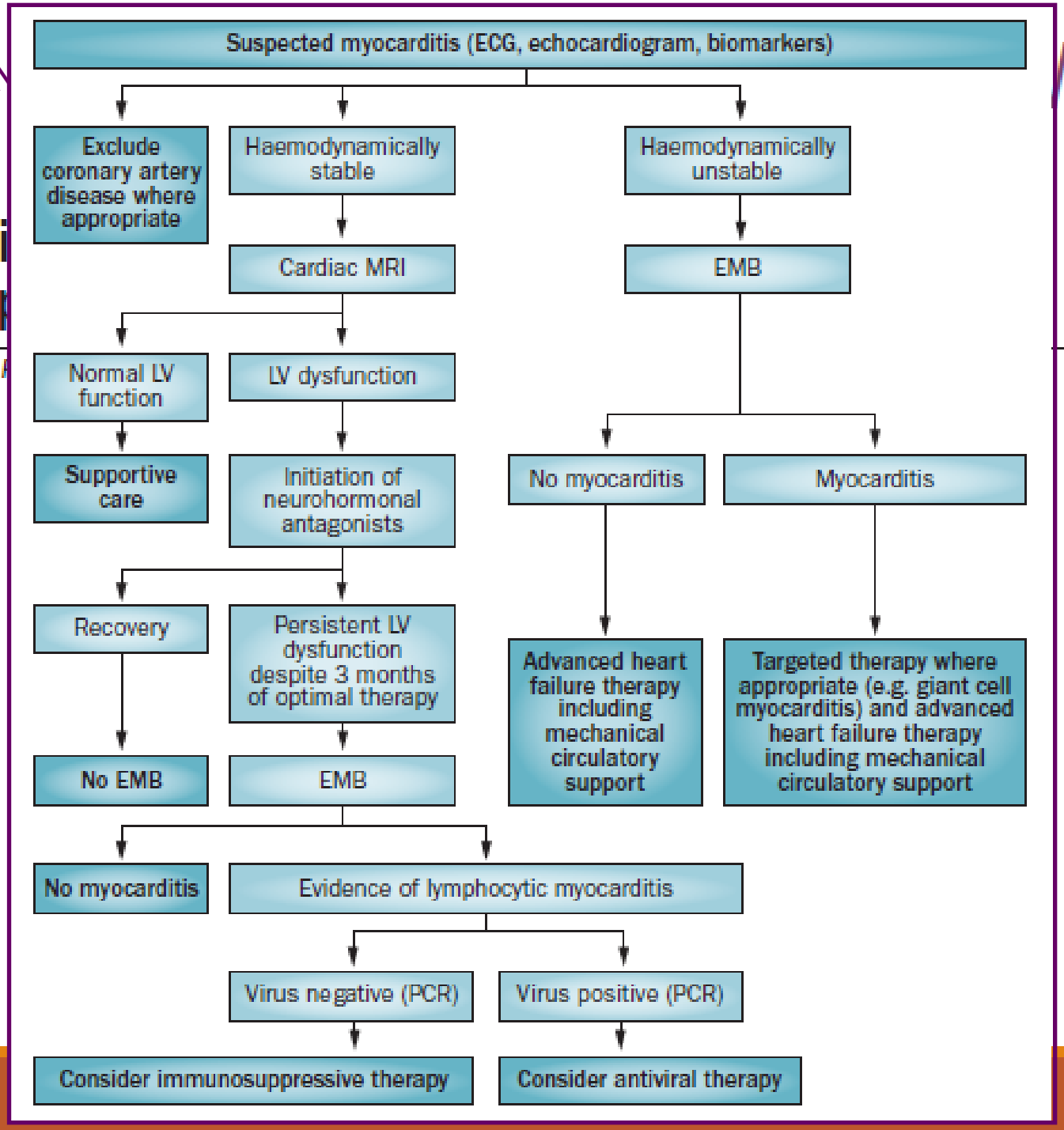
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 68, NO. 21, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.09.937

FIGURE 4 **Algorithm for the Evaluation of Suspected Myocarditis**



Endomyocardial biopsy (EMB) should be performed in those patients with clinically suspected unexplained acute myocarditis who require inotropic or mechanical circulatory support, Mobitz type 2 second degree or higher heart block, sustained or symptomatic ventricular tachycardia or failure to respond to guideline-directed medical management within 1 to 2 weeks. In other clinical scenarios of clinically suspected acute myocarditis, EMB may be helpful, but CMR may be considered as an initial diagnostic test to identify inflammation. Reprinted with permission from Bozkurt et al. (176). *Usually a dilated cardiomyopathy. Fulminant myocarditis may have normal end diastolic diameter with mildly thickened walls. Exclude ischemic, hemodynamic (valvular, hypertensive), metabolic, and toxic causes of cardiomyopathy as indicated clinically. CMR = cardiac magnetic resonance; COR = Class of recommendation; LOE = Level of Evidence; MRI = magnetic resonance imaging.


Suspected myocarditis (ECG, echocardiogram, biomarkers)
Exclude coronary artery disease where appropriate
Haemodynamically stable
Haemodynamically unstable
Cardiac MRI
EMB
Normal LV function
LV dysfunction
Supportive care
Initiation of neurohormonal antagonists
No myocarditis
Myocarditis
Recovery
Persistent LV dysfunction despite 3 months of optimal therapy
Advanced heart failure therapy including mechanical circulatory support
Targeted therapy where appropriate (e.g. giant cell myocarditis) and advanced heart failure therapy including mechanical circulatory support
No EMB
EMB
No myocarditis
Evidence of lymphocytic myocarditis
Virus negative (PCR)
Virus positive (PCR)
Consider immunosuppressive therapy
Consider antiviral therapy

