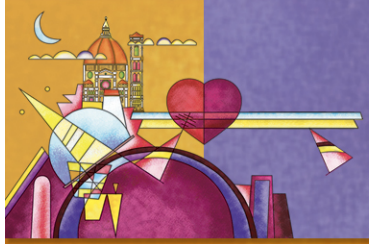


Conoscere e Curare il Cuore 2018

VENERDI' 16 MARZO

COME MIGLIORARE LA TERAPIA DELLA MIOCARDITE: RUOLO DI RM E BIOPSIA MIOCARDICA

Alida Caforio

Divisione di Cardiologia
Dipartimento di Scienze Cardiologiche Toraciche e Vascolari
Università degli Studi di Padova

E-mail: alida.caforio@unipd.it

Conflict of interest

Speaker fees, travel reimbursement:
Shire, Genzyme, Menarini
(none in relation to this talk)

Alida LP Caforio, MD, PhD, FESC

Dept Cardiological ,Thoracic and Vascular Sciences

University of Padova

E-mail: alida.caforio@unipd.it

Myocarditis – *a difficult disease*


TRAITÉ
DE
LA STRUCTURE
DU CŒUR,
DE SON ACTION,
ET
DE SES MALADIES.
Par M. SENAC, Médecin Consultant du Roy.
TOME PREMIER.
A PARIS,
Chez JACQUES VINCENT, rue de vieux-vis l'Eglise de S. Severin, à l'Ange.
M. DCC. XLIX.
AVEC APPROBATION ET PRIVILEGE DU ROY.

"The inflammation of the heart is difficult to diagnose and when we have diagnosed it, can we then treat it better?"

Jean Baptiste de Senac, 1749

What is myocarditis?

- **Definition** (Circulation, 1995 WHO/ISFC classification; Eur Heart J, 1999; AHA statements 2006, 2016; ESC 2008, Eur Heart J 2013)
  - **Myocarditis is an inflammatory disease of the myocardium and is diagnosed by established histological, immunological and immunohistochemical criteria**
- **Histological features (Dallas criteria on EMB)**
- **Myocarditis forms**
  - **idiopathic,**
  - **Infectious (mainly viral) and/or autoimmune**

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], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William I cKenna[13] Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis – *ESC 2013 Task Force diagnostic criteria*

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)

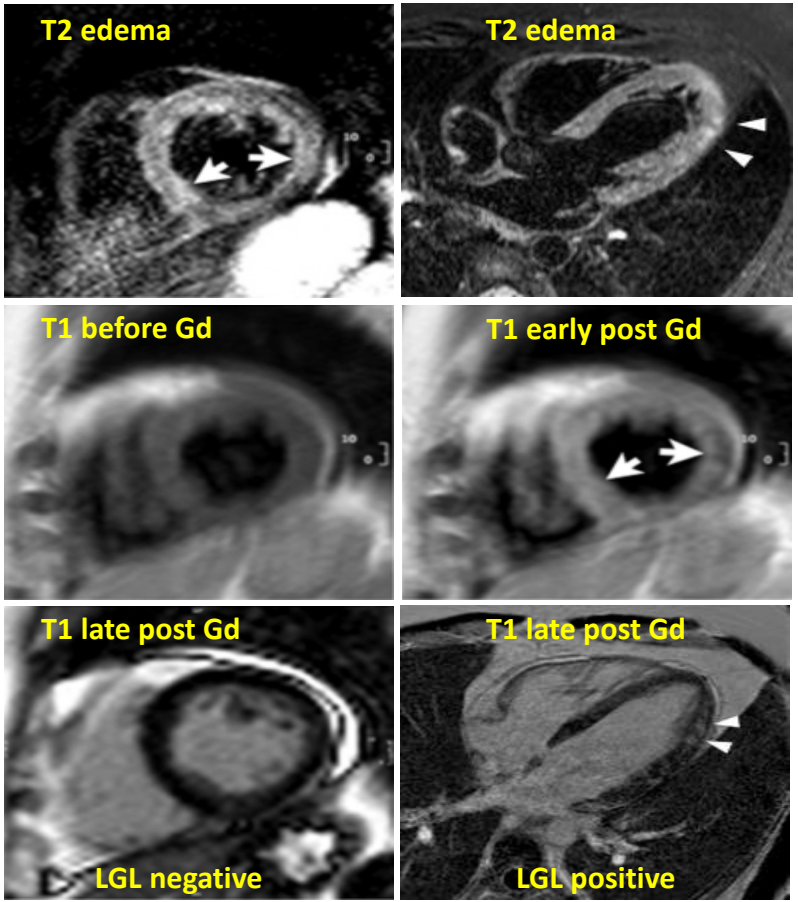
Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis - *ESC 2013 Task Force diagnostic criteria: III-CMR*

Quality of myocardial tissue	cMRI-sequence
Edema	T2w-IR-sequence
Hyperemia and capillary leakage	T1w-SE-IR-sequence before and shortly after gadolinium application (early gadolinium enhancement, EGE)
Acute necrosis or fibrosis (scar)	T1w-SE-IR-sequence late after gadolinium application (late gadolinium enhancement, LGE)



Friedrich MG et al. J Am Coll Cardiol 2009;53:1475

Clinically suspected Myocarditis – *ESC 2013 Task Force diagnostic criteria*

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

Clinical presentations[a]

Acute chest pain, pericarditic, or pseudo-ischaemic

Clinically suspected Myocarditis in the presence of:

➔ **1 or more of the clinical presentations**

and

1 or more of the diagnostic criteria from different categories *

➔ **in asymptomatic patients at least 2 diagnostic criteria should be met**

*after exclusion of coronary heart disease, cardiac defect/ vitium, congenital cardiac anomaly etc.

Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis - *ESC 2013 Task Force diagnostic criteria: III-role of CMR*

Long-Term Follow-Up of Biopsy-Proven Viral Myocarditis

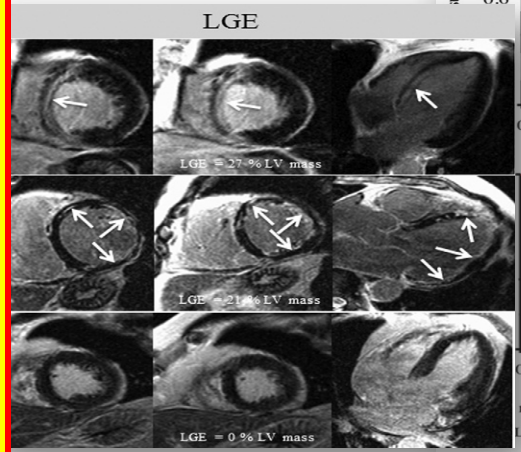
Predictors of Mortality and Incomplete Recovery

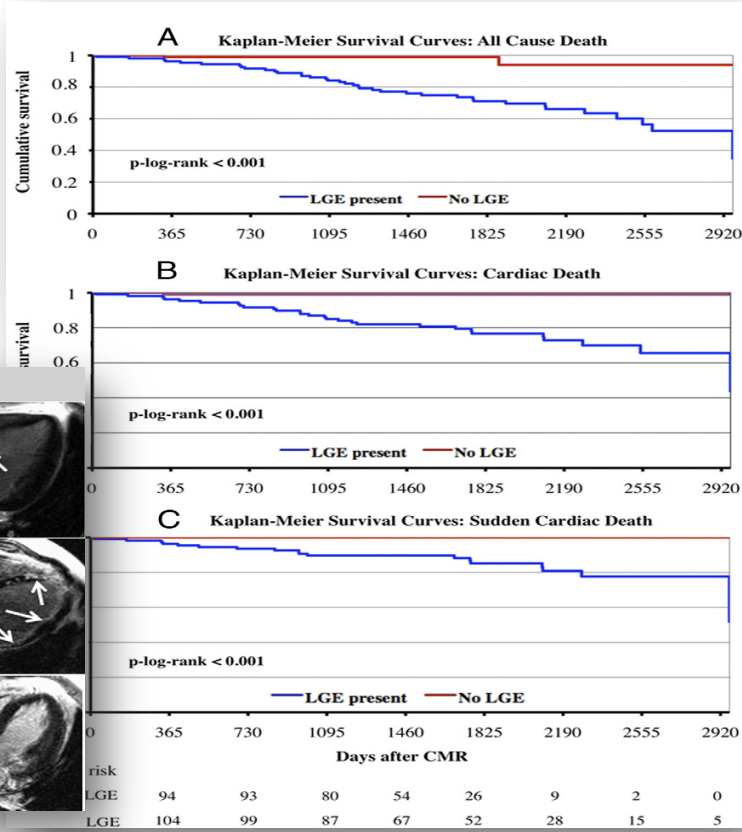
Stefan Grün, MD,* Julia Schumm, MD,* Simon Greulich, MD,* Anja Wagner, MD,† Steffen Schneider, PHD,‡ Oliver Bruder, MD,‡ Eva-Maria Kispert, RN,* Stephan Hill, MD,* Peter Ong, MD,* Karin Klingel, MD,§ Reinhardt Kandolf, MD,§ Udo Sechtem, MD,* Heiko Mahrholdt, MD*

F

-Accuracy of CMR is low in biopsy-proven myocarditis with CHF/DCM or arrhythmia presentation

-CMR does not provide etiological diagnosis and does not have independent prognostic value in biopsy proven myocarditis





Grün S et al., J Am Coll Cardiol 2012; 59: 1604-1615

MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries)

Table 2 **Potential causes of an elevated troponin adapted from Agewall *et al.*[11]**

(1) Coronary causes
- Plaque rupture or erosion
- Coronary artery spasm
- Spontaneous coronary dissection
- Acute aortic dissection with coronary extension
- Coronary microvascular disorders
- Spontaneous coronary thrombosis—thrombophilia disorders
- Coronary emboli
- Sympathomimetic agents—cocaine, methamphetamines

(2) Non-coronary causes

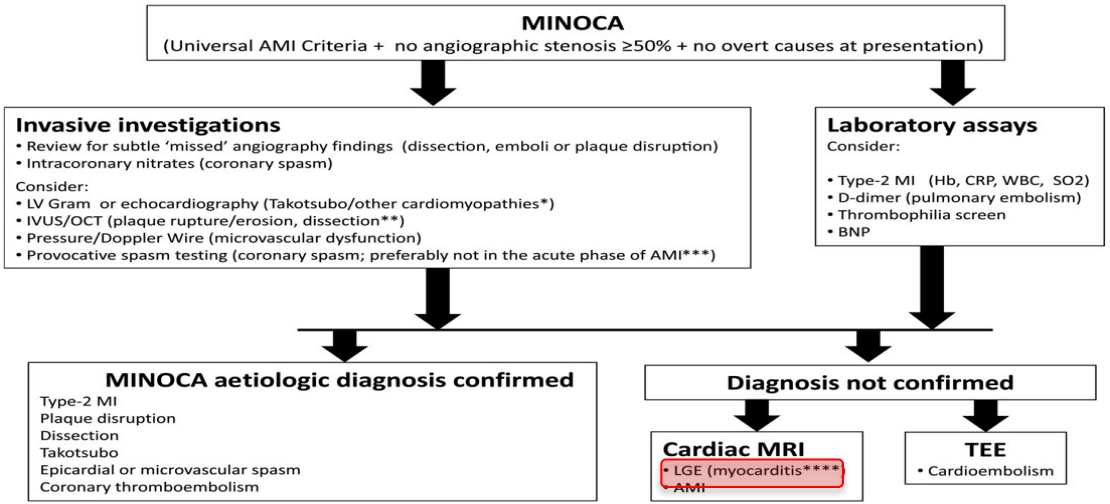
(a) Associated with cardiac disorders
- Myocarditis
- Takotsubo cardiomyopathy
- Cardiomyopathies
- Cardiac trauma
- Strenuous exercise
- Tachyarrhythmias
- Cardiotoxins—chemotherapeutic agents

(b) Associated with extra-cardiac disorders
- Stroke
- Pulmonary embolism
- Sepsis
- Adult respiratory distress syndrome
- End-stage renal failure

