Ecocardiochirurgia 2014
Milano, 5-7 Maggio 2014

Cardio-RM. Il paradosso di una metodica di riferimento per la diagnosi di una cardiopatia potenzialmente mortale ma sostanzialmente negata ai cardiologi.

Rimane ancora un ruolo per gli ultrasuoni nella diagnosi ?
Come impostare l'esame RM e quali livelli di certezza raggiungiamo ?

Alberto Roghi
Laboratorio di RM Cardiaca
Dipartimento Cardio-Toraco-Vascolare A.De Gasperis
A.O.Niguarda Ca' Granda, Milano

RM cardiaca e miocardite: vantaggi e limiti

- cinesi regionale, volumi, FE, massa VS
- STIR, (T2 mapping, T1 mapping)
- early enhancement
- late gadolinium enhancement

- artefatti da tachicardia, respiro
- esame lungo (40 min)
- no shock, PM
- accesso
- competenza operatore

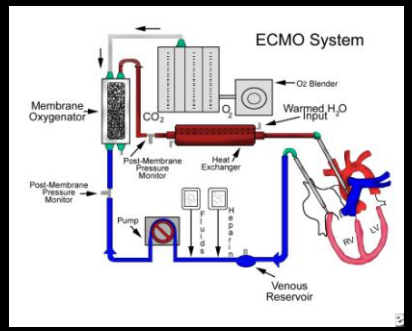
- Bias di selezione delle miocarditi a basso profilo di rischio
- Ridotta utilità nei quadri a rapido deterioramento
- Utile nei quadri di difficile inquadramento diagnostico
- Significato prognostico del LGE persistente sconosciuto

risk variables
co-pathologies

Myo-Pericarditis Diagnostic Criteria

infective
autoimmune
drugs
chemical

Clinical presentation



Comparison of values of laboratory and imaging techniques in myocarditis

Technique	n	Sensitivity (%)	Specificity (%)	Positive Predictive Value	Negative Predictive Value	Reference(s)
Troponin T	80	53	96	93	56	74
Troponin I	88	34	89	—	—	75
EMB-H	71	10–36	98	—	—	10,11,38
EMB-IH	20	80	85	—	—	76
Gallium-67 scintigraphy	71	87	86	36	98	38
Ultrasonic tissue characterization	106	100	91	—	—	29
AMA vs. EMB-H	50	91–100	31–44	28–33	93–100	63
AMA vs. EMB-IH	65	65	71	86	41	77
CMR-T1	37	84	100	—	—	13
CMR GE-T1	27	100	100	—	—	54
CMR-IR-GRE	44	88	91	—	—	57
CMR						
T2/LGE/gRE	48	84/44/80	74/100/68			58
Any 2		76	95.5	—	—	

AMA = indium-antimyosin antibody scintigraphy; CMR = cardiac magnetic resonance imaging; EMB-H = endomyocardial biopsy-histological study; EMB-IH = immunohistochemical study; GE T1 = gadolinium-enhanced T1-weighted; gRE = global (early) relative enhancement; IRGRE = inversion recovery gradient echo pulse sequence; LGE = late gadolinium enhancement.

Skouri JACC 2006

ECHOCARDIOGRAPHY AND MYOCARDITIS

- LV SEGMENTAL WALL MOTION – VOLUMES- THICKNESS
- PERICARDIAL EFFUSION
- RV SYSTOLIC FUNCTION
- ASSOCIATE CARDIAC DISEASES

- BACKSCATTER
- TISSUE DOPPLER VELOCITIES
- LONGITUDINAL STRAIN DOPPLER

Table 7

Proposed Diagnostic CMR Criteria (i.e., Lake Louise Consensus Criteria) for Myocarditis

In the setting of clinically suspected myocarditis,* CMR findings are consistent with myocardial inflammation, if at least 2 of the following criteria are present:

- Regional or global myocardial SI increase in T2-weighted images.†
- Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.‡
- There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images ("late gadolinium enhancement").§

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.

Relationship between myocardial edema and myocardial mass during the acute and convalescent phase of myocarditis Zagrosek et al. J Cardiov Magn Res 2008

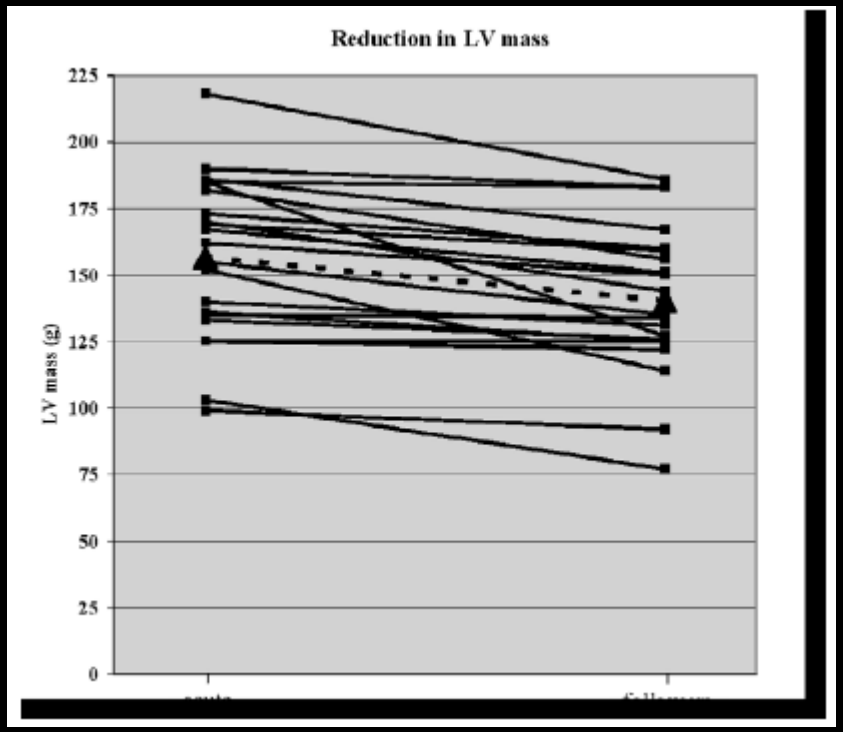
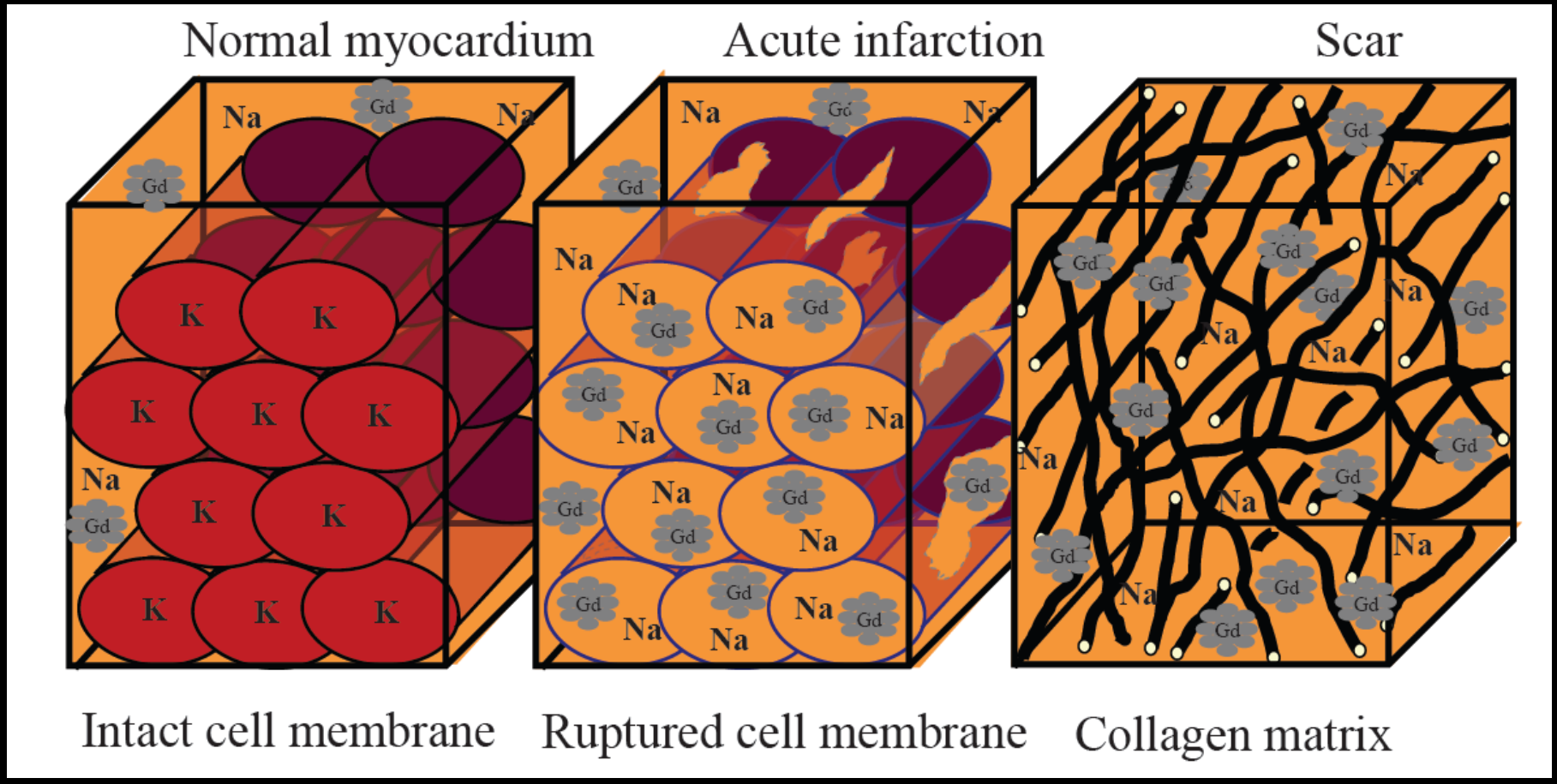