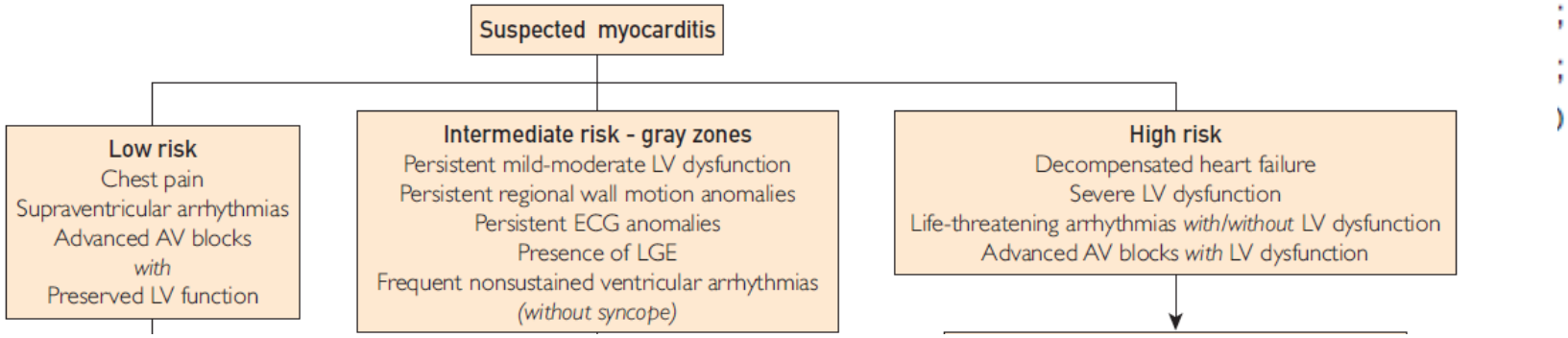
Prognosi

Mayo Clin Proc 2016; 9 (9): 1256

MAYO CLINIC

CrossMark

Myocarditis in Clinical Practice



Mayo Clin Proc 2016; 9 (9): 1256

MAYO CLINIC

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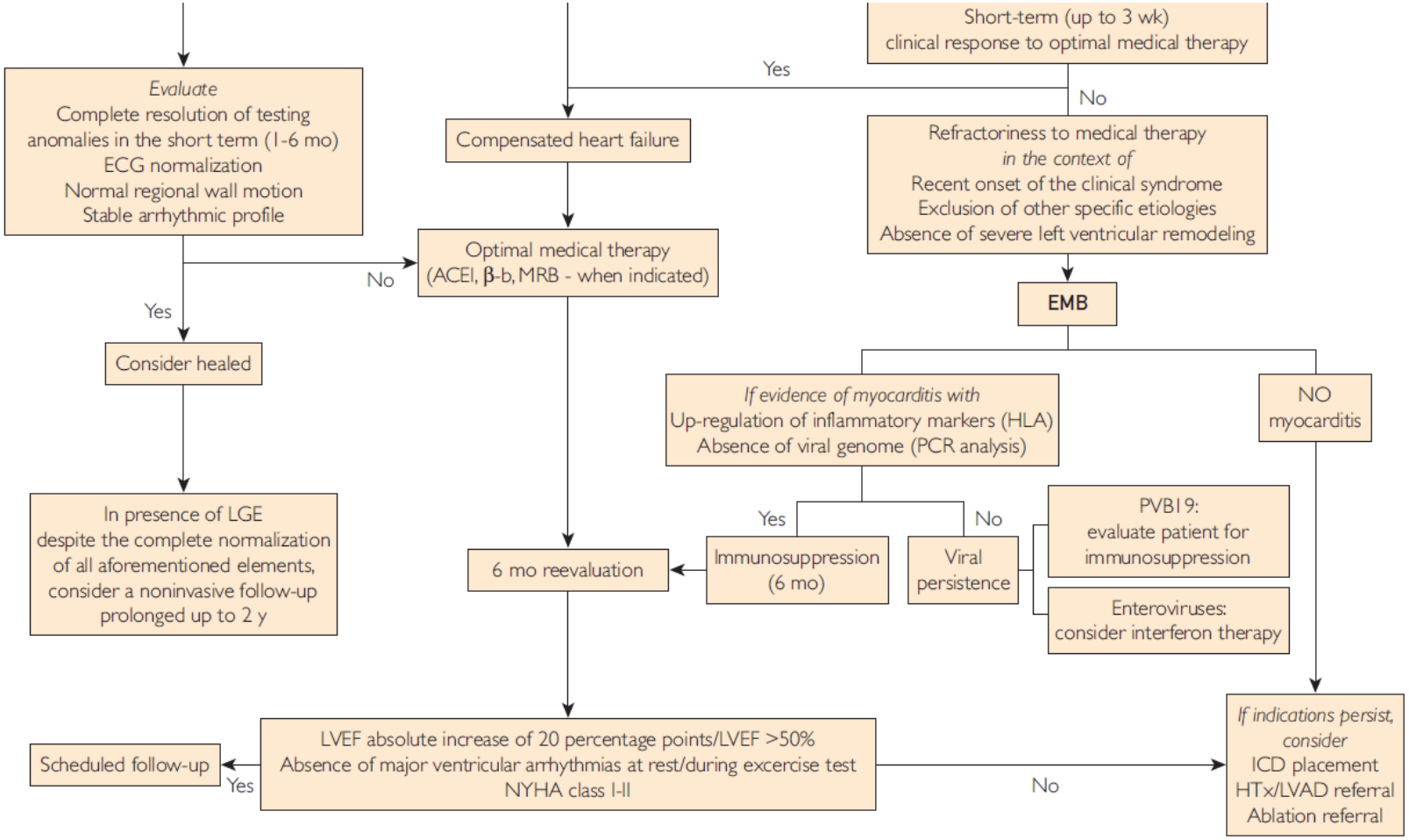
Myocarditis in Clinical Practice



Terapia

Usefulness of Immunosuppression for Giant Cell Myocarditis

Am J Cardiol 2008

Leslie T. Cooper Jr, MD[a,*], Joshua M. Hare, MD[b], Henry D. Tazelaar, MD[c], William D. Edwards, MD[d], Randall C. Starling, MD[e], Mario C. Deng, MD[f], Santosh Menon, MD[g], G. Martin Mullen, MD[h], Brian Jaski, MD[i], Kent R. Bailey, PhD[j], Madeleine W. Cunningham, PhD[k], and G. William Dec, MD[l], for the Giant Cell Myocarditis Treatment Trial Investigators

Immunosuppressive Therapy for Active Lymphocytic Myocarditis

Virological and Immunologic Profile of Responders Versus Nonresponders

Circulation 2003

Andrea Frustaci, MD; Cristina Chimenti, MD, PhD; Fiorella Calabrese, MD; Maurizio Pieroni, MD; Gaetano Thiene, MD; Attilio Maseri, MD

European Heart Journal (2009) 30, 1995–2002
doi:10.1093/eurheartj/ehp249

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study

Andrea Frustaci[1,2*], Matteo A. Russo[3,4], and C

Randomized, Placebo-Controlled Study for Immunosuppressive Treatment of Inflammatory Dilated Cardiomyopathy

Two-Year Follow-Up Results

Circulation 2001

Romuald Wojnicz, MD; Ewa Nowalany-Kozielska, MD; Celina Wojciechowska, MD; Grażyna Glanowska, MD; Przemysław Wilczewski, MD; Tomasz Niklewski, MD; Marian Zembala, MD, PhD; Lech Poloński, MD, PhD; Marius M. Rozek, MD; Jan Wodniecki, MD, PhD

Corticosteroids for viral myocarditis (Review)

Chen HS, Wang W, Wu SN, Liu JP

- Inclusi (con criteri "larghi") 8 RCT (5 english, 3 cinesi)
- Nessun beneficio sulla mortalità
- Tendenza al miglioramento di FE
- Forte eterogeneità, ***very low*** *grade of quality*
- La BEM non era un requisito in nessuno degli studi
- In ogni caso, non era prevista l'immunoistochimica

➢ Sono necessari RCT più ampi e di migliore qualità

THE COCHRANE COLLABORATION®

2013

Intravenous immunoglobulin for presumed viral myocarditis in children and adults (Review)

Robinson J, Hartling L, Vandermeer B, Klassen TP

- Selezionati solo due studi (62 adulti + 83 pediatrici)
- ***Very low*** *grade of quality*

➢ La terapia con immunoglobuline non può essere raccomandata (nonostante i *case report* favorevoli)

THE COCHRANE COLLABORATION®

2015

G Ital Cardiol 2013; 14: 504

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marco Anzini, Michele Moretti, Marco Merlo, Andrea Perkan, Rossana Bussani, Gianfranco Sinagra

Dipartimento Cardiovascolare, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste

Tabella 3. Protocolli di terapia immunosoppressiva nelle miocarditi.