European Heart Journal
doi:10.1093/eurheartj/ehw149

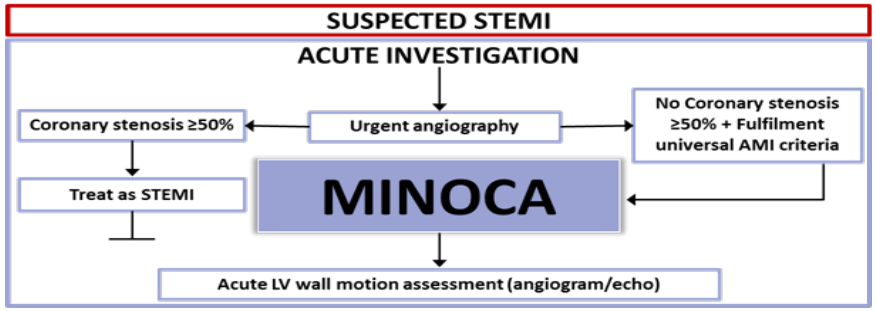
CURRENT OPINION

ESC working group position paper on myocardial infarction with non-obstructive coronary arteries



Agewall S et al, Eur Heart J 2016

Diagnostic test flow chart in MINOCA



SUSPECTED DIAGNOSIS AND FURTHER DIAGNOSTIC TESTS

	Non-invasive	Invasive
Myocarditis	**TTE Echo** (Pericardial effusion) **CMR** (Myocarditis, pericarditis)	**Endomyocardial biopsy** (myocarditis)
Coronary (epicardial/ microvascular)	**TTE Echo** (Regional wall motion abnormalities, embolic source) **CMR** (small infarction) **TOE/Bubble Contrast Echo** (Patent foramen ovale, atrial septal defect)	**IVUS/OCT** (Plaque disruption/dissection) **Ergonovine/Ach test** (Spasm) **Pressure/Doppler wire** (Microvascular dysfunction)
Myocardial disease	**TTE Echo** **CMR** (Takotsubo, others)	
Pulmonary Embolism	**D-dimer**(Pulmonary embolism) **CT scan** (Pulmonary embolism) **Thrombophilia screen**	
Oxygen supply/ demand imbalance- Type 2 MI	**Blood test,** **Extracardiac investigation**	

www.escardio.org/guidelines 2017 ESC Guidelines for the Management of AMI-STEMI (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx095)

Clinically suspected Myocarditis *-Role of CMRI in directing therapy?*

- Management of ventricular dysfunction and of arrhythmia in keeping with current ESC guidelines
- ICD implantation should be deferred until resolution of the acute episode
- DAPT and anticoagulants stopped in MINOCA presentation with CMRI with positive Lake-Louise criteria (myocarditis pattern)
- No use of NSAIDs and colchicine unless associated pericarditis (pericardial pain, high RCP, pericardial effusion)

Caforio A et al., Eur Heart J 2013;34:2636-2648

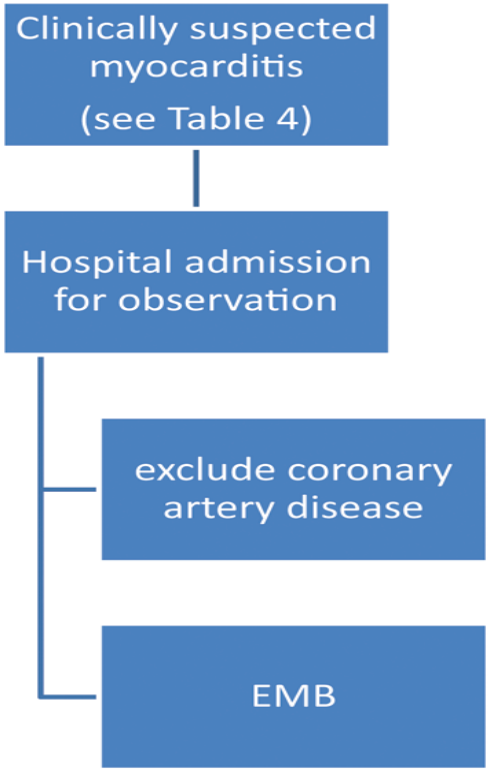
Diagnostic criteria and proposed diagnostic approach for clinically suspected myocarditis

Ancillary features which support the clinical suspicion of myocarditis include:

- Fever ≥38.0°C at presentation or within the preceding 30 days with or without evidence of a respiratory (chills, headache, muscle aches, general malaise) or gastrointestinal (decreased appetite, nausea, vomiting, diarrhoea) infection;
- peri-partum period[121];
- previous clinically suspected or definite myocarditis (according to the criteria set in *Table 4*);
- personal and/or family history of allergic asthma, other types of allergy, extra-cardiac autoimmune disease, toxic agents;
- family history of DCM, myocarditis (according to the present criteria).

Recommendation

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



From Task Force on Myocarditis-WG Position Statement, Eur Heart J 2013

Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies

A Scientific Statement From the American Heart Association

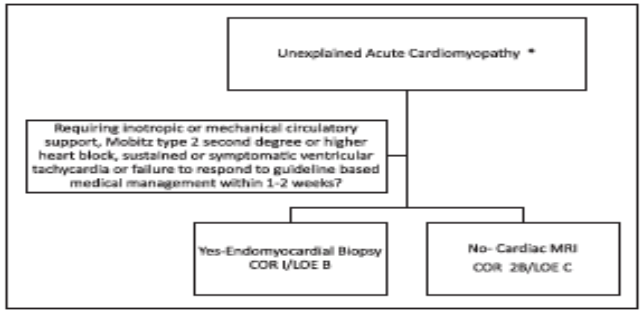


Figure 2. Algorithm for the evaluation of suspected myocarditis in the setting of unexplained acute cardiomyopathy.

Recommendations With Strong Level of Consensus for Myocarditis

4. EMB should be performed in those patients with clinically suspected unexplained acute myocarditis who require inotropic support or MCS and those with Mobitz type 2 second-degree or higher heart block, sustained or symptomatic ventricular tachycardia, or failure to respond to guideline-based medical management within 1 to 2 weeks *(Level of Evidence C).*

Table 3. Diagnostic Criteria for Clinically Suspected Myocarditis

Clinical presentations*
Acute chest pain, pericarditic, or pseudoischemic
New onset (days up to 3 mo) or worsening of dyspnea at rest or exercise, and/or fatigue, with or without signs of left- and/or right-sided heart failure
Subacute/chronic (>3 mo) or worsening of dyspnea at rest or exercise, and or fatigue with or without left- and/or right-sided heart failure
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 New abnormal 12-lead ECG and/or Holter stress testing, any of the following: first- to third-degree atrioventricular block or bundle-branch block; ST/T-wave changes; 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 (echocardiogram/angiography/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 Edema and/or LGE of classic myocarditic pattern (see Role of Cardiac MRI in Suspected Myocarditis)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories in the absence of (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%) or (2) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, hyperthyroidism). Suspicion is higher with higher number of fulfilled criteria. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TnI, troponin I; and TnT, troponin T.

*If the patient is asymptomatic, ≥2 diagnostic criteria should be met.

Reprinted from Caforio et al[248] by permission of Oxford University Press.

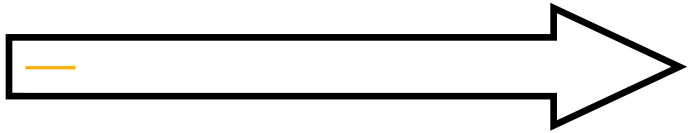
Recommendations With Uncertainty for Myocarditis

1. EMB may be considered in those patients with clinically suspected myocarditis who meet the criteria listed in Table 3[248] *(Level of Evidence C).*

Myocarditis - *Prognosis*

Myocarditis

Dilated Cardiomyopathy



Acute myocarditis
resolves in about 50%
of the patients in the first 2-4 weeks

25% will develop persistent cardiac dysfunction
and 12– 25% may acutely deteriorate
and either die or progress to end-stage DCM
with a need for heart transplantation

A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis

Alida L.P. Caforio[1]*, Fiorella Calabrese[2], Annalisa Angelini[2], Francesco Tona[1], Annalisa Vinci[1], Stefania Bottaro[1], Angelo Ramondo[1], Elisa Carturan[2], Sabino Iliceto[1], Gaetano Thiene[2], and Luciano Daliento[1]

Aims Myocarditis may be idiopathic, viral, and/or immune; frequency of these forms and prognosis are ill-defined. We aimed at identifying aetiopathogenetic and prognostic markers in myocarditis, including viral genome on endomyocardial biopsy (EMB) by polymerase chain reaction (PCR) and serum anti-heart autoantibodies (AHA).

Methods and results We studied 174 patients, 110 males, aged 36 ± 18 years, median follow-up 23.5 months, range 10–54; 85 patients had active myocarditis and 89 borderline myocarditis (no diffuse or severe inflammation) (Dallas criteria). Serum AHA were detected by indirect immunofluorescence. PCR was used to detect virus. Six-year actuarial survival was 73%. AHA were found in 56% of patients and positive PCR in 26%. Univariate predictors of death/transplantation were young age, longer symptom duration, giant cell myocarditis, NYHA II–IV, positive PCR, presentation with LV dysfunction, clinical signs/symptoms of heart failure, and echocardiographic and haemodynamic indexes of cardiac dysfunction. By Cox univariate analysis, highest risk was conferred by clinical signs/symptoms of left (HR = 4.3, CI 1.7–10.8, $P = 0.002$) and right heart failure (HR 3.4, CI 1.5–7.3, $P = 0.002$).

Conclusion In myocarditis, biventricular dysfunction at diagnosis was the main predictor of death/transplantation. AHA identified immune-mediated myocarditis in the majority of cases. Viral genome was a univariate predictor of adverse prognosis. Our approach of using AHA and positive PCR as aetiopathogenetic markers should help patient selection and recruitment in future studies on aetiological therapy.