Table 3: CMR results in acute myocarditis and at follw-up

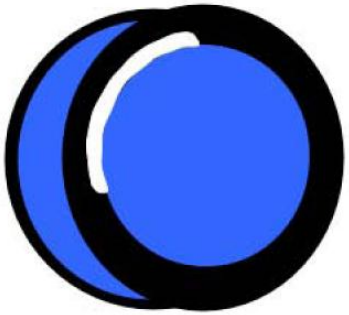
Variable	*Acute*	*Follow-up*	*Difference between means*	*P-value acute vs. follow-up*
LV mass (g)	156.66 ± 30.56	140.33 ± 28.30	-16.33	<0.0001
LV mass/height (g/cm)	0.90 ± 0.15	0.80 ± 0.12	-0.10	0.0001
LVEDV (ml)	158.10 ± 40.01	153.57 ± 37.50	-4.52	0.395
LVEDV/height (ml/cm)	0.89 ± 0.19	0.85 ± 0.19	-0.04	0.2859
Ejection fraction (%)	59.95 ± 6.39	64.14 ± 5.26	4.19	0.015
T2 ratio	2.41 ± 0.39	1.68 ± 0.29	-0.72	<0.0001


Normal myocardium
Acute infarction
Scar
Na
Gd
K
Intact cell membrane
Ruptured cell membrane
Collagen matrix

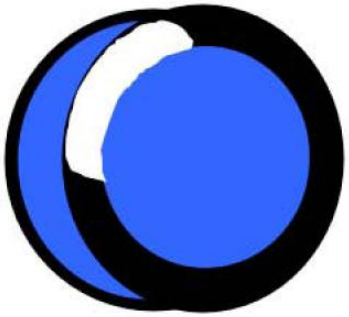
LATE ENHANCEMENT

Ischemic

A. Subendocardial Infarct



B. Transmural Infarct



Nonischemic

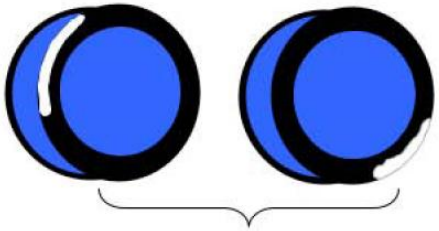
A. Mid-wall HE

- Idiopathic Dilated Cardiomyopathy
- Myocarditis

- Hypertrophic Cardiomyopathy
- Right ventricular pressure overload (e.g. congenital heart disease, pulmonary HTN)

- Sarcoidosis
- Myocarditis
- Anderson-Fabry
- Chagas Disease

B. Epicardial HE



- Sarcoidosis, Myocarditis, Anderson-Fabry, Chagas Disease

C. Global Endocardial HE

- Amyloidosis, Systemic Sclerosis, Post cardiac transplantation

Clinical presenting patterns of acute myocarditis and CMR features

Alberto Roghi, Daniela Lanza, Patrizia Pedrotti, Angela Milazzo, Ornella Rimoldi, Stefano Pedretti

Ospedale Niguarda Cà Granda Magnetic Resonance Unit and Università Vita-Salute San Raffaele Milan, Italy

Abstract

BACKGROUND: acute myocarditis (AM) clinical onset can span from subclinical disease to acute heart failure (AHF) ventricular fibrillation (VF) or sudden cardiac death in young adults. Myocarditis may cause arrhythmias both in the acute inflammatory period and in the chronic phase, as a consequence of electrical remodeling. Aim of the study was to evaluate the relationship between myocardial oedema and late enhancement (LGE) extension and clinical presenting patterns of acute myocarditis by means of cardiac magnetic resonance imaging (CMR).

METHODS: Seventy-three consecutive patients (pts) referred for suspected myocarditis from 2007 to 2010 were analyzed. Symptoms, ECG changes, reduced myocardial function, elevated creatine kinase, positive troponin T, suggested AM. Coronary artery disease was excluded at angiography. The diagnosis was confirmed by CMR (Siemens Avanto 1.5 Tesla) performed within 2 weeks after the onset of symptoms, according to the presence of signal hyperintensity at STIR images (edema), associated with concordant LGE (0.1mmol/Kg gadobutrol) at CE-IR images. FU scan was performed at 3 months. The areas of enhancement were measured by commercial software and expressed as percentage of the LV mass. Data are x ±SD, significant difference p<0.05.