Farmaco	Dosaggio
Protocollo utilizzato da Wojnicz et al.[56]	
Prednisone	1 mg/kg/die per 12 giorni, quindi riduzione della dose di 5 mg/die ogni 5 giorni fino alla dose di 0.2 mg/kg/die, per un totale di 90 giorni
Azatioprina	1 mg/kg/die per un totale di 100 giorni
Protocollo utilizzato da Frustaci et al.[57]	
Prednisone	1 mg/kg/die per 4 settimane, quindi 0.33 mg/kg/die per 5 mesi
Azatioprina	2 mg/kg/die per 6 mesi
Protocollo utilizzato presso la S.C. di Cardiologia di Trieste[4]	
Prednisone	50 mg/m^2/die per 2 settimane indi scalo di 0.3 mg/kg per 2 mesi, quindi scalo gradualmente fino allo stop (6 mesi)
Azatioprina	75 mg/m^2/die per 6 mesi
Ciclosporina[a]	10 mg/kg/die (2 somministrazioni) per 6 mesi

[a]in casi selezionati (es. miocardite a cellule giganti) o in caso di persistente attività infiammatoria nonostante terapia con prednisone.

G Ital Cardiol 2013; 14: 504

Aspetti controversi e gestionali sulle miocarditi: dalla letteratura al paziente

Marcc ... iinagra

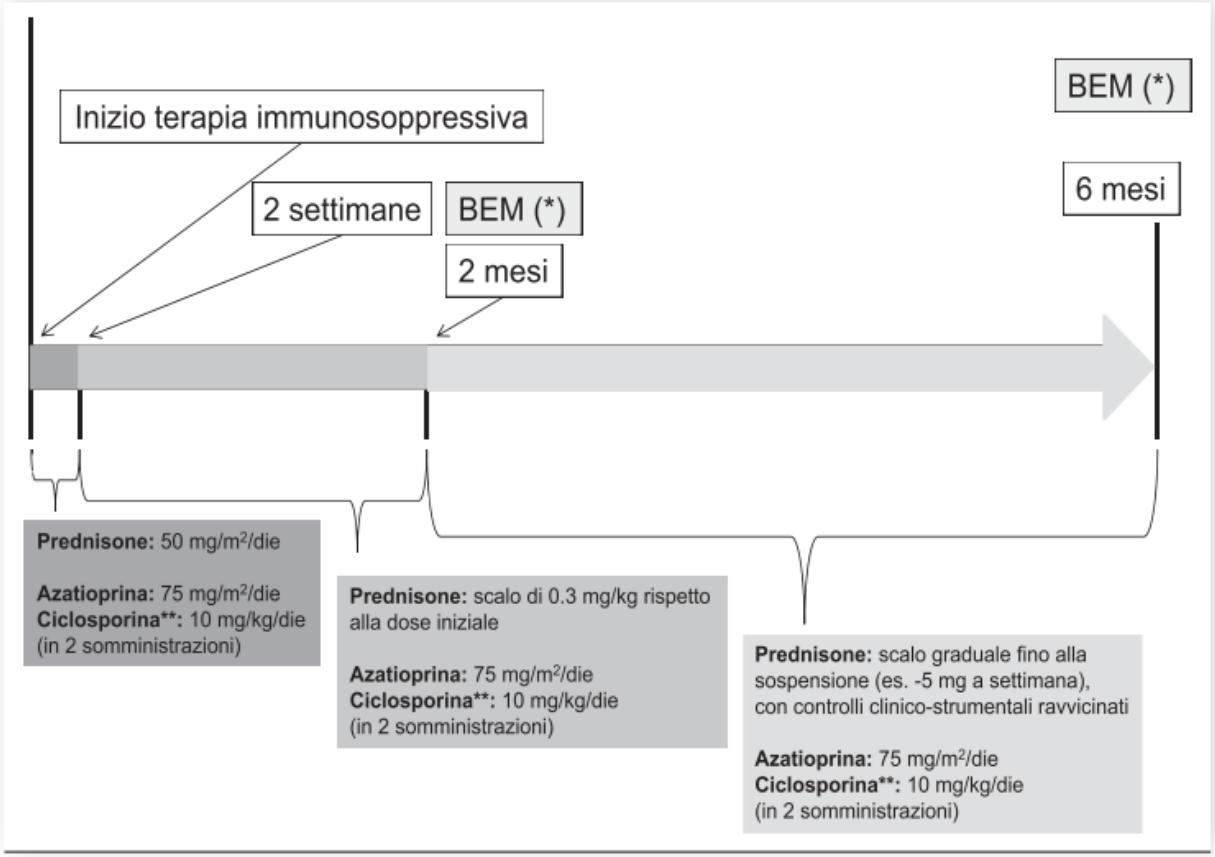


Figura 4. Protocollo di terapia immunosoppressiva nelle miocarditi utilizzato presso il Dipartimento Cardiovascolare di Trieste.
BEM, biopsia endomiocardica.
*possibile considerare controllo con BEM a 2 e 6 mesi.
**in casi selezionati (es. miocardite gigantocellulare) o nei casi di persistente attività nonostante terapia con prednisone.

JACC Vol. 6, No. 5
November 1985:1078–82

A Nonsteroid Anti-Inflammatory Drug Exacerbates Coxsackie B3 Murine Myocarditis

MARIA ROSA COSTANZO-NORDIN, MD, ELIZABETH A. REAP, BS,
JOHN B. O'CONNELL, MD, FACC, JOHN A. ROBINSON, MD, PATRICK J. SCANLON, MD, FACC

Il modello animale (topo) di miocardite virale riproduce bene quello umano (tre fasi analoghe)

L'uso dell'ibuprofene (sulla carta favorevole, per effetto immunomodulante, mediato dalle prostaglandine) si è rivelato in effetti controproducente

Dimostrazione istologica, con valutazione dell'infiltrato infiammatorio e della necrosi

Circulation

ORIGINAL RESEARCH ARTICLE

Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis

Multicenter Lombardy Registry

to 63% of cases.[36] Nonsteroidal anti-inflammatory drugs were frequently used without increased risk, particularly in uncomplicated AM at presentation (in 67.6%). This finding does not support the evidence that nonsteroidal anti-inflammatory drugs worsen the prognosis of viral myocarditis as observed in murine models.[37] β-Blockers,