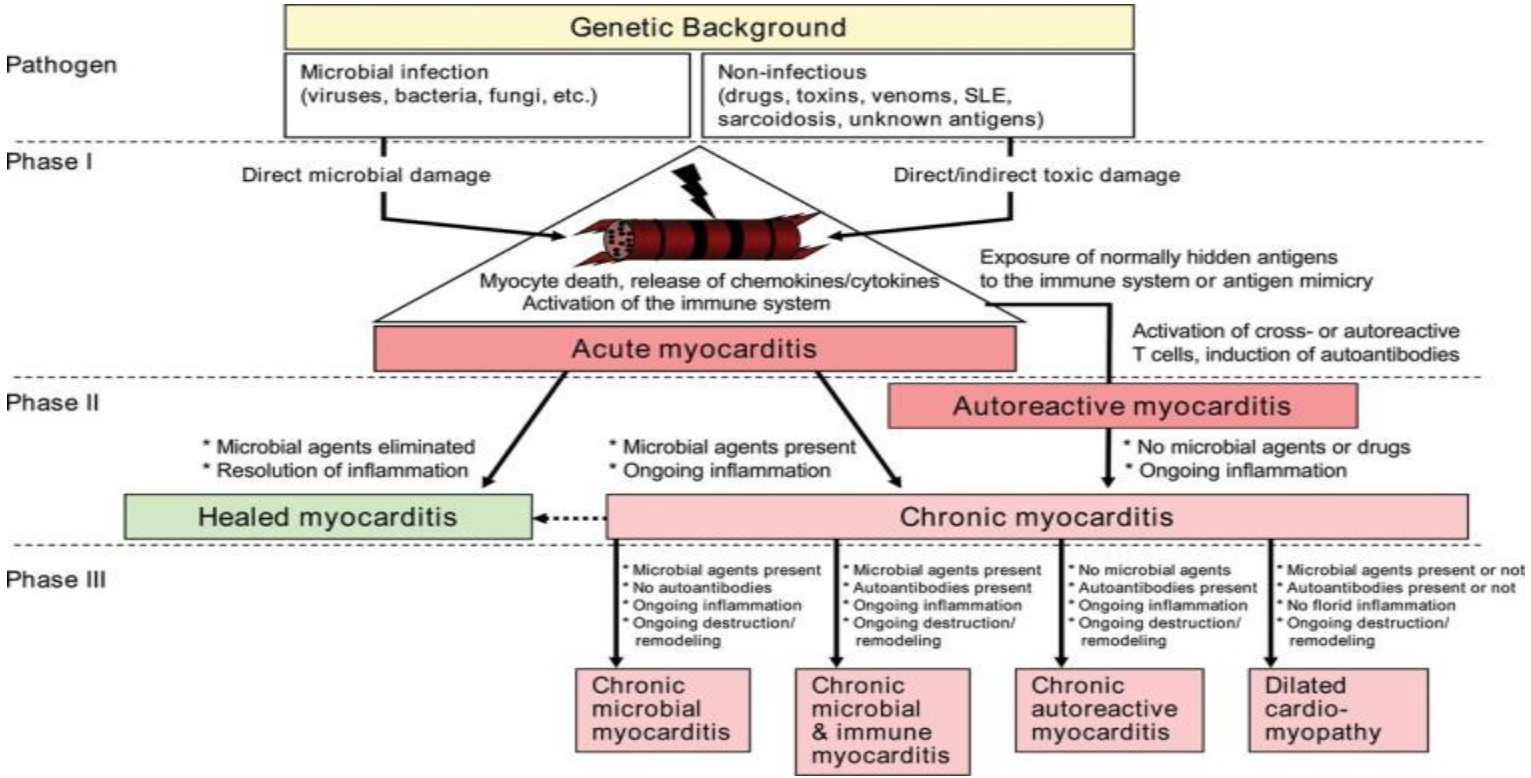
Eur Heart J 2007; 28:1326-33

Univariate predictors of death/ Tx in AM

	Alive n=124	Dead/Tx n=26	p
NYHA(II,III, or IV)(%)	54 (43)	22 (85)	0.001
Symptom duration (mo)	2 ±5	10 ± 17	0.000
Echo- FE (%)	45 ±14	31 ± 10	0.000
WPM(mmHg)	12 ± 8	17 ± 7	0.03
LVSP (mmHg)	117 ± 20	101 ± 26	0.03
RVEDP(mmHg)	5 ± 4	15 ± 20	0.000
PAD	11 ± 7	15 ± 6	0.01
Angio-LVEF(%)	49 ± 17	28 ± 17	0.001
Clinical RV failure (%)	21(17)	12 (46)	0.001
Clinical LV failure (%)	49 (40)	20 (77)	0.001

Role of EMB in directing etiology-specific treatment ?

Myocarditis – *different entities*



Caforio A et al., Eur Heart J 2013;34:2636-2648

Myocarditis - *Aetiology*

INFECTIOUS	IMMUNE-MEDIATED	TOXIC
Bacterial	Allergens: e.g. penicillin	Drugs: e.g catecholamine cocaine
Spirochetal		
Fungal	Alloantigens: e.g. heart-transplant rejection	Heavy metals
Protozoal		
Parasitic		Physical agents
Rickettsial		
Viral: coxsackievirus, cytomegalovirus, dengue virus, echovirus, encephalomyocarditis, Epstein–Barr virus, hepatitis A, hepatitis C virus, herpes simplex virus, herpes zoster, HIV, influenza A and B, Junin virus, lymphocytic choriomeningitis, measles, mumps, parvovirus, poliovirus, rabies, respiratory syncytial, rubella, rubeola, vaccinia, varicella–zoster, variola, and yellow fever virus	Autoantigens: e.g. myosin in giant-cell myocarditis and in virus-negative myocarditis , myocarditis associated to organ and non-organ-specific autoimmune diseases	Various Agents, e.g sting bites

Caforio A et al., Eur Heart J 2013;34:2636-2648

Etiological forms of biopsy-proven myocarditis

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

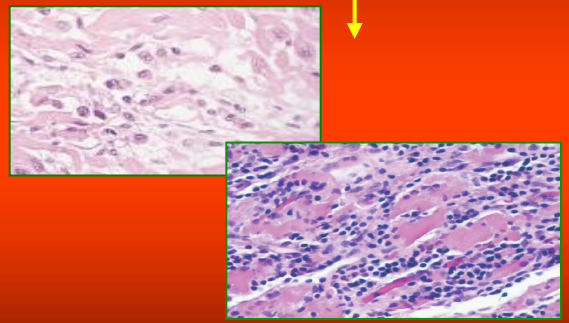
Histological myocarditis with positive viral PCR and positive cardiac aabs (*Table 2*).

N.B. A follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac aabs, e.g. post-infectious autoimmune disease.

Caforio et al. Eur Heart J 2013; 34:2636-48

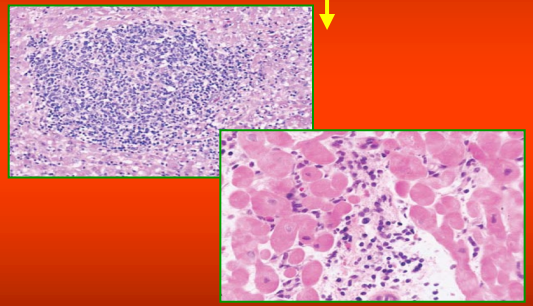
Myocarditis - *Dallas-Criteria*

Inflammatory infiltate with Myocyte necrosis



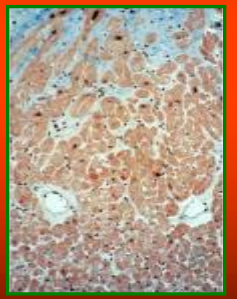
Acute Myocarditis

Inflammatory infiltrate without myocyte necrosis with/without fibrosis



Borderline Myocarditis

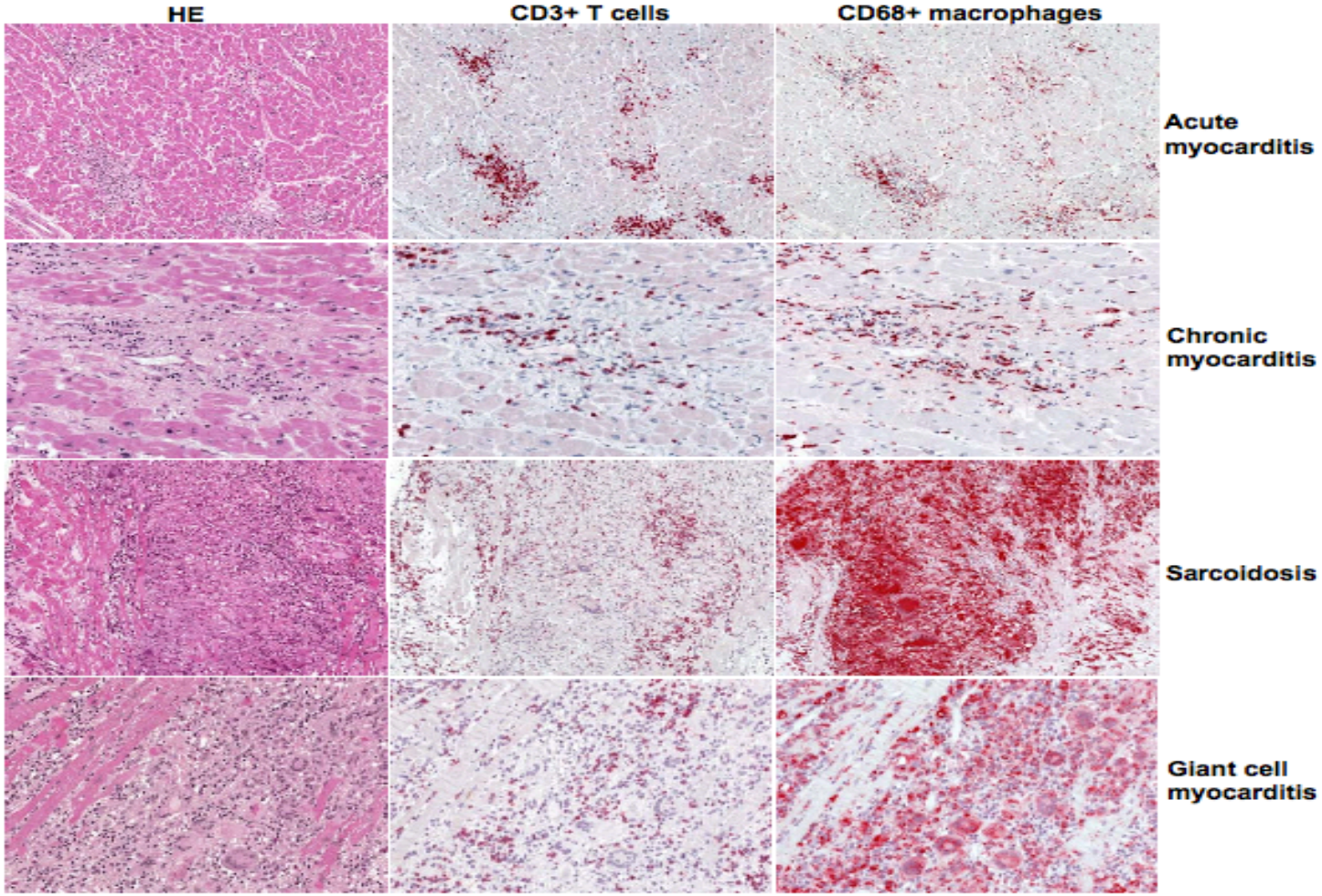
No inflammatory infiltrate, No myocyte necrosis ± Fibrosis



Healed Myocarditis

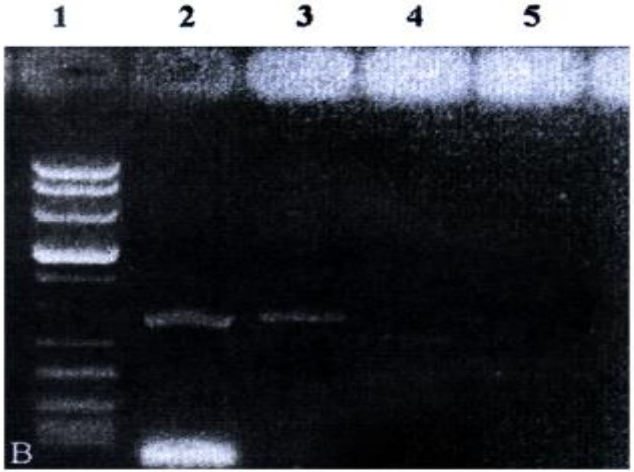
Only histological investigation of myocardial biopsies according to the Dallas-criteria is obsolete!

Aretz et al.: Am J Cardiovasc Pathol 1987;1:3.