RESULTS: According to the initial clinical picture pts were divided into two groups: group 1 (G1;n= 62), presenting with chest pain; group 2 (G2; 11 pts), presenting with AHF or VF. Age, LV volumes and functional parameters were similar in the 2 groups. In G2 LVEF was slightly lower. G2 showed a larger percentage of edema 33 ± 23 vs 9 ± 7 (p<0.0001) and LGE 19 ± 20 vs 8 ± 6 (p<0.05). In all pts LVEF was significantly inversely correlated to edema (R= 0.49 p<0.0001), LGE (R= 0.4 p=0.001) and LV mass index (R=0.44 p<0.001). At FU LV volumes and function did not change, edema (G1 p<0.0001; G2p<0.04) and LGE (G1p<0.002;G2 p<0.05) were significantly reduced in both groups. In G2 3 pts had refractory ventricular arrhythmias (VT) and an ICD implanted.

CONCLUSIONS: Pts with AM presenting with AHF or VF at admission showed significantly larger percentage of edema and LGE directly correlated to contractile dysfunction, these features might help to identify higher-risk pts such as those with unstable VT

Background

Myocarditis has been recognized as a precursor of dilated cardiomyopathy in 21 % of patients at three years from the presenting episode (1), a finding corroborated by the high prevalence of viral genomes in patients with DCM. DCM is currently the most frequent reason for heart transplantation (2). Post-mortem histology identifies myocarditis in 8.6% to 12% of cases of sudden death in young adults. The actual incidence and prevalence of myocarditis is still unclear and likely to be underestimated. The initial clinical manifestation of myocarditis ranges from asymptomatic to presentations with symptoms and signs of acute myocardial infarction escalating to cardiogenic shock. Chest pain,ventricular arrhythmias, and acute or chronic heart failure can occur during the course of the disease. Hence, the diagnosis of myocarditis based on the clinical presentation alone is usually not reliable. The conventional diagnostic tools ECG and echocardiography have a low sensitivity and specificity. Patients often undergo coronary angiography in order to exclude coronary artery disease. Cardiovascular magnetic resonance (CMR) imaging has become a valuable noninvasive imaging tool for diagnosis of both acute myocarditis and its chronic sequelae, enabling a reproducible assessment of disease and guiding patient management. The pathological substrate is acute inflammation with concomitant cardiomyocyte reversible or irreversible injury, regional vasodilation leading to increased microvascular permeability increasing the water content of the myocytes and of the interstitium (oedema)(4). The activation of the cytokines activate the transformation of myofibroblasts and the production of collagen fibrils. There is a good diagnostic conformity between CMR and endomyocardial biopsy results; hence, in patients with clinically suspected myocarditis performing CMR as a primary step seems reasonable both to diagnose the disease and to stratify risk. CMR allows an accurate assessment of LV global and regional function and characterises tissue as oedematous, necrotic or fibrotic in a single scan. Most importantly, serial CMR studies can have an impact on patients' management. The predictive value of CMR derived parameters and their impact on short term outcome need to be elucidated.

Objective

Aim of the study was to evaluate the relationship between myocardial oedema (STIR) and late enhancement (LGE) extension and clinical presenting patterns of acute myocarditis by means of cardiac magnetic resonance imaging derived parameters(CMR).

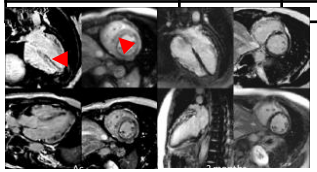
Materials & Methods

Seventy-three consecutive patients (pts) referred for suspected myocarditis from 2007 to 2010 were analyzed in a retrospective manner. Symptoms, ECG changes, myocardial function, elevated creatine kinase, positive troponin T, suggested AM. Coronary artery disease was excluded at angiography in all patients. The diagnosis was confirmed by CMR (Siemens Avanto 1.5 Tesla) performed within 2 weeks after the onset of symptoms, according to the presence of signal hyperintensity at STIR images (oedema), associated with concordant LGE (0.1mmol/Kg gadobutrol) at CE-IR images. FU scan was performed at 3 months. Active inflammation/oedema was defined as an increase of signal intensity in STIR images in the myocardium related to that in the skeletal muscle. It was calculated as T2 ratio, with a cutoff > 2. The areas of enhancement were measured by commercial software and expressed as percentage of the LV mass. Data are x ±SD, significant difference p<0.05.

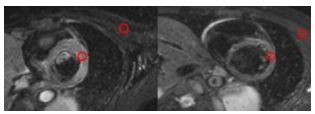
Population

According to initial clinical picture pts were divided into two groups: group 1 presenting with chest pain; group 2 presenting with Acute Heart Failure or Ventricular Fibrillation.

First MRI scan	Group 1 N=62	Group 2 N=11	*P*-value
Age	31±11	40±	0.019
Gender	9♀ (15%)	4♀ (36%)	0.18
LVEDV/BSA	76±15	72±17	0.44
LVESV/BSA	28±10	30±12	0.50
LVEF	64±8	58±14	0.06
LVMI	78±18	88±24	0.11
Arrhythmia	1/62(0.01%)	4/11(36%)	0.0002
ACE inhibitors	43/62	4/11	ns
		1/11	ns

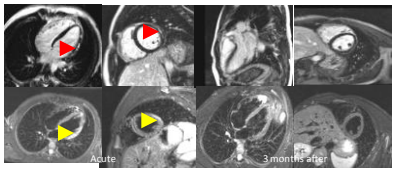


Representative Late Gadolinium Enhancement (LGE) of a patient in Group 2 (BG) in the acute phase and at Follow Up. There is diffuse myocardial enhance ment sparing only a subendo cardial rim (red arrows). LV function is severely impaired EF 24%. At FU focal patchy areas of LGE are detectable with concomitant recovery of function EF 58%.

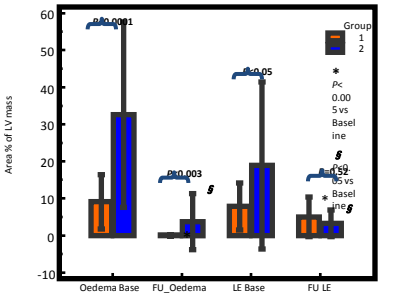


STIR images T2 ratio 3.5 acute and 1.7 at FU

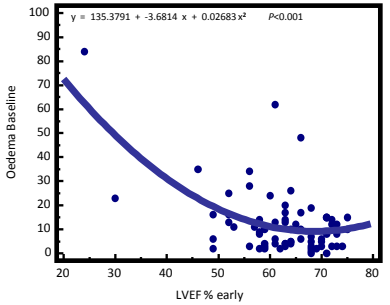
Results



Representative Late Gadolinium Enhancement (LGE) top panels of a patient in Group 1(GR) in the acute phase and at Follow Up. There is subepicardial enhance ment (red arrows) in the lateral wall from base to apex. Acute inflammation/oedema is present in the same regions on STIR images (yellow arrows) T2 ratio. Normal LV function:EF 66%. At FU a subepicardial rim of LGE is still detectable at the apex and in the lateral wall. Absence of active inflammation on STIR images T2 ratio ;EF 75%.