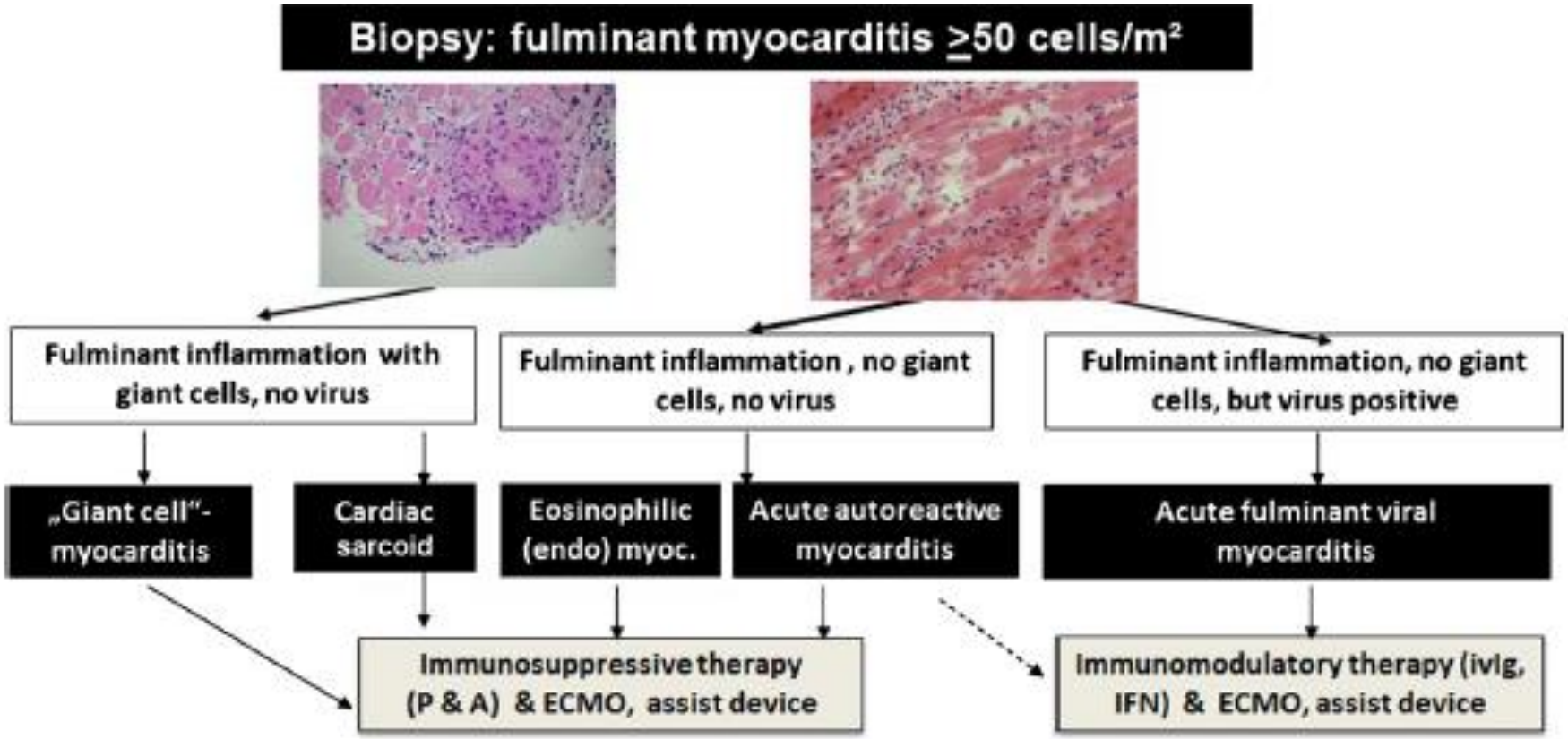
Miocarditi fulminanti

Curr Heart Fail Rep (2014) 11:166–177
DOI 10.1007/s11897-014-0196-6

MANAGEMENT OF HEART FAILURE (TE MEYER, SECTION EDITOR)

Management of fulminant myocarditis: A diagnosis in search of its etiology but with therapeutic options

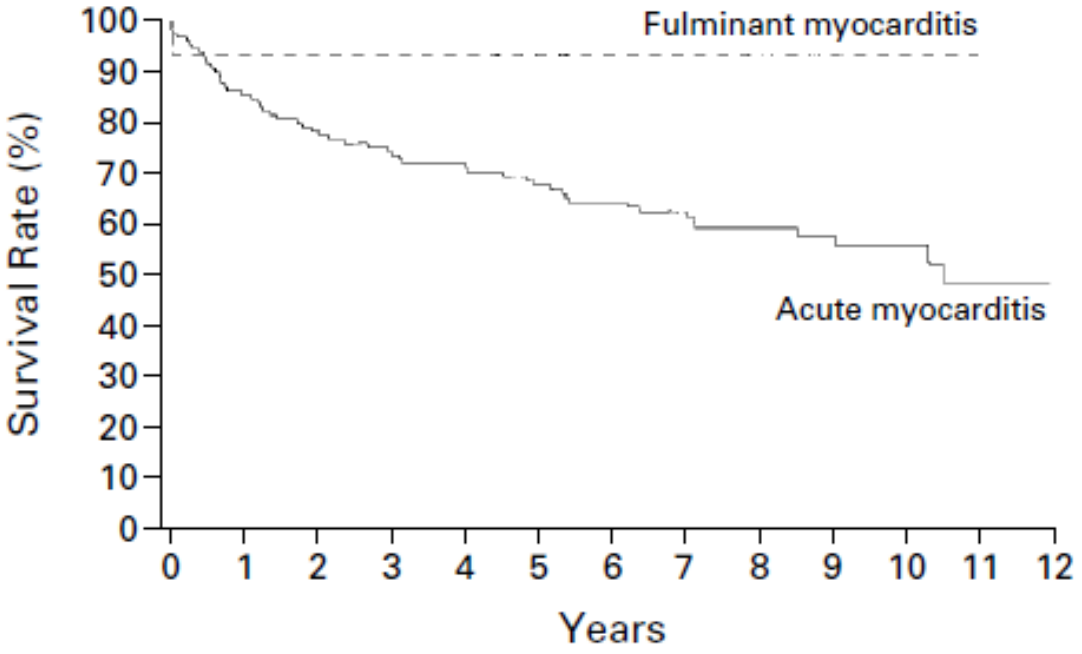
Bernhard Maisch · Volker Ruppert · Sabine Pankuweit