HE
CD3+ T cells
CD68+ macrophages
Acute myocarditis
Chronic myocarditis
Sarcoidosis
Giant cell myocarditis

Myocarditis – *Molecular biology*

Polymerase chain reaction (PCR)

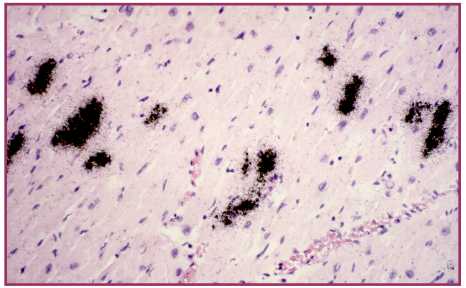


1	2	3	4	5
DNA Marker	AV+ control	EMB AV- PCR +	house-keeping gene	negative control

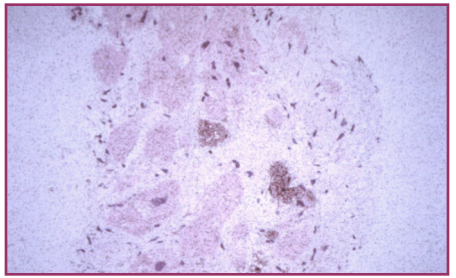
Calabrese et al, cardiacvascular Research 2003; 60: 11-25

Klingel et al, Med Microbiol Immunol 2004; 193: 101-107

In situ-Hybridisation

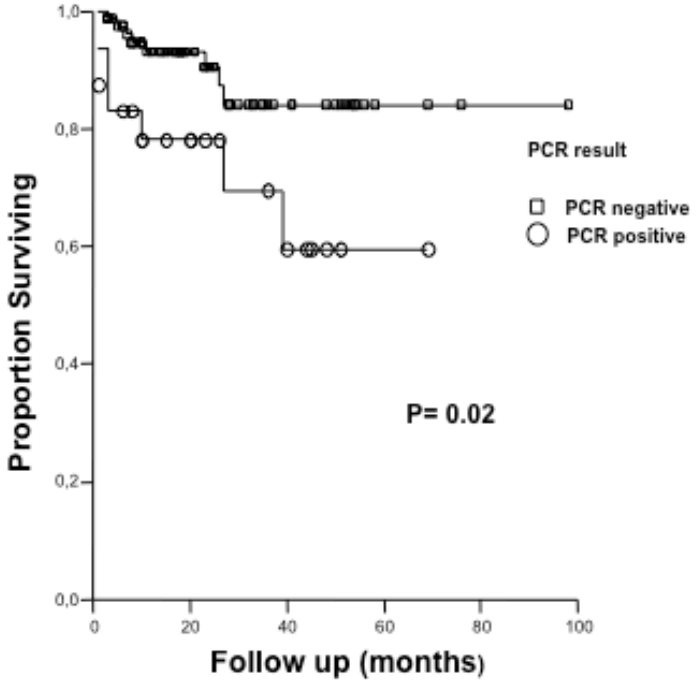


acute infection



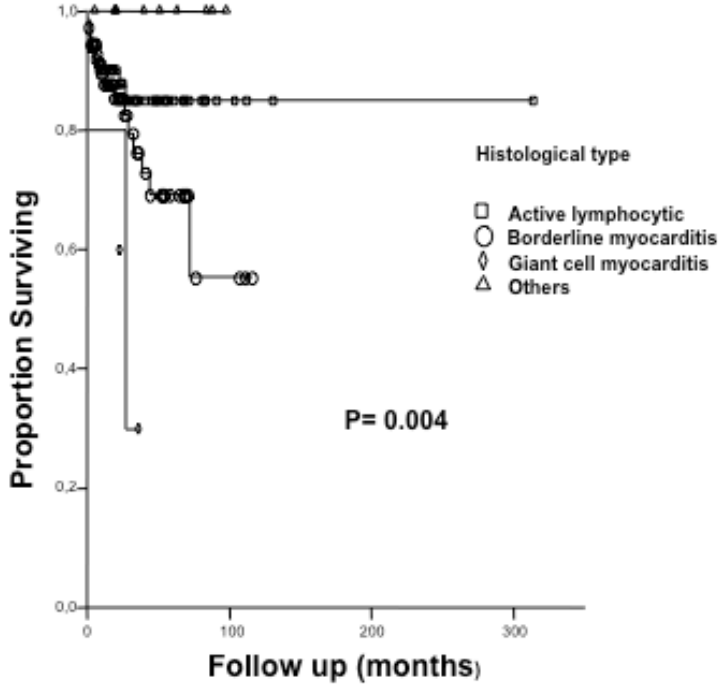
Persisting infection

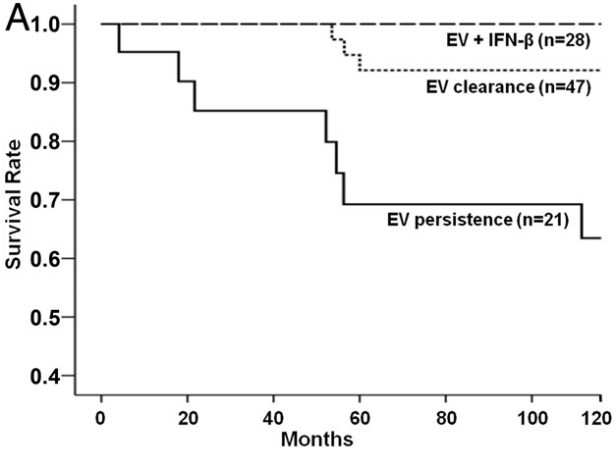
AM: Actuarial survival and PCR result

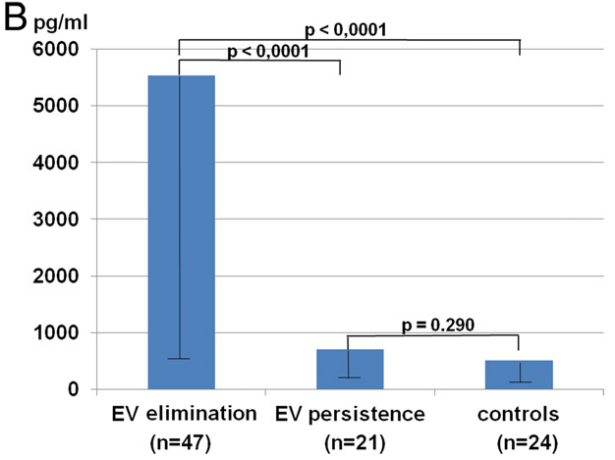


AM: Actuarial survival and histology type

Eur Heart J 2007; 28:1326-33







Research Correspondence

Interferon-Beta Improves Survival in Enterovirus-Associated Cardiomyopathy

D. Lassner, PhD
Jessica von Schlippenbach, MD
Wolfgang Poller, MD
Heinz-Peter Schultheiss, MD

Figure 1 **Mortality Rate in EV-Positive Patients and Serum IFN-β Levels**

(A) Mortality rate among patients positive for enterovirus (EV) infection: unadjusted survival according to virus analysis at follow-up. Spontaneous or drug-induced enterovirus clearance was associated with a significantly reduced mortality rate in comparison to patients who had enterovirus persistence ($p = 0.0005$ by the log-rank test). **(B)** Serum interferon-beta (IFN-β) levels were significantly elevated in patients who cleared the virus spontaneously. A lack of IFN-β production with low levels as seen in controls was found in all patients with persisting infection.

JACC Vol. 60, No. 14, 2012
October 2, 2012:1295–6

ESC recommendations for immunomodulation in myocarditis

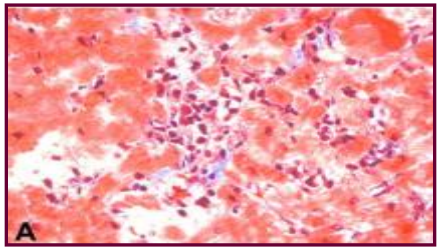
High dose intravenous immunoglobulin

High dose intravenous immunoglobulin (IVIG) modulates the immune and inflammatory response by a variety of mechanisms and is used in a number of systemic autoimmune diseases.[170] Its use has been associated with improved left ventricular ejection fraction in chronic symptomatic heart failure of various causes,[171] but IVIG was ineffective in the IMAC controlled trial of recent-onset DCM in which only 15% of patients had biopsy-proven myocarditis of non-specified cause.[172] Nevertheless, IVIG has no major side-effects and may be used in myocarditis refractory to conventional heart failure therapy, both viral and autoimmune forms, particularly if autoantibody-mediated.[3] In the absence of multi-centre randomized studies in biopsy-proven myocarditis/DCM of viral or autoimmune origin, we do not give recommendations for the use of IVIG.

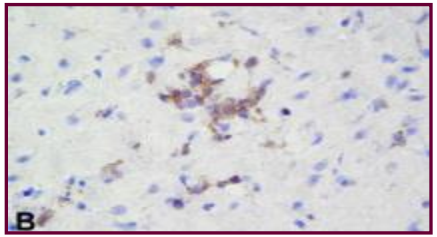
Caforio et al. Eur Heart J 2013; 34:2636-48

Myocarditis – *Immunohistology*

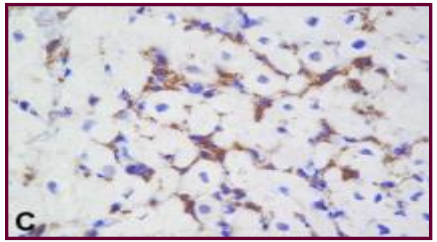
Masson-Trichrom-colouring

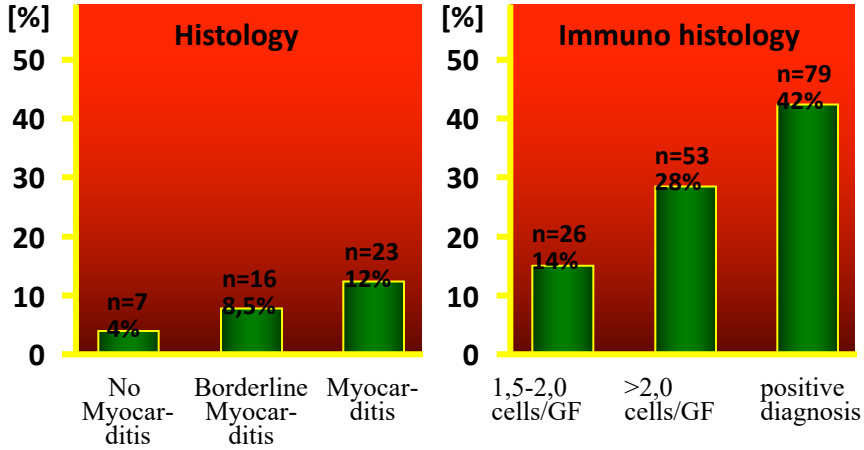


T-Lymphocytes (CD3)



Macrophages





Schultheiß, Z Kardiol 1993; 82: Suppl. 4

Klingel et al, Med Microbiol Immunol 2004; 193: 101-107

Predictors of Outcome in Patients With Suspected Myocarditis

Ingrid Kindermann, MD; Michael Kindermann, MD; Reinhard Kandolf, MD; Karin Klingel, MD; Burkhard Bültmann, MD; Thomas Müller; Angelika Lindinger, MD; Michael Böhm, MD

Background—The objective of this study was to identify the prognostic indicators in patients with suspected myocarditis who underwent endomyocardial biopsy.

Methods and Results—Between 1994 and 2007, 181 consecutive patients (age, 42±15 years) with clinically suspected viral myocarditis were enrolled and followed up for a mean of 59±42 months. Endomyocardial biopsies were studied for inflammation with histological (Dallas) and immunohistological criteria. Virus genome was detected by polymerase chain reaction. The primary end point was time to cardiac death or heart transplantation. In 38% of the patients (n=69), the Dallas criteria were positive. Immunohistological signs of inflammation were shown in 50% (n=91). Genomes of cardiotropic virus species were detected in 79 patients (44%). During follow-up, 22% of the patients (n=40) reached the primary end point. Three independent predictors were identified for the primary end point, namely New York Heart Association class III or IV at entry (hazard ratio, 3.20; 95% confidence interval, 1.36 to 7.57; P=0.008), immunohistological evidence of inflammatory infiltrates in the myocardium (hazard ratio, 3.46; 95% confidence interval, 1.39 to 8.62; P=0.008), and β-blocker therapy (hazard ratio, 0.43; 95% confidence interval, 0.21 to 0.91; P=0.027). Ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic dimension index were predictive only in univariate, not in multivariate, analysis. Neither the Dallas criteria nor the detection of viral genome was a predictor of outcome.