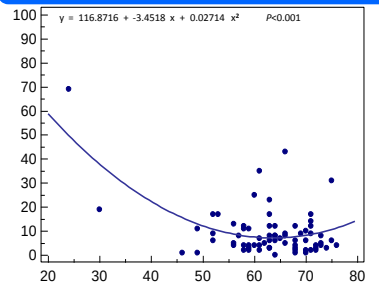


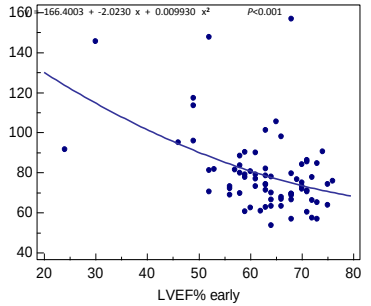
The extension of the area of oedema and LG enhancement was significantly Larger in Group 2. In both groups there was a significant reduction after 3 months. * *P*< 0.005 vs Baseline § *P*<0.05 vs Baseline



The amount of oedema, LGE and LV Mass index are significantly inversely correlated with global systolic function (EF). The correlation is non linear as only a few cases showed a severely depressed systolic function. In those cases (see example on the left) LV function at 3 months was normalised. In Group 2 3/11(27%) patients had life threatening arrhythmias, one ICD was implanted.

Results





Conclusions

- In a population of patients suffering from acute myocarditis clinical presentation with arrhythmias or acute HF has corresponding more severe CMR features of oedema and non-ischemic pattern fibrosis.
- Global ventricular contractility in the acute phase is dependent on the amount of oedema, LGE and LV mass.
- CMRI features of acute myocarditis add short term prognostic value to the initial clinical presentation.
- Limitations of this study: the independent predictive value of CMR derived parameters will have to be tested systematically in larger population longitudinal studies.

References

1. D'Ambrosio A, Patti G, Manzoli A, et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. Heart 2001;85:499–504.
2. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807–16.
3. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.
4. Friedrich, M. G. Nat. Rev. Cardiol. 2010;7, 292–306.

The Authors do not have any conflict of interest to declare

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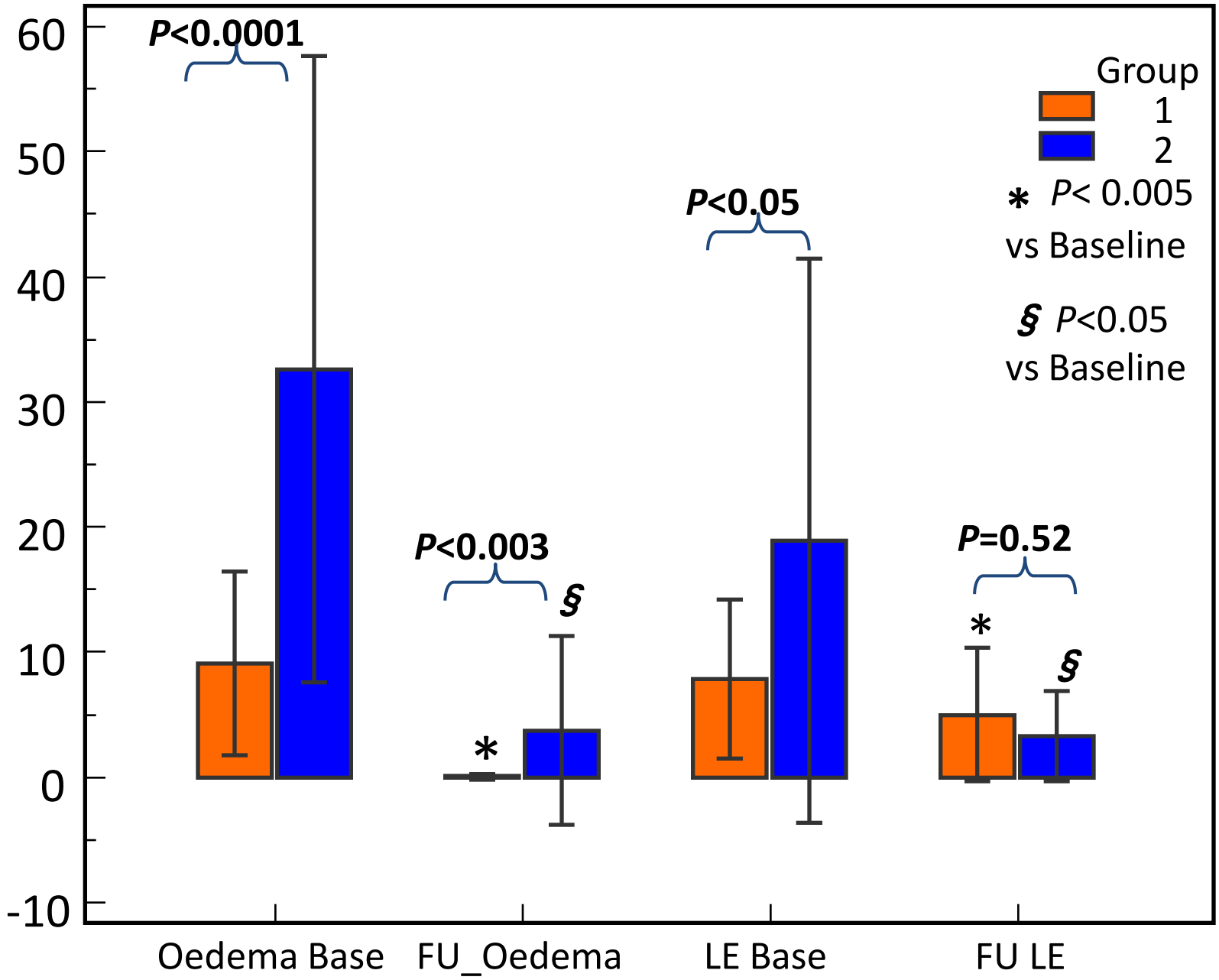
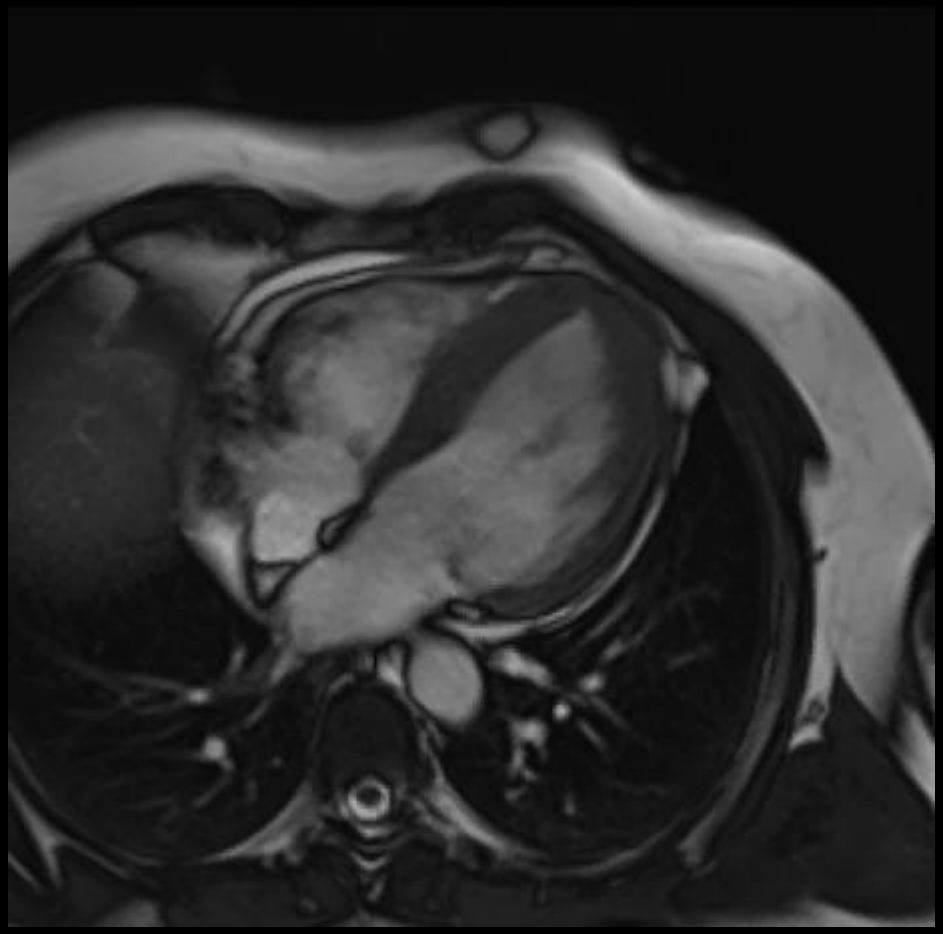
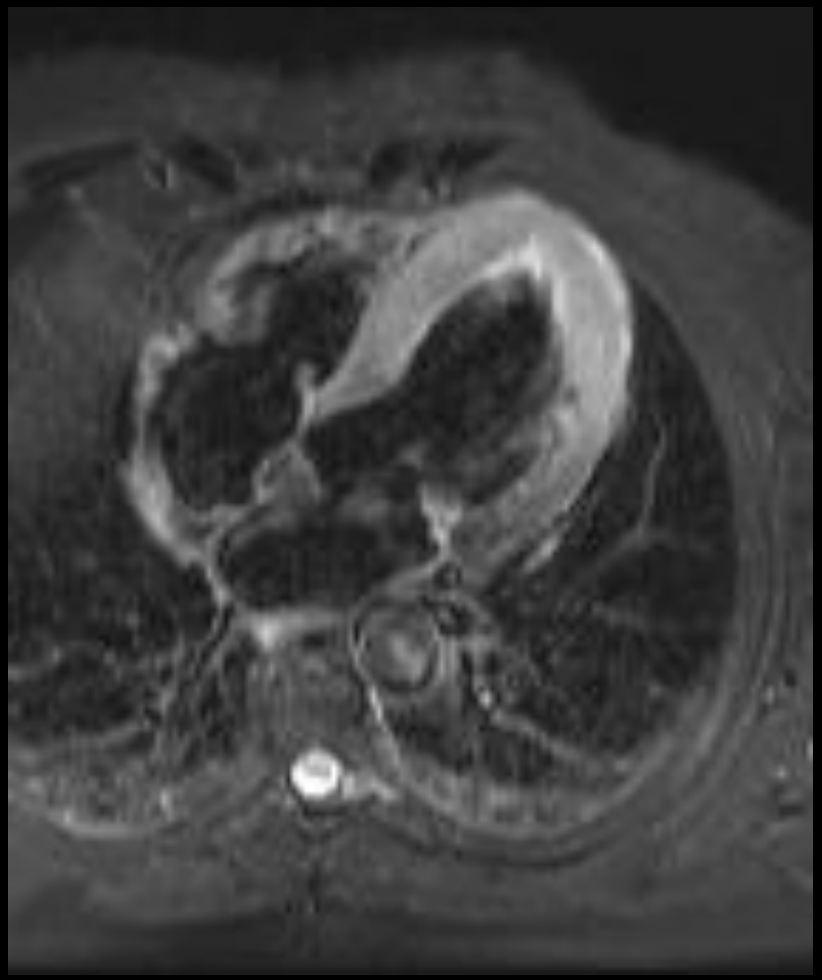
Arrhythmia	1/62(0.01%)	4/11(36%)	0.0002
ACE inhibitors	43/62	4/11	ns
β-blockers	9/62	1/11	ns