The New England Journal of Medicine 2000; 342: 690

LONG-TERM OUTCOME OF FULMINANT MYOCARDITIS AS COMPARED WITH ACUTE (NONFULMINANT) MYOCARDITIS

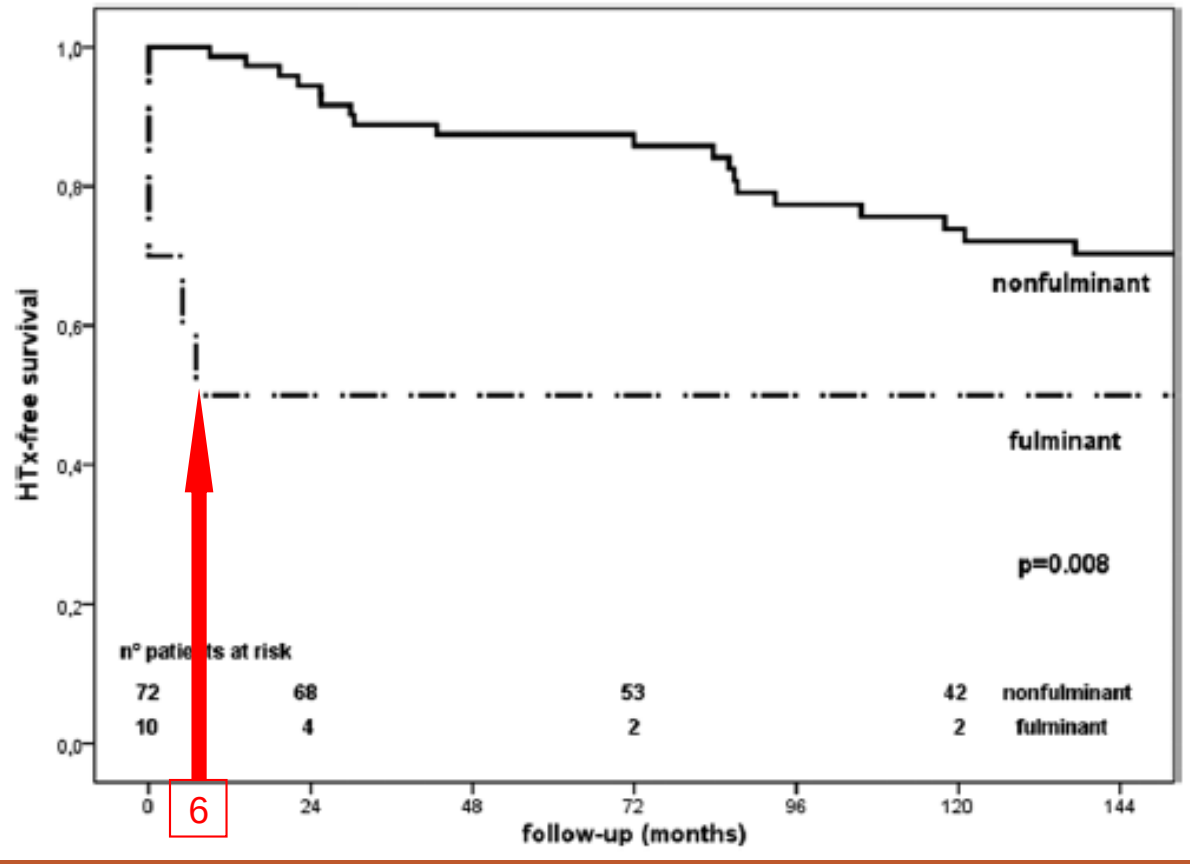
ROBERT E. MCCARTHY III, M.D., JOHN P. BOEHMER, M.D., RALPH H. HRUBAN, M.D., GROVER M. HUTCHINS, M.D., EDWARD K. KASPER, M.D., JOSHUA M. HARE, M.D., AND KENNETH L. BAUGHMAN, M.D.



Long-Term Evolution and Prognostic Stratification of Biopsy-Proven Active Myocarditis

Circulation 2013;128: 2384

Marco Anzini, MD; Marco Merlo, MD; Gastone Sabbadini, MD; Giulia Barbati, PhD; Gherardo Finocchiaro, MD; Bruno Pinamonti, MD; Alessandro Salvi, MD; Andrea Perkan, MD; Andrea Di Lenarda, MD; Rossana Bussani, MD; Jozef Bartunek, MD, PhD; Gianfranco Sinagra, MD, FESC

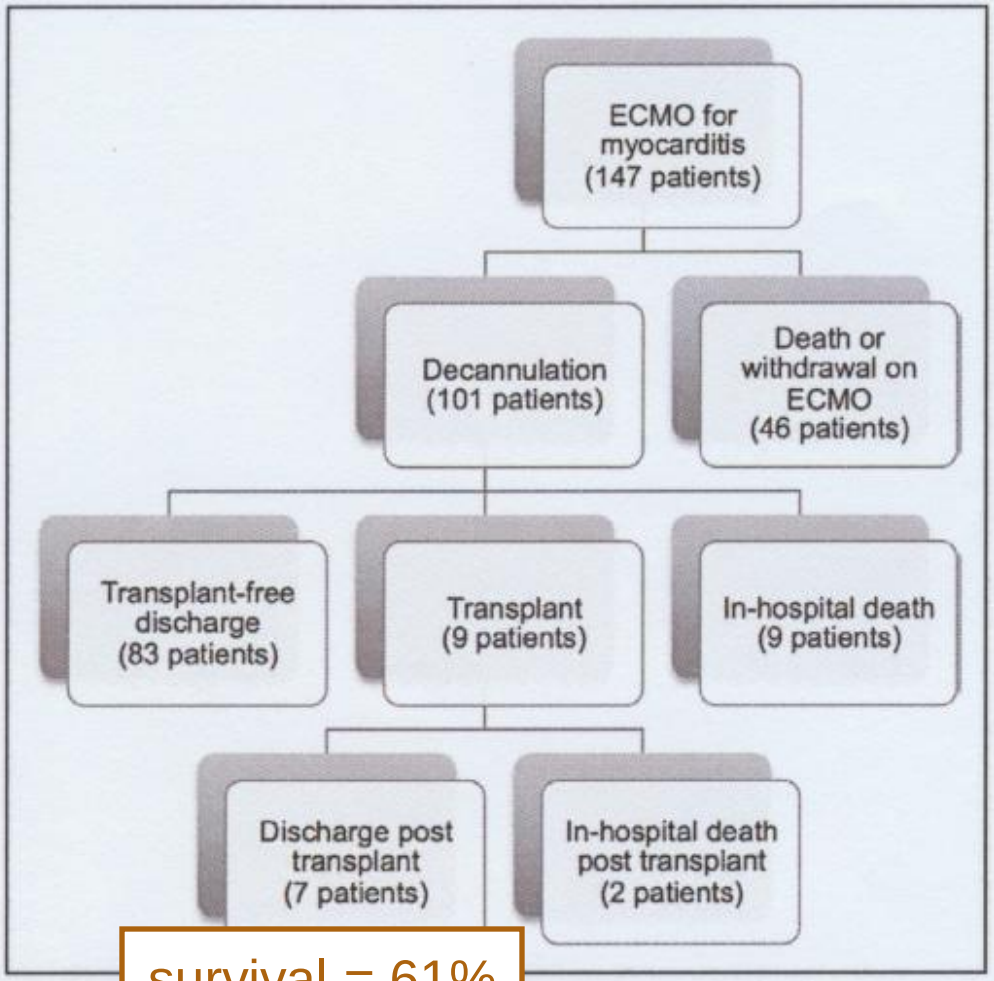


Crit Care Med 2015; 43: 1016

Extracorporeal Membrane Oxygenation for the Support of Adults With Acute Myocarditis

J. Wesley Diddle
Peter T. Rycus, M

ELSO Registry (1995 → 2011)