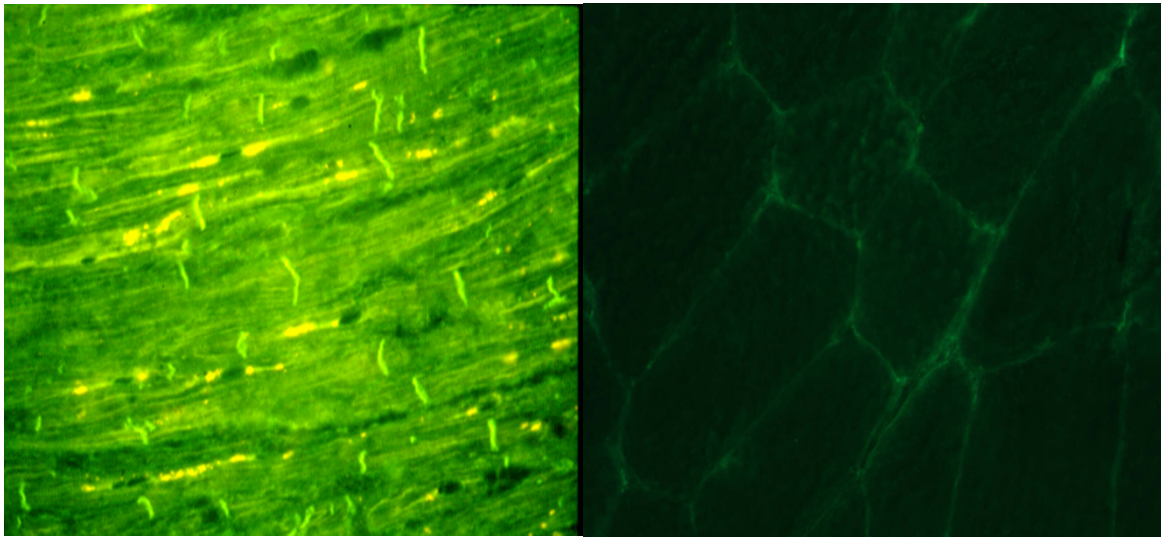
Conclusions—For patients with suspected myocarditis, advanced New York Heart Association functional class, immunohistological signs of inflammation, and lack of β-blocker therapy, but not histology (positive Dallas criteria) or viral genome detection, are related to poor outcome. (***Circulation***. **2008;118:639-648.**)

Prospective biopsy-proven myocarditis Padua cohort (1997-2017)

- 314 patients (203 male), median age 37 yrs (I;III qtl 25;50).
  - Biopsy-proven isolated or in the context of SIDs
- Dedicated multidisciplinary cardiological and immunological follow-up, median (I;III qtl) of 38 months (13;90).
- 45 consecutive patients on immunosuppressive treatment:
  - Indications:
    - virus-negative on EMB
    - NYHA II-IV with EF <50%, refractory to standard therapy with or without arrhythmia, chest pain or troponin release
    - normal coronary arteries.

Caforio, Marcolongo et al, In preparation 2018

Standard Indirect immunofluorescence (IFI-S): circulating organ-specific anti-heart autoantibody (AHA) and anti-intercalated disk (AIDA) patterns



Positive AHA and AIDA on human myocardium (left) and negative human skeletal muscle (x400).

Caforio et al. JACC. 1990.
Caforio et al. Circulation, 2007.
Caforio et al. Heart 2010

Univariate predictors of death/transplant in biopsy-proven myocarditis

	Alive (n=236)	Death/Tx (n=43)	p
Female gender, n (%)	78 (33)	23 (53,5)	0,01
NYHA II to IV at diagnosis, n (%)	109 (46)	31 (73)	0,001
Left heart failure at diagnosis, n (%)	95 (40)	32 (76)	0,000
FE Vsx Eco (%)	42 (30; 55)	27 (23; 40)	0,000
AIDA Positive, n (%)	62 (35)	4 (14)	0,025
AECA positive, n (%)	8 (4,7)	5 (21)	0,01
ANA positive, n (%)	20 (11)	10 (34)	0,003

Caforio, Marcolongo et al, In preparation 2018

Major Criteria of Autoimmune Disease

Witebsky E, Rose NR

- Mononuclear cell infiltrate and abnormal HLA expression in the target organ (organ-specific disease) or in various organs (nonorgan-specific disease) in the absence of infectious agents

- Circulating autoantibodies (Abs) and/or autoreactive lymphocytes in patients (pts) and family members

- Abs and/or autoreactive lymphocytes within the affected organ
- Identification and isolation of autoantigen(s) (Ags) involved
- Disease induction in animals after immunization with Ags and/or passive transfer of serum, Abs and/or lymphocytes
- **Efficacy of immunosuppression/immunomodulation in pts**

- *Autoimmune disease= fullfillment of 2 or more major criteria*

IMMUNOSUPPRESSION:

standard clinical use in:

- graft rejection or graft versus host disease (GVHD)
- systemic autoimmune/autoinflammatory diseases
- allergic/hypersensitivity reactions
- systemic vasculitis
- non-infectious granulomatous diseases
- organ-specific autoimmune diseases:
  - *Renal, pulmonary*
  - *haematological*
  - *gastrointestinal/hepatic*
  - *endocrine, eye*
  - *cutaneous, neurological*
  - ***cardiac***
  - *others?*

CONVENTIONAL IMMUNOSUPPRESSANTS

- **corticosteroids**
  prednisone, methylprednisolone
- **antimetabolites**
  cyclophosphamide
  azathioprine
  methotrexate
  mycophenolate mofetil
  leflunomide
- **calcineurin inhibitors**
  cyclosporine, tacrolimus
- **mTor inhibitors**
  sirolimus, everolimus

AZATHIOPRINE:

-from 1 to 2 mg/Kg/day p.o., usually in combination with prednisone at the beginning

-Good steroid sparing action, safe, usually well-tolerated, not expensive

For a safer use it's worth checking TPMT (**thiopurine methyltransferase**) activity in patients' peripheral blood before starting treatment.

The drug takes several weeks to fully exert immunosuppressive action!

OTHER IMMUNOSUPPRESSIVE/MODULATORY TOOLS

BIOLOGICAL AGENTS

- High Dose I.V. Immunoglobulins (HDIVIG)
- Monoclonal antibodies (MoAbs)

PHYSICAL TOOLS

- Plasma Exchange
- Photopheresis
- Immuneadsorption
- Splenectomy, local irradiation

I.S. FOR BIOPSY-PROVEN AUTOIMMUNE MYOCARDITIS:
WHY SHOULD WE TREAT IT?

EVIDENCE IS GROWING THAT I.S. IS ABLE TO:

- ✓ *dismantle the immunological "machinery" that fosters myocardial inflammation and myocardial damage/impairment*
- ✓ *prevent life-threatening arrhythmia*
- ✓ *prevent relapses and evolution to D.C.M.*

Myocarditis associated with systemic autoimmune and immune-mediated diseases

ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2649–2662
doi:10.1093/eurheartj/ehx321

CURRENT OPINION
Heart failure/cardiomyopathy

Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease

Alida L.P. Caforio[1]*, Yehuda Adler[2], Carlo Agostini[3], Yannick Allanore[4], Aris Anastasakis[5], Michael Arad[6], Michael Böhm[7], Philippe Charron[8,9], Perry M. Elliott[10], Urs Eriksson[11], Stephan B. Felix[12], Pablo Garcia-Pavia[13], Eric Hachulla[14], Stephane Heymans[15,16], Massimo Imazio[17], Karin Klingel[18], Renzo Marcolongo[3], Marco Matucci Cerinic[19], Antonis Pantazis[20], Sven Plein[21], Valeria Poli[22], Angelos Rigopoulos[23], Petar Seferovic[24], Yehuda Shoenfeld[25], Josè L Zamorano[26], and Ales Linhart[27]

Systemic lupus erythematosus

Recommendation

(1) EMB, applying histology, immunohistology and (RT-)PCR for detection of infectious agents, may be useful for diagnosis of SLE myocarditis, since SLE patients are at high risk of infection due to the disease itself and to immunosuppressive treatment.[22,82]

Systemic sclerosis

(2) EMB may be considered in patients with clinically suspected myocarditis; immunosuppressive treatment is indicated in EMB-proven infection-negative myocarditis.[22,63,66,85]

Sarcoidosis

(2) Corticosteroids are the first line treatment.[16,48] Other immunosuppressive drugs may be valid alternatives (see Supplementary material online, *Table S9*).[16,48]

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)

(2) The diagnosis of EGPA myocarditis may reinforce the indication to immunosuppression.[67,68]

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

Recommendation

(1) Since cardiovascular GPA involvement may predict poor prognosis and/or higher risk of relapse,[103,104] an upgraded immunosuppressive regimen may be considered.[105]

Inflammatory myopathies

(1) Myocarditis may be found in IMs patients with or without myositis-specific Abs and it may be an indication to a more intensive immunosuppressive regimen.[70,107,109–111]

Myasthenia gravis

(2) Myasthenia gravis patients with GCM myocarditis should be promptly treated with adequate immunosuppression according to the patient's age and the clinical condition.[22,72,73]

Autoinflammatory diseases

(1) Myocarditis, although uncommon, should be suspected in some non-hereditary AD, such as Still's disease and Behçet's disease if cardiac red flags similar to other SIDs are present.[136,137]

ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2649–2662
doi:10.1093/eurheartj/ehx321

Myocardial and Pericardial Diseases
ESC Working Group

Usefulness of Immunosuppression for Giant Cell Myocarditis

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

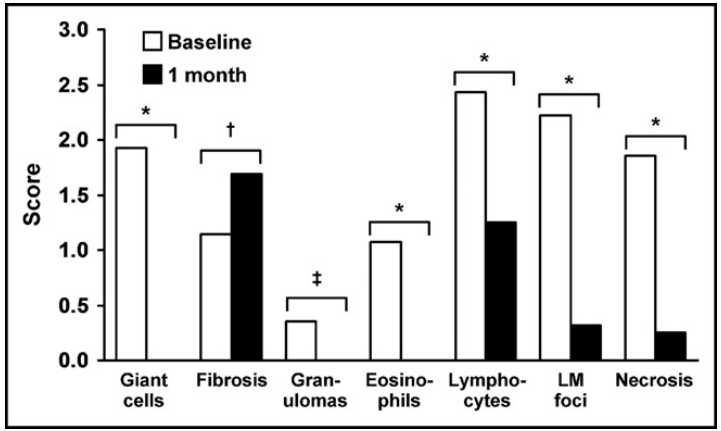


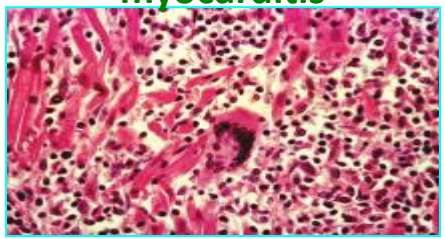
Figure 1. Average histologic scores by blinded analysis at baseline and day 30 in subjects enrolled in the GCM Treatment Trial. *p <0.001, †p = 0.43, ‡p = 0.01. LM = lymphocytic myocarditis.