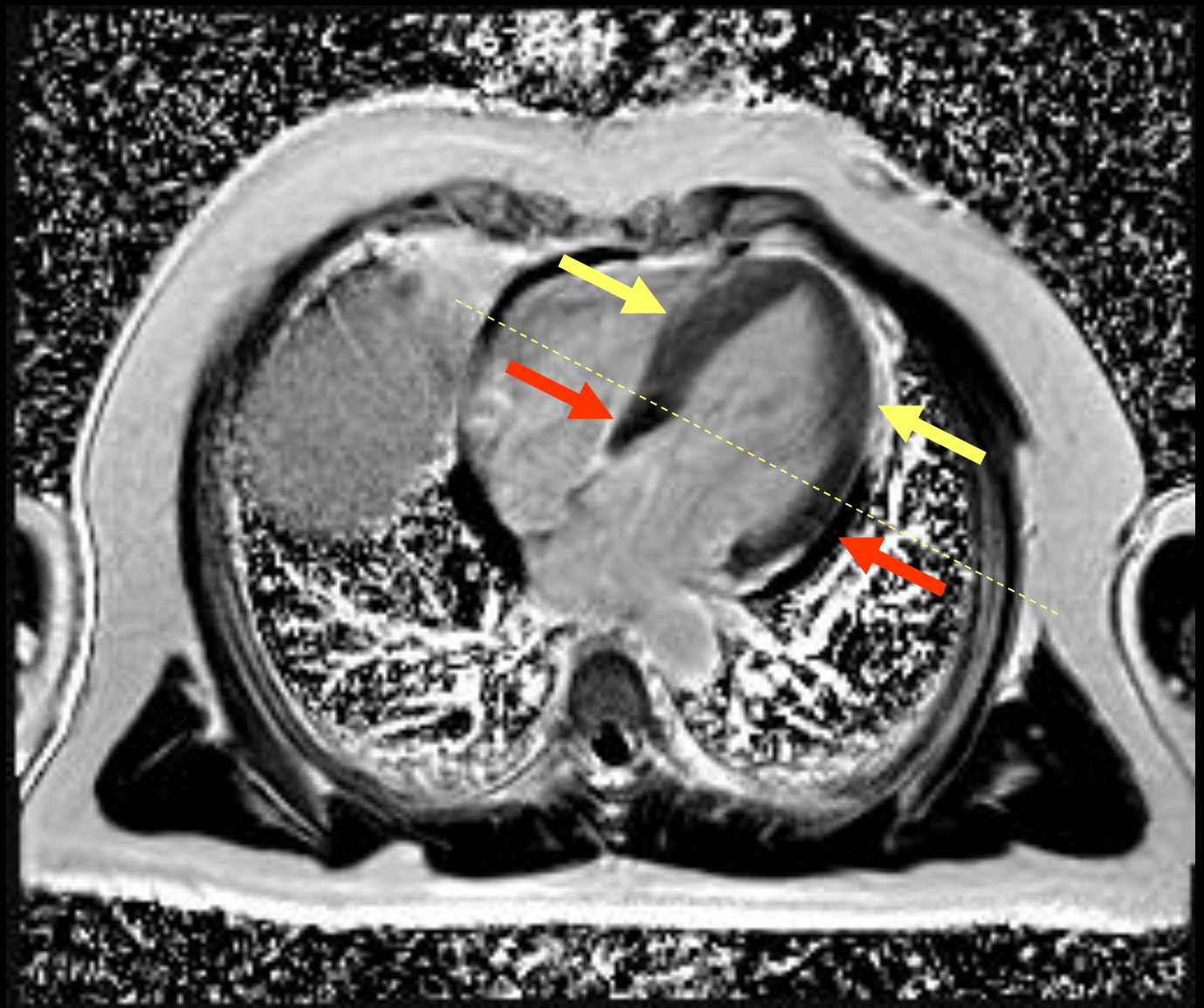

60
50
40
30
20
10
0
-10
P<0.0001
P<0.05
P<0.003
P=0.52
§
*
*
§
Group
1
2
* P< 0.005
vs Baseline
§ P<0.05
vs Baseline
Oedema Base
FU_Oedema
LE Base
FU LE