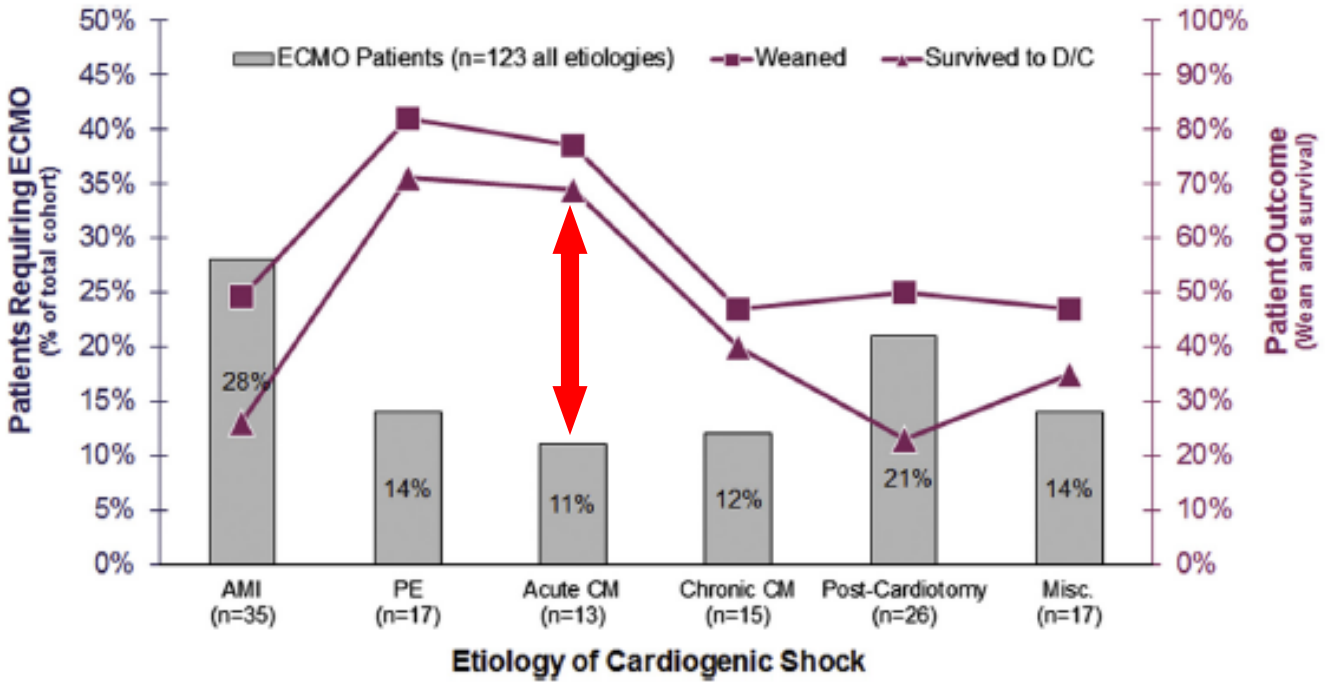
survival = 61%

Figure 1 atients supported with extracorporeal membrane oxygenation (ECMO) for acute myocarditis.

Clinical Features and Outcomes in Adults With Cardiogenic Shock Supported by Extracorporeal Membrane Oxygenation

Am J Cardiol 2015; 116: 1624

Brett J. Carroll, MD[a], Ravi V. Shah, MD[a,b], Venkatesh Murthy, MD, PhD[c], Stephen A. McCullough, MD[d], Nosheen Reza, MD[d], Sunu S. Thomas, MD[b], Tae H. Song, MD[e], Christopher H. Newton-Cheh, MD, MPH[b], Janice M. Camuso, RN[e], Thomas MacGillivray, MD[e], Thoralf M. Sundt, MD[e], Marc J. Semigran, MD[b], Gregory D. Lewis, MD[b], Joshua N. Baker, MD[e], and José P. Garcia, MD[e,*]



Clinical Outcomes in Fulminant Myocarditis Requiring Extracorporeal Membrane Oxygenation: A Weighted Meta-Analysis of 170 Patients

J Card Fail 2014; 20: 400

RICHARD CHENG, MD,[1] RORY HACHAMOVITCH, MD,[2] MICHELLE KITTLESON, MD, PhD,[1] JIGNESH PATEL, MD, PhD,[1] FRANCISCO ARABIA, MD,[1] JAIME MORIGUCHI, MD,[1] FARDAD ESMAILIAN, MD,[1] AND BABAK AZARBAL, MD[1]

In fulminant myocarditis, where recovery of cardiac function is expected if the patient survives the acute phase of the disease, temporary support can be crucial…our pooled analysis suggests that more than **2/3** of patients requiring ECMO survive…

…we suspect that part of the efficacy of ECMO depends on the **natural history** of the underlying disease entity: ECMO has been associated with limited outcomes in disease entity where the **reversibility** is guarded such as in chronic or dilated CMP…

Crit Care Med 2015; 43: 1016

Extracorporeal Membrane Oxygenation for the Support of Adults With Acute Myocarditis

J. Wesley Diddle
Peter T. Rycus, M

ELSO Registry (1995 → 2011)