Table 2
Serum antibody titers in acute giant cell myocarditis

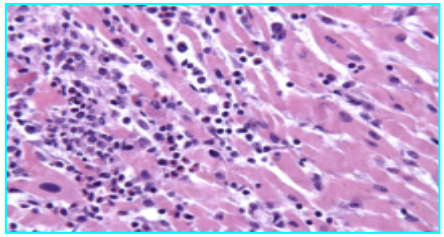
Subject ID	Antihuman Cardiac Myosin	Anti-β1 Adrenergic Receptor	Anti-β2 Adrenergic Receptor
1	1:100	1:400	1:400
2	1:100	1:3,200	1:1,600
3	1:200	1:6,400	1:3,200
4	1:1,600	1:1,600	1:1,600
5	<1:100	1:3,200	1:3,200
8	1:800	1:6,400	1:3,200
10	1:6,400	1:25,600	1:12,800
11	1:100	1:3,200	1:3,200
Positive control	1:6,400	1:25,600	1:25,600
Negative control	1:100	1:800	1:800

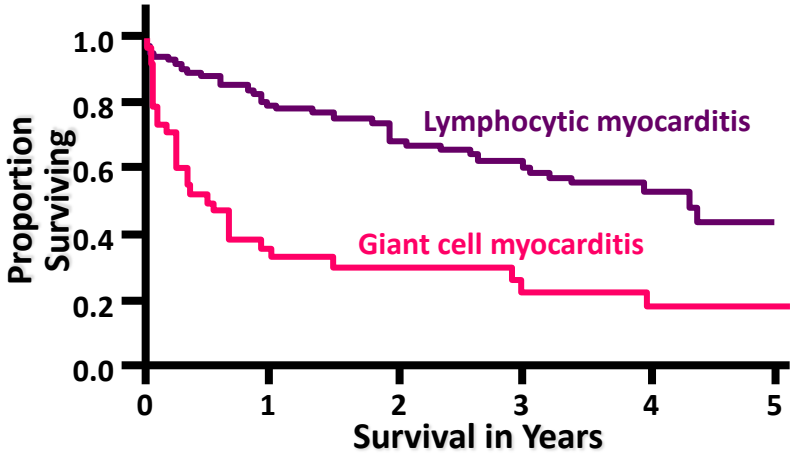
Myocarditis – *Arrhythmias*

Giant cell myocarditis



eosinophilic myocarditis with necrosis





Negative prognosis without immunosuppressive therapy

Heart failure therapy, catecholamines, IABP, LVAD (bridge-to-recovery, bridge-to-transplant))

OKT3-AK, Cyclosporin, Methylprednisolon

Elimination of allergens Methylprednisolon

Cooper LT et al, Circulation 2007;116:2216-2233

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 Cristina Chimenti[1,2,4]

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

Aims To evaluate the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy.

Methods and results This randomized, double-blind, placebo-controlled study included 85 patients with myocarditis and chronic (>6 months) heart failure unresponsive to conventional therapy, with no evidence of myocardial viral genomes. Patients received either prednisone 1 mg kg^{-1} day^{-1} for 4 weeks followed by 0.33 mg kg^{-1} day^{-1} for 5 months and azathioprine 2 mg kg^{-1} day^{-1} for 6 months (43 patients, Group 1) or placebo (42 patients, Group 2) in addition to conventional therapy for heart failure. Primary outcome was the 6 month improvement in left-ventricular function. Group 1 showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left-ventricular dimensions and volumes compared with baseline. None of Group 2 patients showed improvement of ejection fraction, that significantly worsened compared with baseline. No major adverse reaction was registered as a result of immunosuppression.

Conclusion These data confirm the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy. Lack of response in 12% of cases suggests the presence of not screened viruses or mechanisms of damage and inflammation not susceptible to immunosuppression.

I.S. FOR BIOPSY-PROVEN AUTOIMMUNE MYOCARDITIS: WHO SHOULD BE TREATED?

- ✓ **Patients with no evidence of viral genome or other infectious agents on e.m.b**
- ✓ **Before starting I.S., particular attention should be payed to:**
  - *latent systemic infection (bacterial, viral, protozoan)*
  - *recent or hidden malignancy*
  - *critical impairment of liver and/or kidney function*
  - *severe immunodeficiency condition*
  - *major psychiatric disorders, alcohol and/or drug abuse*
  - *concomitant pregnancy and lactation*

R. Marcolongo, Hematology and Clinical Immunology, University Hospital, Padua, Italy

ESC recommendations for immunosuppression in myocarditis

Recommendations

21. Immunosuppression should be started only after ruling out active infection on EMB by PCR.
22. Based on experience with non-cardiac autoimmune disease, the task group recommends consideration of immunosuppression in proven autoimmune (e.g. infection-negative) forms of myocarditis, with no contraindications to immunosuppression, including giant cell myocarditis, cardiac sarcoidosis, and myocarditis associated with known extra-cardiac autoimmune disease.[10,99]
23. Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia and in some forms of infection-negative eosinophilic or toxic myocarditis with heart failure and/or arrhythmia.
24. Immunosuppression may be considered, on an individual basis, in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression.
25. Follow-up EMB may be required to guide the intensity and the length of immunosuppression.

Caforio et al. Eur Heart J 2013; 34:2636-48

Immunosuppressive Therapy Improves Both Short- and Long-Term Prognosis in Patients With Virus-Negative Nonfulminant Inflammatory Cardiomyopathy

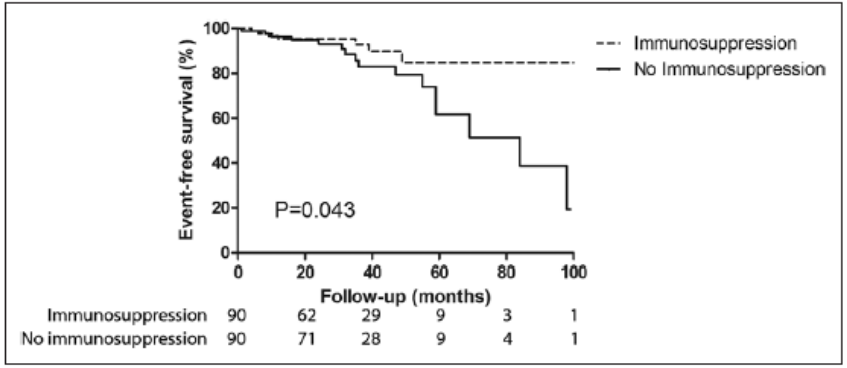
METHODS AND RESULTS: Within the Innsbruck and Maastricht Cardiomyopathy Registry, a total of 209 patients fulfilled the criteria for infl-CMP using endomyocardial biopsy (≥14 infiltrating inflammatory cells/mm²). A total of 110 (53%) patients received immunosuppressive therapy and 99 (47%) did not. To correct for potential selection bias, 1:1 propensity score matching was used on all significant baseline parameters, resulting in a total of 90 patients per group. Baseline characteristics did not significantly differ between both patient groups, reflecting optimal propensity score matching. After a median follow-up of 31 (15–47) months, immunosuppressive therapy resulted in an improved long-term outcome (eg, heart transplantation–free survival) as compared with standard heart failure therapy alone (Log-rank *P*=0.043; hazard ratio, 0.34 [95% CI, 0.17–0.92]) and in a significant larger increase of left ventricular ejection fraction after a mean of 12 months follow-up, as compared with patients receiving standard heart failure treatment only (12.2% versus 7.3%, respectively; *P*=0.036).

CONCLUSIONS: To conclude, this study suggests that immunosuppressive therapy in infl-CMP patients results in an improved heart transplantation–free survival as compared with standard heart failure therapy alone, underscoring the urgent need for a large prospective multicenter trial.

Table 2. Causes of Death/Heart Transplantation in Both Treatment Groups

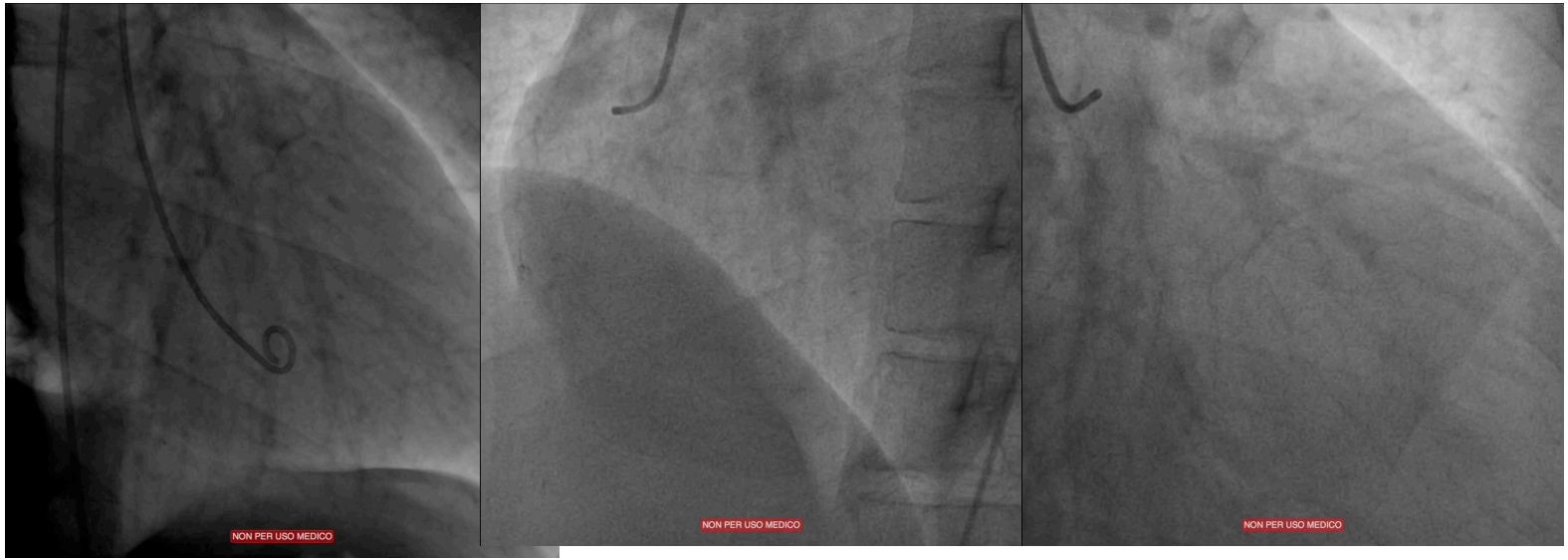
	No Immunosuppression (n=90)	Immunosuppression (n=90)
Progressive heart failure	10*	0
Sudden cardiac death	5	2
Noncardiac	2	3
Cancer	0	1

*Including 3 patients who underwent heart transplantation in a nonurgent setting.



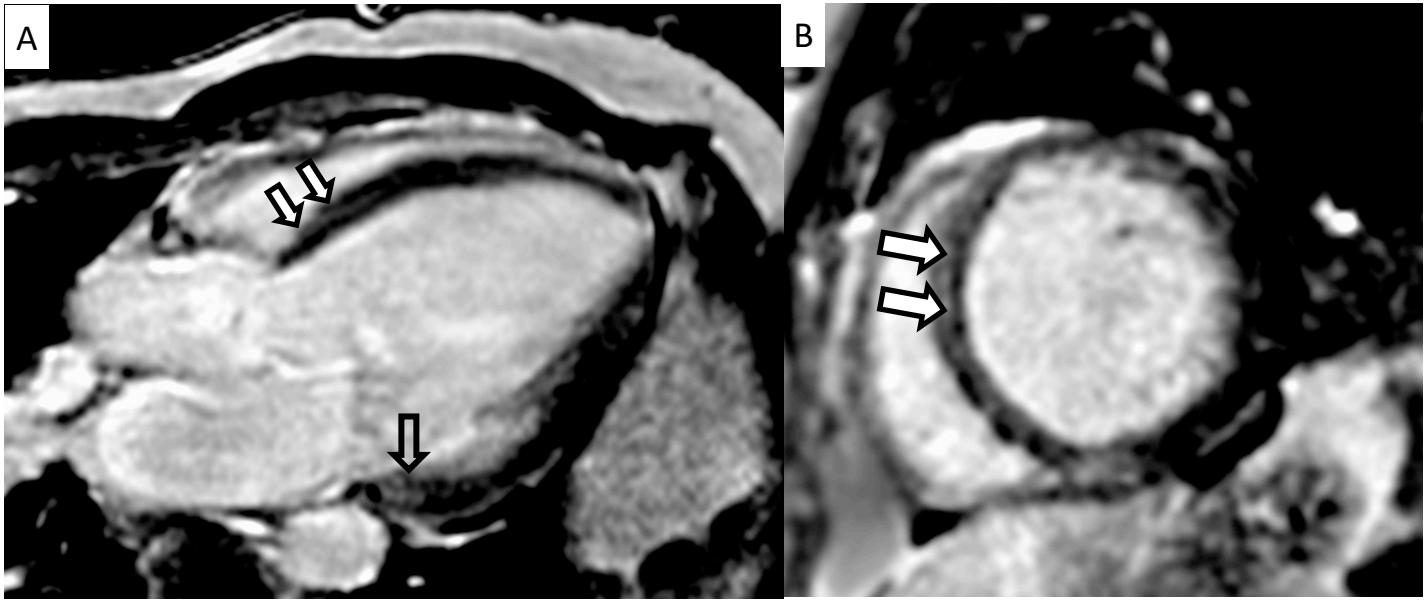
Circ Heart Fail. 2018;11:e004228. DOI: 10.1161/CIRCHEARTFAILURE.117.004228