ACUTE MYOCARDITIS: PATTERN A





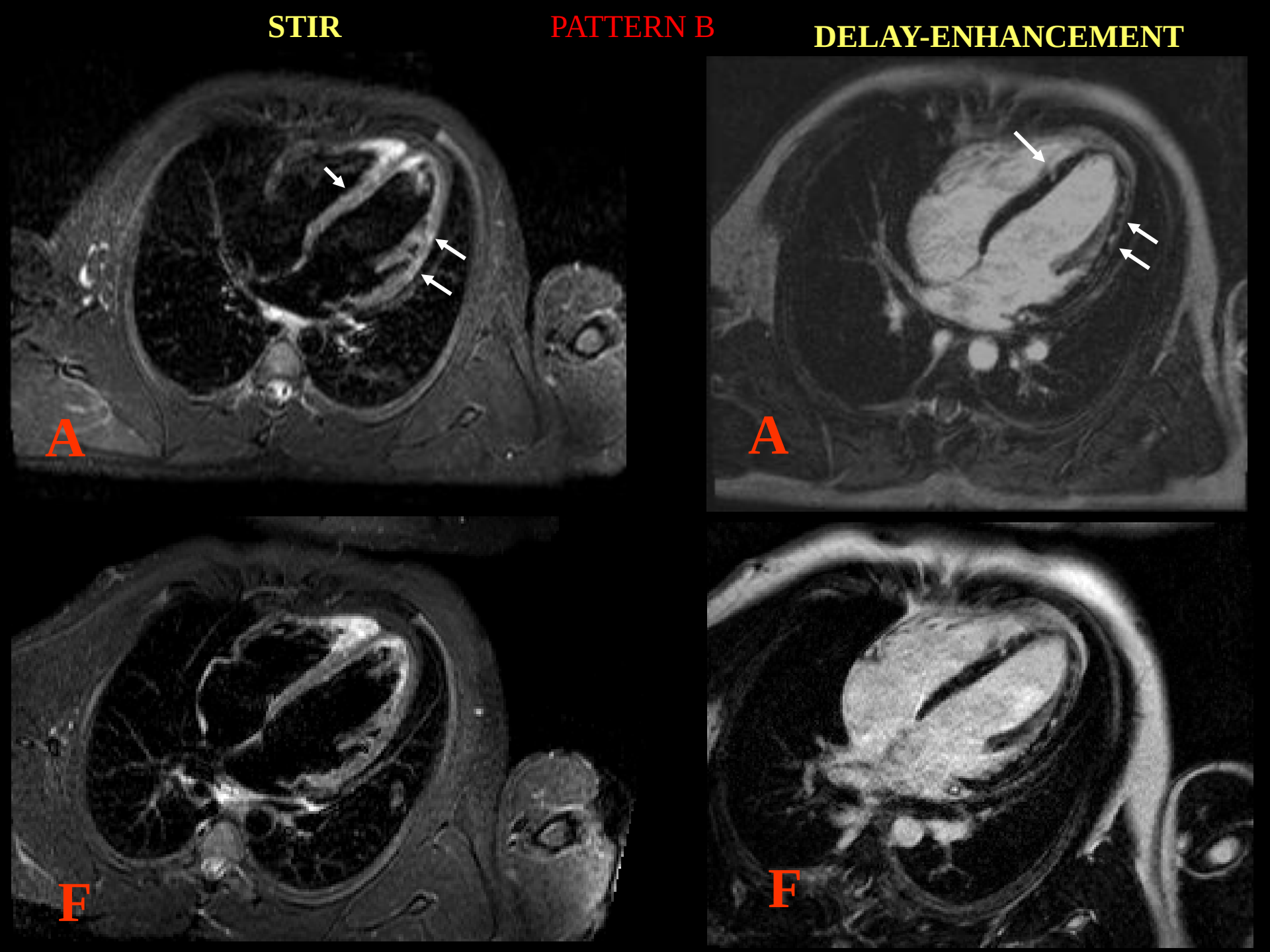
ACUTE MYOCARDITIS:
PATTERN A
DIFFUSE DELAY ENHANCEMENT



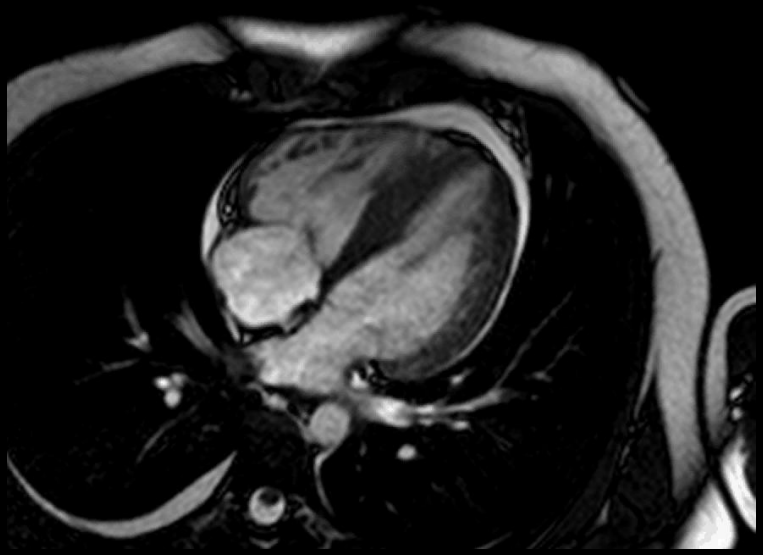
STIR

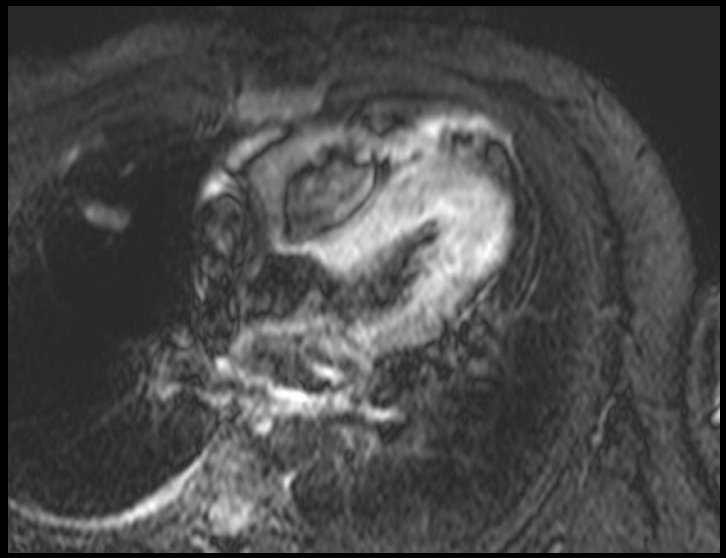
PATTERN B

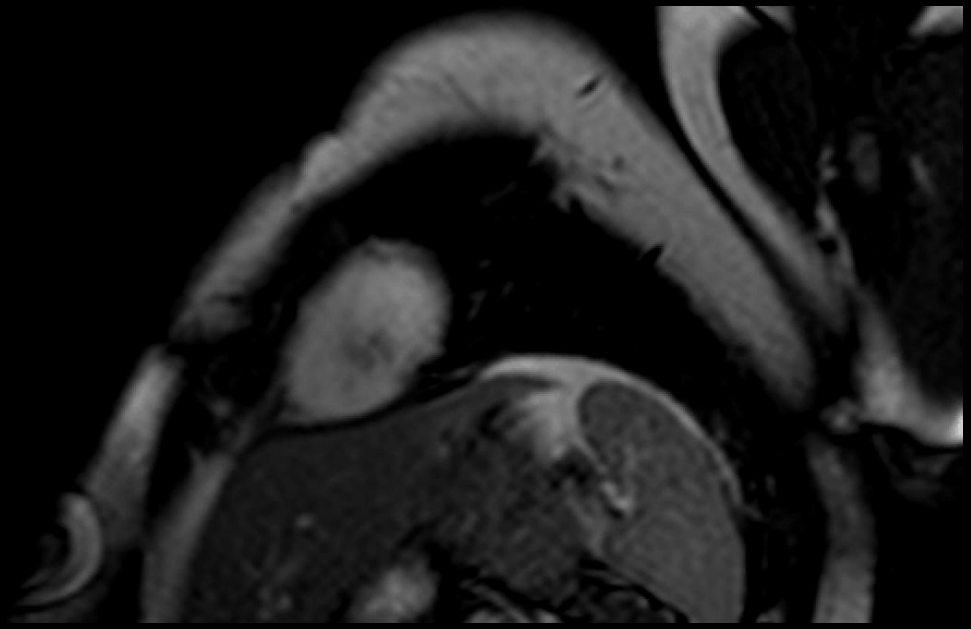
DELAY-ENHANCEMENT

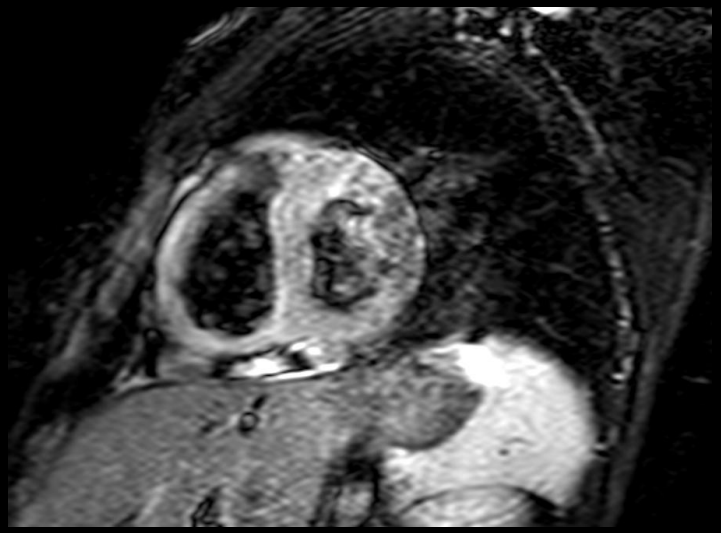


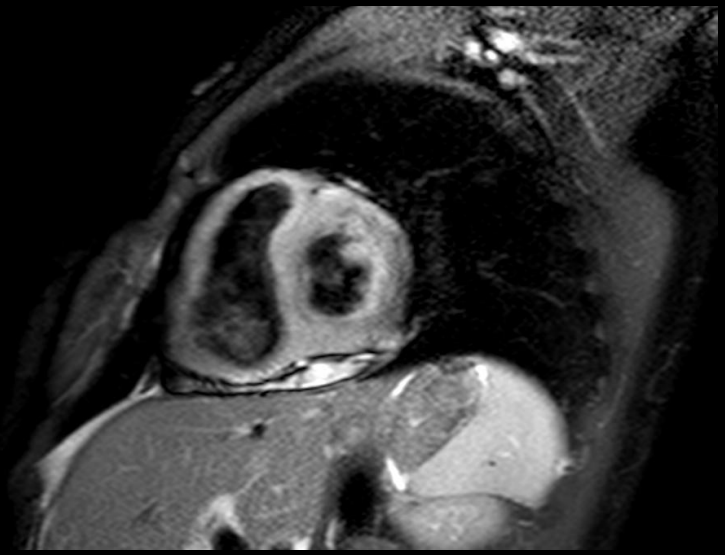
…Caro Roghi, potresti vedere la RM cardiaca fatta qui da noi di questo ragazzo ricoverato ieri sera per dolore toracico, ST sopralivellato e movimento di troponina ? Il Radiologo propende per amiloidosi cardiaca…











Data e ora della visita:

21/02/2013 17:52

Referto, eventuali prescrizioni e terapia

Trasferito per miocardite acuta dall'ospedale di
Tre giorni fa iperpiressia, dal giorno successivo astenia e cefalea ed esordio di dolore toracico anteriore. In PS a
tachicardia sinusale con marcato sopraslivellamento ST anterosettale ed enzimi cardiaci elevati (tpnTHS 5600) all'ECO FE conservata (>60%), versamento pericardico. Eseguita RM cuore con riscontro di disfunzione contrattile ed edema diffuso con SIV 16mm. ECO stamane 45%.
Diuresi non nota. Movimento enzimatico renale ed epatico in peggioramento.