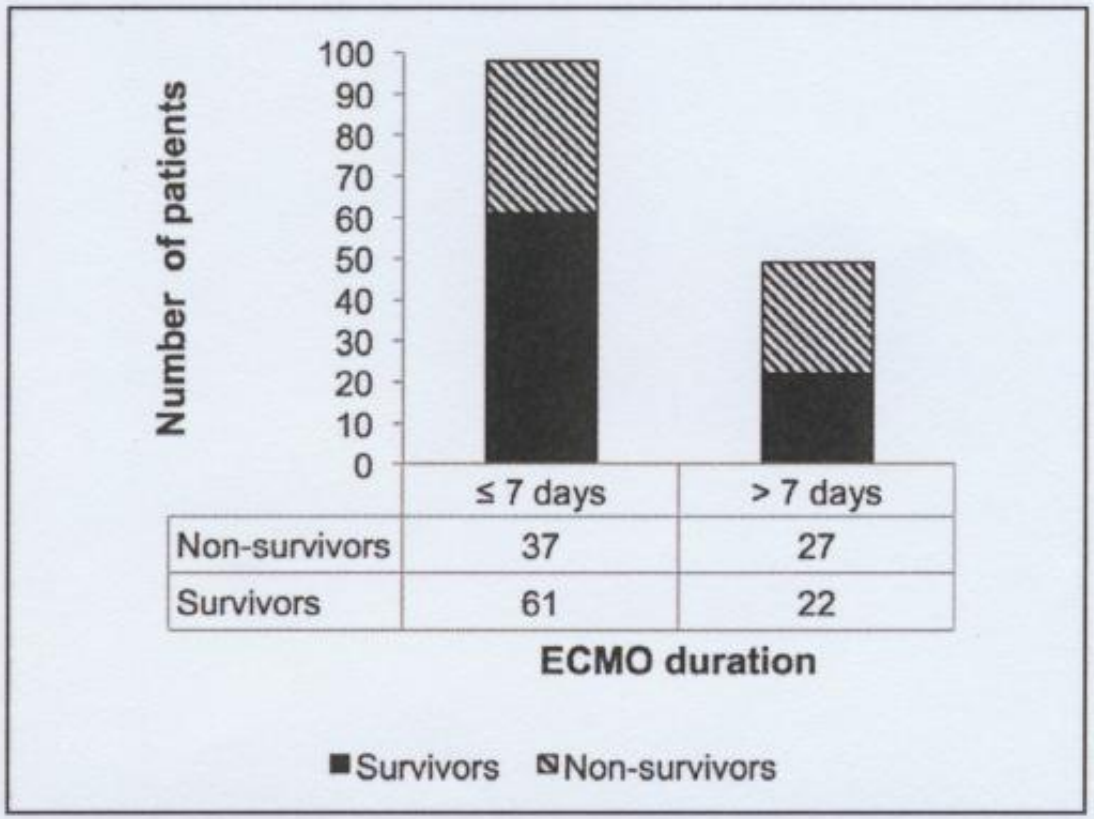


Figure 2. Bar graph demonstrating difference in transplant-free survival in patients with acute myocarditis supported with extracorporeal membrane oxygenation (ECMO) for ≤ 7 days versus > 7 days (62% vs 45%, $p = 0.053$).