Cardiac catheterisation

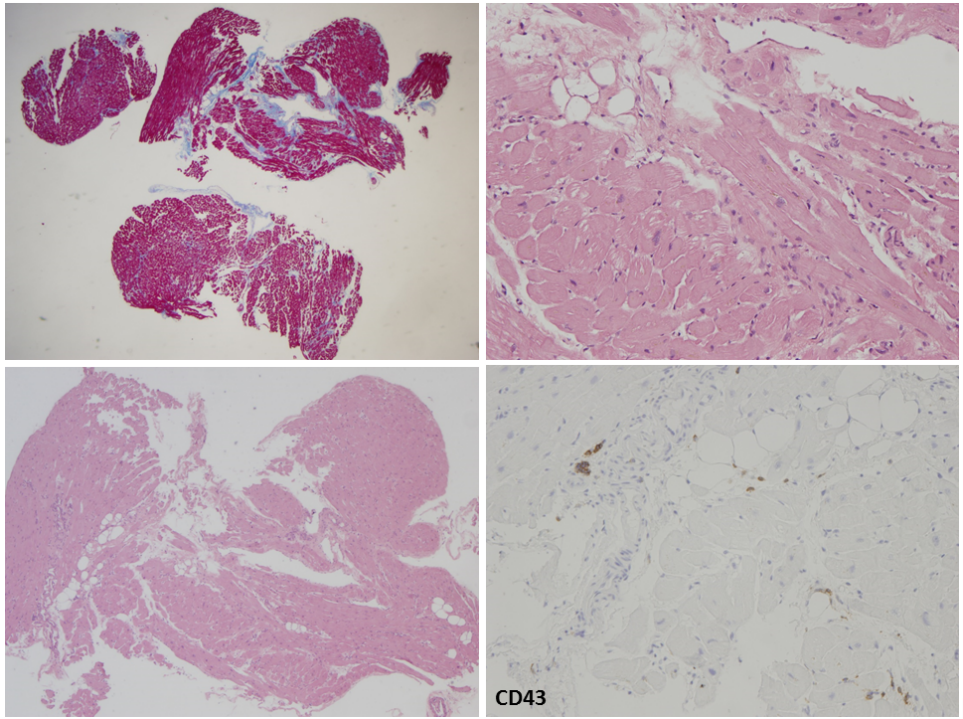


Cardiac catheterisation: normal coronary arteries, severe LV dilation (142 ml/m2) , severe systolic dysfunction LVEF (20%), mild-moderate MR, diffuse hypokinesis, normal pulmonary pressures, mildly reduced cardiac index (2.49 L/min/m2), EMB (4 pieces, no complications)

Acute Phase
(courtesy dr Perazzolo Marra): LGE patterns



Post-contrast T1-Irsequence, 3-chamber long axis view: (A) LGE midwall pattern in infero-lateral LV basal wall (dark arrow) and in the interventricular septum (empty white arrow), confirmed in short axis view (B).

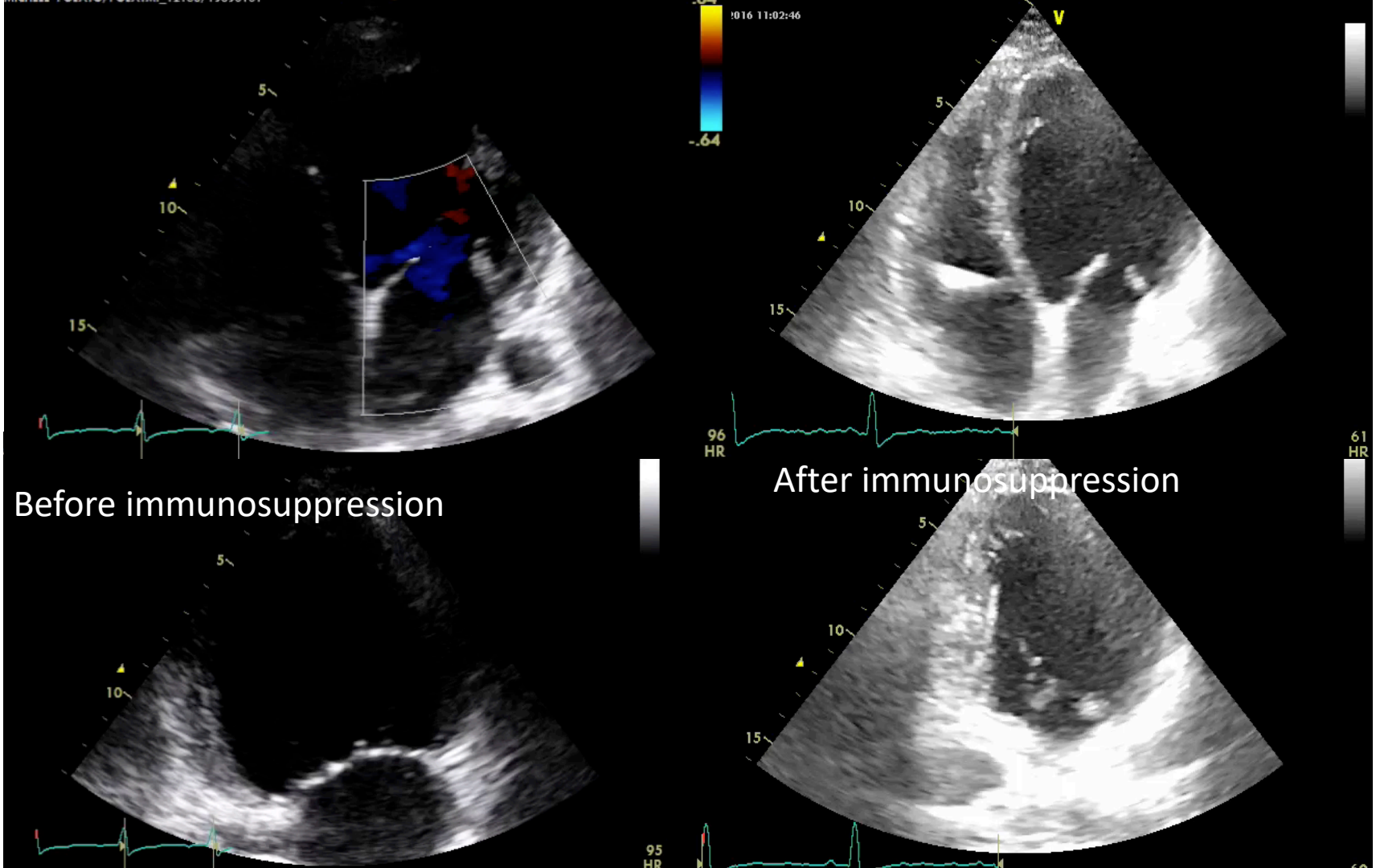


Courtesy, Prof. C Basso, and Prof. G Thiene Cardiac Pathology,Dept of cardiological thoracic &vascular sciences, University of Padova

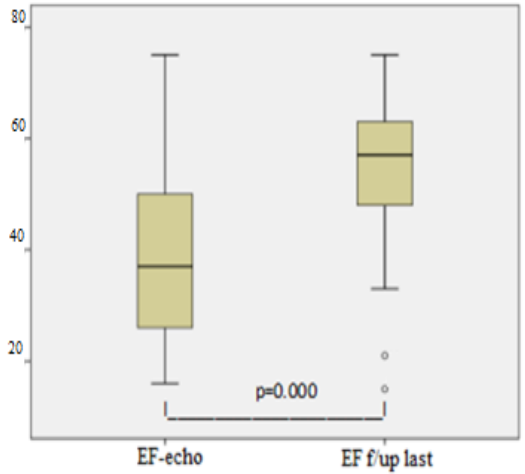
Histology: active lymphocytic myocarditis, interstitial oedema, plurifocal lymphomonocytic infiltrates. Increased myocyte dimensions,dysmetric nuclei,perinuclear halos, and cytoplasmic vacuolisation. ImmunoHx: focal CD45+,CD43+,CD3pos, (>7/mm2), CD68+ associated with myocyte necrosis. Conclusion: chronic active virus-negative lymphomonocytic myocarditis, evolving into DCM.

Negative PCR, NT PCR for cardiotropic viruses:
adenov, HSV, EBV,HHV6; PVB19; CMV;influenza A, B; EV.

AHA positive


Before immunosuppression
After immunosuppression

Echocardiographic biventricular function pre and post-immunosuppression (median 2 yrs)



	Pre-therapy	Post-therapy	p
Biplane echocardiographic LVEF (%)	37 (26; 50)	59 (48; 65)	0,000
FAC (%)	35 (28; 48)	50 (44; 59,5)	0,001

Caforio, Marcolongo et al, In preparation 2018

Recommendation 7:

- In familial and non-familial pedigrees with biopsy proven inflammatory DCM in the index case, cardiac-specific autoantibody (AHA) test at baseline and at follow-up should be considered in symptom-free relatives with or without cardiac abnormalities (e.g. ECG, echocardiography, CMR).
- Non-invasive cardiac screening with echocardiography and ECG may be more frequent in relatives with cardiac autoantibodies.
- Immunomodulatory and/or immunosuppressive therapy in biopsy-proven non-infectious inflammatory DCM should be considered
- Physical activity should be restricted in DCM with underlying biopsy-proven active phase of myocarditis.

European Heart Journal (2016) 37, 1850–1858
doi:10.1093/eurheartj/ehv727

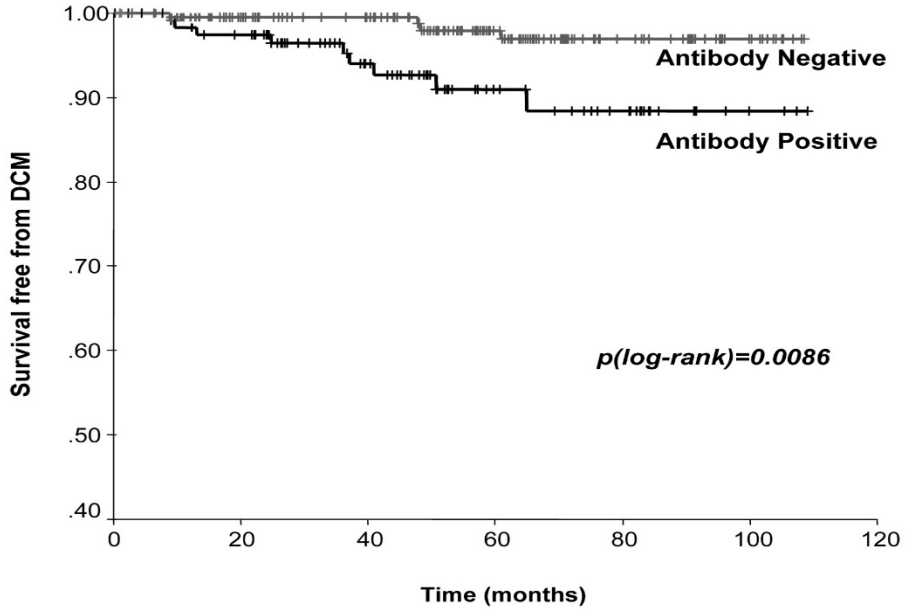
ESC REPORT

Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto[1*], Perry M. Elliott[2], Eloisa Arbustini[3], Yehuda Adler[4], Aris Anastasakis[5], Michael Böhm[6], Denis Duboc[7], Juan Gimeno[8], Pascal de Groote[9,10], Massimo Imazio[11], Stephane Heymans[12,13], Karin Klingel[14], Michel Komajda[15], Giuseppe Limongelli[16], Ales Linhart[17], Jens Mogensen[18], James Moon[19], Petronella G. Pieper[20], Petar M. Seferovic[21], Stephan Schueler[22], Jose L. Zamorano[23], Alida L.P. Caforio[24], and Philippe Charron[25,26]