ECMO

EXTRA **C**ORPOREAL **M**EMBRANE **O**XYGENATION

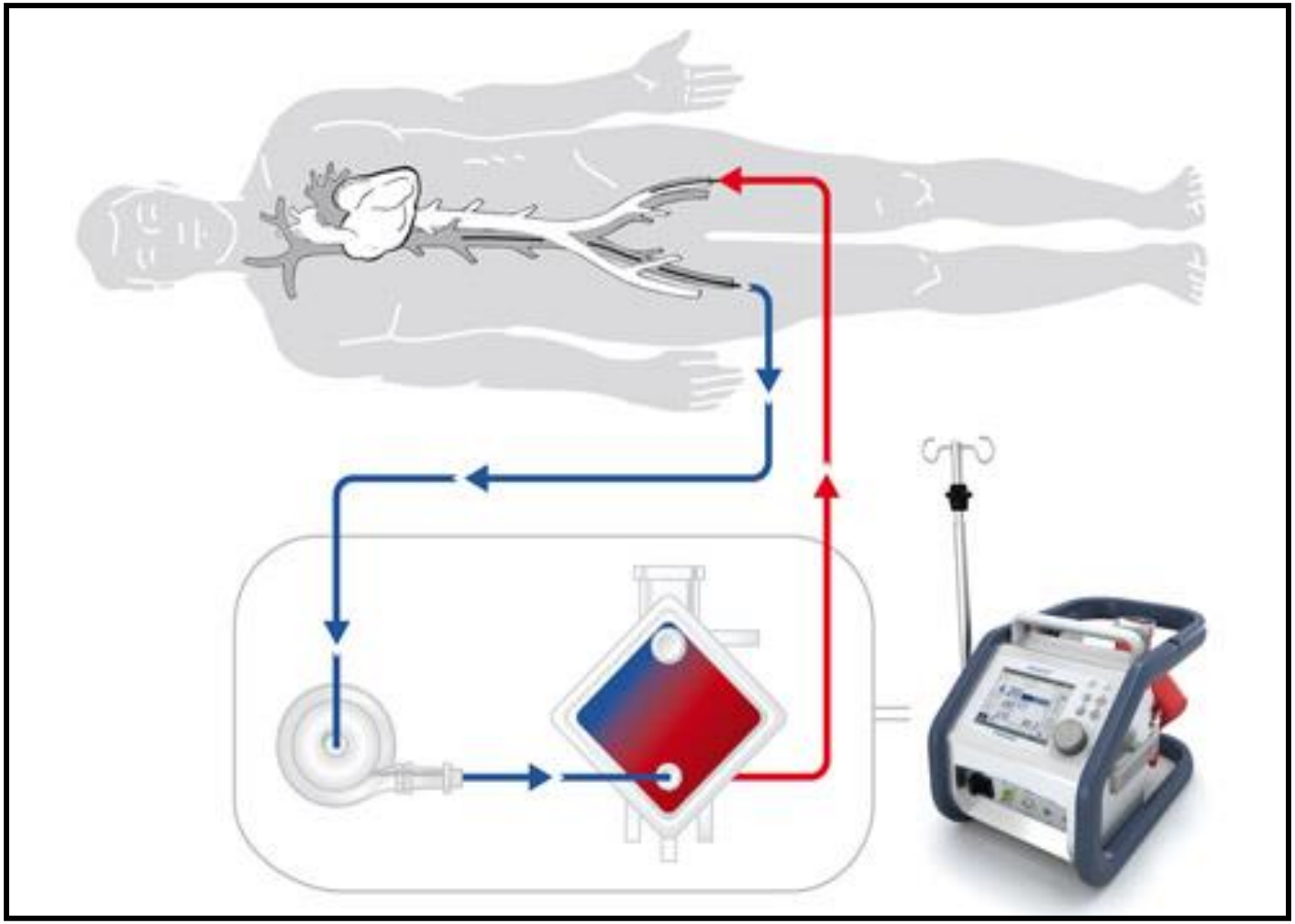
PROVIDES PROLONGED RESPIRATORY AND CARDIAC SUPPORT

DOES NOT TREAT UNDERLYING PATHOLOGY

ALLOWS SUPPORT WHILST DISEASE RESOLVES OR REVERSES

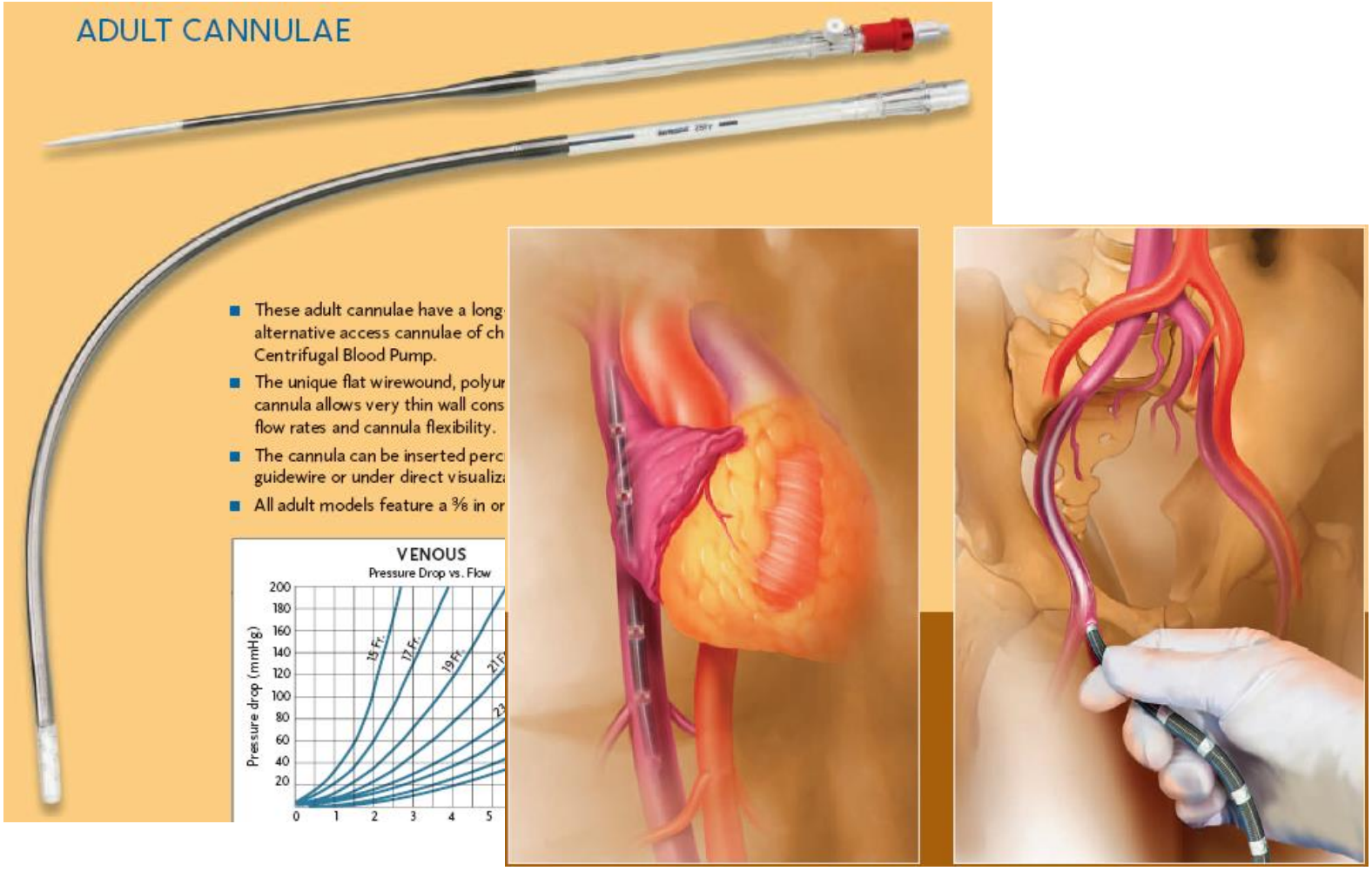
ONLY APPROPRIATE IF UNDERLYING PATHOLOGY IS POTENTIALLY REVERSIBLE

Veno-Arterial



Hill J.D. N Engl J Med. 1972;286:629-634

Circuits and Cannulae



Follow up

TABLE 4. Proposal for the Scheduled Follow-up of Patients With Myocarditis

Variable	Low risk	Intermediate risk	High risk
Time of clinical reevaluations	1 mo, 6 mo, 2 y	3 mo, 6 mo, 12 mo, then yearly	3 wk, 3 mo, 6 mo, 12 mo, then yearly
Noninvasive testing	Assess ECG and echocardiographic normalization between 1 and 6 mo. Cardiac MRI is recommended	Periodic evaluation of LVEF and LV remodeling (ECG) Periodic evaluation of the arrhythmic burden (Holter monitoring) Annual evaluation of arrhythmia induction during exercise test Cardiac MRI with LGE evaluation, if not assessed at disease presentation	
Exercise restriction	Yes, for 2 y	Yes, lifetime	Yes, lifetime
Lifetime follow-up	No, if normalization at 2 y	Yes	Yes
Lifetime therapy	No, if normalization at 2 y	Yes	Yes

ECG = electrocardiography; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = LV ejection fraction; MRI = magnetic resonance imaging.

Mayo Clin Proc. ■ September 2016;91(9):1256-1266 ■ http://dx.doi.org/10.1016/j.mayocp.2016.05.013
www.mayoclinicproceedings.org

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 19–33
doi:10.1093/eurheartj/ehy730

SPECIAL ARTICLE
Sports cardiology

Recommendations for participation in competitive and leisure time sport in athletes

Table 10 **Recommendations for athletes with myocarditis**

	Class/level of evidence
1. General consensus exists that athletes with diagnosis of myocarditis should be restricted from exercise programmes for a period of 3–6 months, according to the clinical severity and duration of the illness, LV function at onset, and extent of inflammation on the CMR. This time period is considered appropriate to ensure clinical and biological resolution of the disease.[3,4,105,118–120]	Class IIb/Level C
2. Individuals with previous myocarditis have an increased risk for recurrence and silent clinical progression of the disease. Therefore, athletes with previous myocarditis should undergo a periodical re-assessment, particularly within the first 2 years.	Class IIa/ Level C
3. It is reasonable for athletes to resume training and competition after a myocarditis if all of the following criteria are met: (1) LV systolic function has returned to the normal range. (2) Serum biomarkers of myocardial injury have normalized. (3) Clinically relevant arrhythmias, such as frequent or complex repetitive forms of ventricular or supraventricular arrhythmias are absent on 24-h ECG monitoring and exercise test.	Class IIa/ Level C
4. The clinical significance of persistent LGE in an asymptomatic athlete with clinically healed myocarditis is unknown, however, myocardial scar is a potential source of ventricular tachyarrhythmias.[111–113] At present, it seems reasonable for these athletes to resume training and participate in competitive sport if LV function is preserved and in the absence of frequent or complex repetitive forms of ventricular or supraventricular arrhythmias during maximal exercise and on 24-h ECG monitoring (including session of training/competition). Asymptomatic athletes with LGE, however, should remain under annual clinical surveillance.	Class III/ Level C

Recommendations

1. Before returning to competitive sports, athletes who initially present with an acute clinical syndrome consistent with myocarditis should undergo a resting echocardiogram, 24-hour Holter monitoring, and an exercise ECG no less than 3 to 6 months after the initial illness *(Class I; Level of Evidence C)*.
2. It is reasonable that athletes resume training and competition if all of the following criteria are met *(Class IIa; Level of Evidence C)*:

   a. Ventricular systolic function has returned to the normal range.
   b. Serum markers of myocardial injury, inflammation, and heart failure have normalized.
   c. Clinically relevant arrhythmias such as frequent or complex repetitive forms of ventricular or supraventricular ectopic activity are absent on Holter monitor and graded exercise ECGs.

   At present, it is unresolved whether resolution of myocarditis-related LGE should be required to permit return to competitive sports.

3. Athletes with probable or definite myocarditis should not participate in competitive sports while active inflammation is present. This recommendation is independent of age, gender, and LV function *(Class III; Level of Evidence C)*.

...tement

Circulation 2015; 132: 273

...ommendations for
...cular Abnormalities:
...rdiomyopathy,
... Cardiomyopathy
...nd Myocarditis

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...on, MD, FAHA, FACC;
...himura, MD, FAHA, MACC;
...eslie T. Cooper, Jr, MD, FAHA, FACC;
...alf of the American Heart Association
... on Clinical Cardiology, Council on
...ar and Stroke Nursing, Council on
...merican College of Cardiology

Grazie per l'attenzione

SAPIENTE È COLUI CHE SA DI NON SAPERE