Prospective Familial Assessment in Dilated Cardiomyopathy

Cardiac Autoantibodies Predict Disease Development in Asymptomatic Relatives



Time	0	20	40	60	80	100
AHA+	121	108	73	39	27	3
AHA-	190	164	145	93	46	16

Number of observations remaining

Caforio et al
Circulation 2007

European Heart Journal (2016) 37, 1850–1858
doi:10.1093/eurheartj/ehv727

Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto[1*], Perry M. Elliott[2], Eloisa Arbustini[3], Yehuda Adler[4], Aris Anastasakis[5], Michael Böhm[6], Denis Duboc[7], Juan Gimeno[8], Pascal de Groote[9,10], Massimo Imazio[11], Stephane Heymans[12,13], Karin Klingel[14], Michel Komajda[15], Giuseppe Limongelli[16], Ales Linhart[17], Jens Mogensen[18], James Moon[19], Petronella G. Pieper[20], Petar M. Seferovic[21], Stephan Schueler[22], Jose L. Zamorano[23], Alida L.P. Caforio[24], and Philippe Charron[25,26]

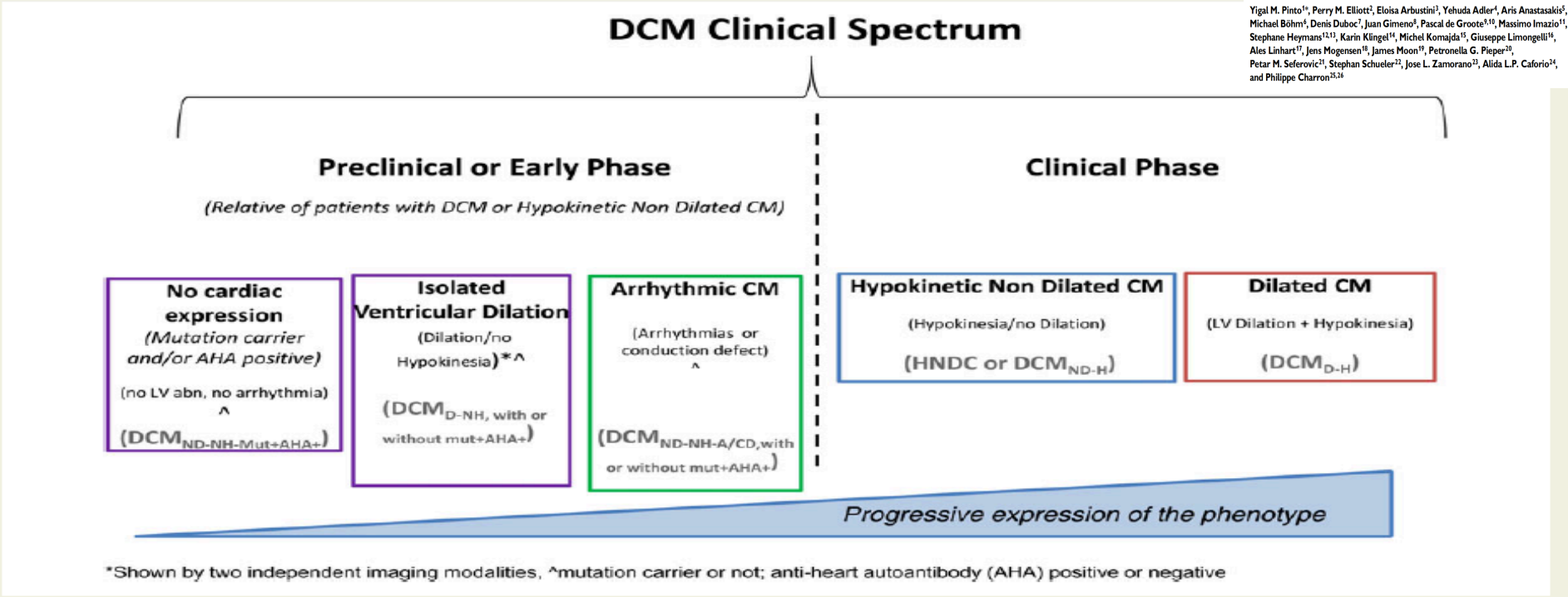
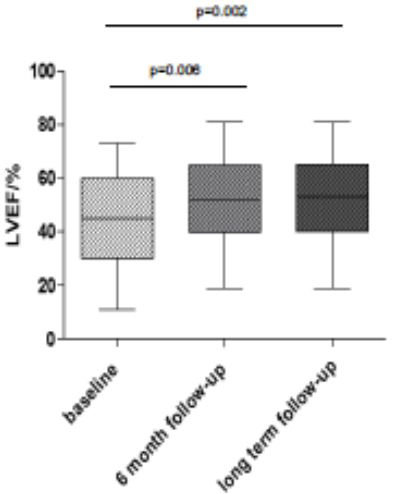


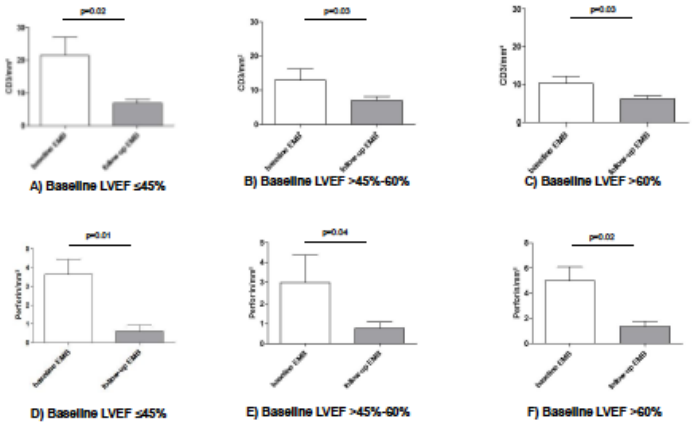
Figure 1 Description of the clinical spectrum of DCM. LV abn, left ventricle abnormality. DCM can be further classified as ND or D (non-dilation/dilation) or NH or H (non-hypokinetic/hypokinetic) or mut+ (mutation carrier) or AHA+ (anti-heart autoantibody positive) or A/CD (arrhythmia/conduction defect).

Long-term outcome of patients with virus-negative inflammatory cardiomyopathy after immunosuppressive therapy

Felicitas Escher, MD [1,2,7,§], Uwe Kühl, PhD [1,2], Dirk Lassner, PhD [1], Wolfgang Poller, MD [3,7], Dirk Westermann, MD [4], Burkert Pieske, MD [2,5,7], Carsten Tschöpe, MD [2,6,7] and Heinz-Peter Schultheiss, MD [1]



Hemodynamic course of total study population.



Immunohistochemical detection of intramyocardial inflammation of subgroup analysis in patients with baseline LVEF ≤45%, LVEF >45%-60%, and LVEF >60%.

Clin Res Cardiol. 2016 Jun 16. [Epub ahead of print]

KEY POINTS FOR A SAFE IMMUNOSUPPRESSION IN AUTOIMMUNE MYOCARDITIS

1. Endomyocardial biopsy
2. Careful selections of candidates to therapy
3. Close interprofessional teamwork
4. Active engagement of patients and their carers by THERAPEUTIC EDUCATION to self-management

(WHO working group on Therapeutic Patient Education, Copenhagen, 1998)

Courtesy Dr. R. Marcolongo, Hematology and Clinical Immunology, University Hospital, Padua, Italy

Summary: Myocarditis and heart failure-the 2018 diagnostic and therapeutic approach

- Diagnose viral myocarditis to avoid potentially harmful immunosuppression.

- Virus-specific anti-viral therapy (though off-label and expensive) for selected cases with virus persistence and symptomatic heart failure refractory to standard therapy **(indication class IIb) .**

- Immunosuppression mandatory **(indication class I)** for:

  Idiopathic (e.g. virus-negative) Giant-cell myocarditis

  Idiopathic eosinophilic myocarditis

  Virus-negative myocarditis associated with other organ specific or non organ-specific autoimmune diseases

- Immunosuppression may be considered **(indication class IIa, TIMIC trial)** in experienced centers for:

  Virus negative myocarditis with persistent heart failure/arrhythmia symptoms and ventricular dysfunction refractory to standard therapy

Conclusions

- **Myocarditis may be suspected by noninvasive cardiac imaging, but diagnosis of certainty and etiological diagnosis is based upon EMB**
- **Transition from autoimmune myocarditis with mild dysfunction or preserved pump function to DCM may take a long latency period**
- **Left and right ventricular dysfunction at diagnosis and autoimmune pathogenesis are associated with negative prognosis in biopsy-proven noninfectious myocarditis and may identify patients who are candidates to immunosuppression/immunomodulation.**
- **Standard immunosoppression is associated with improved biventricular function in proven autoimmune myocarditis.**

Myocarditis – *a difficult disease*

"The inflammation of the heart is difficult to diagnose ***...YES, but***

diagnosis of certainty and etiological diagnosis is

possible in 2018!!

and when we have diagnosed it,

can we then treat it better?" ***YES***

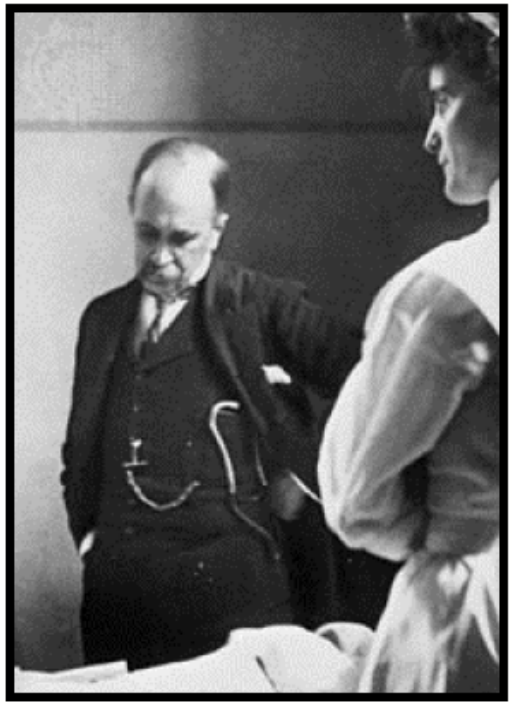

TRAITÉ
DE
LA STRUCTURE
DU CŒUR,
DE SON ACTION,
ET
DE SES MALADIES.
Par M. SENAC, Médecin Consultant du Roy.
TOME PREMIER.
A PARIS,
Chez JACQUES VINCENT, rue de-vis-à-vis l'Eglise de S. Severin, à l'Ange.
M. DCC. XLIX.
AVEC APPROBATION ET PRIVILEGE DU ROY.

Jean Baptiste de Senac, 1749

Acknowledgments: the Padua Myocarditis Heart Team approach

- Cardiology
  - Prof. S Iliceto, Prof G Tarantini, Dr Cacciavillani, Dr Perazzolo-Marra, Dr L Leoni, Dr G Malipiero
- Clinical Immunology
  - Dr Renzo Marcolongo
- Cardiac Pathology
  - Prof. G. Thiene, Prof. C Basso, Prof. A Angelini
- Laboratory Medicine
  - (Prof. C Plebani, Dr. N Gallo, Dr. M Seguso)
- Cardiac Surgery
  - (Prof. G. Gerosa, Prof. T Bottio, Dr V Tarzia)

Take-home message: Biopsy-proven diagnosis and biopsy-guided therapy in myocarditis? ***As soon as possible….Time is muscle, fire is dangerous, we cannot heal a burned-out heart***



"There are three phases to treatment: diagnosis, diagnosis and diagnosis."

William Osler. Principles and Practice of Medicine, 1892