Pallido, estremità fredde, spaventato FC 130 rs PAs 90mmHg, Cuore: ritmo di galoppo, non soffi significativi. Fegato a 2 cm dall'arco costale.
ECO: ventricolo sinistro con spessori parietali aumentati (SIV 15mm) e parete lievemente iperecogene, normali dimensioni endocavitarie (dtd 46mm), diffusa ipocinesi, più marcata a livello del setto interventricolare che presenta anche discinesi e della parete anteriore e laterale. Ventricolo destro anch'esso con spessori parietali aumentati. Significativa disfunzione biventricolare. FE VS 35%. TAPSE 11mm. Lieve insufficienza delle valvole atrioventricolari. (PAPs stimata 36mmHg, nota PVC 16mmHg) Versamento percicardico circumferenziale di grado lieve (5mm).
EGA: ph 7.36, Lat 2.0. Be -6, PCO2 26.

Data Intervento: **22/02/2013**
Modalità: **Emergenza**
Tempo Chirurgico: **03:00 - 04:20**

DIAGNOSI DESCRITTIVA E CODIFICATA

Severa cardiomiopatia ipocinetica, probabile miocardite, bassa portata con anuria, iperpiressia, supporto inotropico massimale, IABP.

42299-ALTRA MIOCARDITE ACUTA
4281-INSUFFICIENZA DEL CUORE SINISTRO (SCOMPENSO
4280-INSUFFICIENZA CARDIACA CONGESTIZIA NON

INTERVENTO DESCRITTIVO E CODIFICATO

ECMO veno-arterioso periferico.

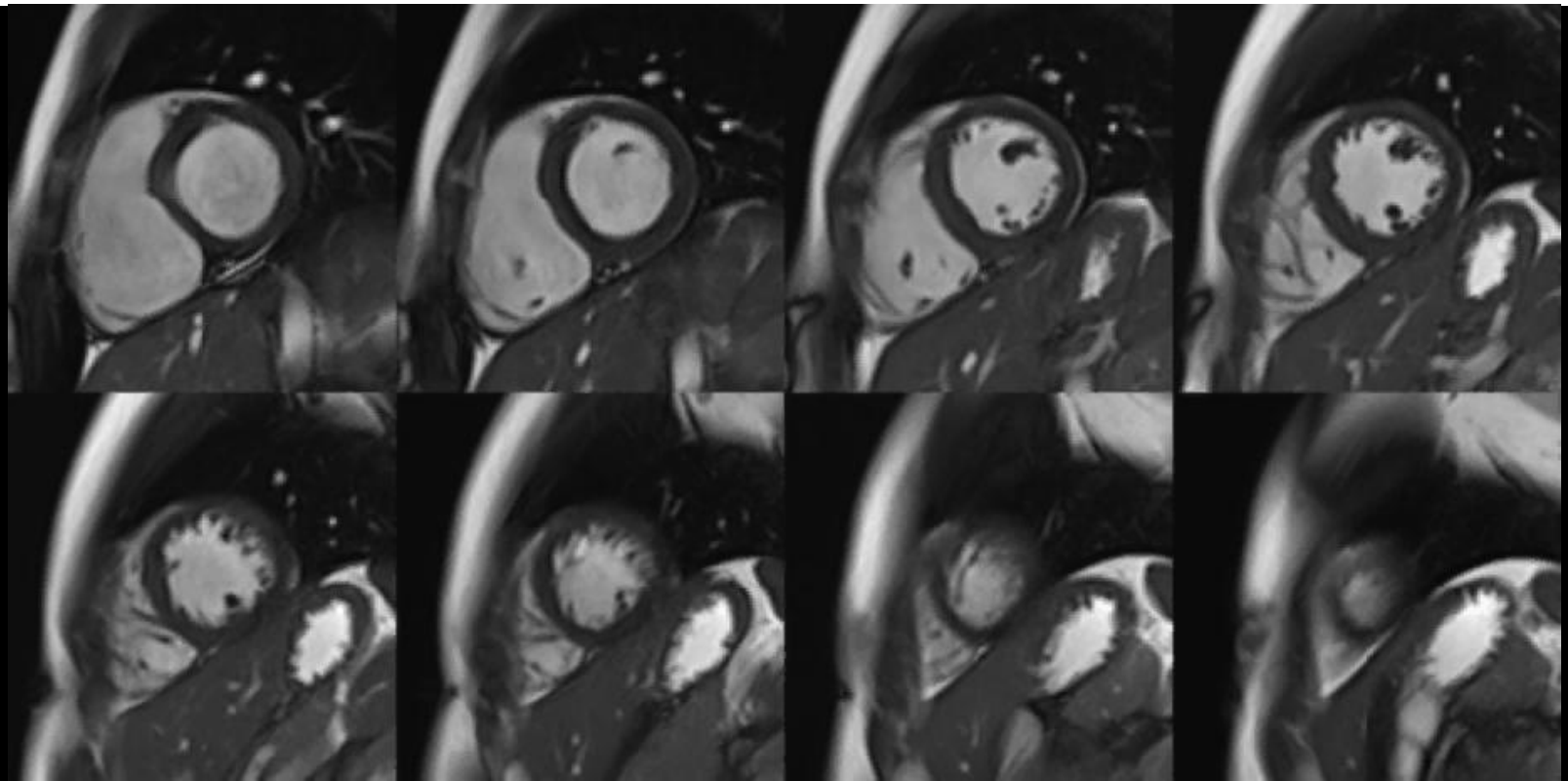
Novembre 2013

VISITA ODIERNA:

Non disturbi di rilievi. Tornato ad attività quotidiane solite senza problemi. Riferisce occasionalmente alla sera la sensazione di dover fare un "respiro più profondo". Non angor da sforzo nè svenimenti.
PA 105/60 mmHg, compenso, toni cardiaci ritmici, validi, MV presente, non edemi.

RM CUORE (ottobre 2013): cinesi e volumi biventricolari normali, lieve dilatazione biatriale, non evidenza di edemi/flogosi nè di fibrosi del miocardio. VSx: VTD 169 mml massa cardiaca 118 g (indicizzata 66 g/m2), FE 65%.
ECG (5/11/2013): Ritmo sinusale, FC 70 bpm, QRS stretto , nei limiti (ad aprile 2013 onde T inferiori difasiche)

ECG HOLTER delle 24 ore (30/4/2013): ritmo sinusale (FC media 81 bpm), rari battiti ectopici sopraventricolari e ventricolari, non sintomi durante la registrazione.
EMATOCHIMICA (3/9/2013): glicemia 90 Na 143 K 4,5 AST 18 persistenza positività IgM toxoplasma anti-toxoplasma IgG+, PCR 0,02 VES 2 Gb 7,8 Hb 11,5 piastrine 204 mila linfociti 37%.



Miocardite acuta e shock cardiogeno:

• ECO : frequente l'evidenza di funzione sistolica conservata con evidenza di incremento degli spessori e lieve ipocinesi

• ECG sopralivellato diagnostico ma non specifico di gravità

• Troponina: temere l'evoluzione rapida nei casi di imponente dismissione (>1000 ng/ml)

• Parametri vitali: frequentemente a lungo conservati nei pz giovani, rapido deterioramento (< 6 h)

• RM cardiaca: raramente utile nei casi più gravi, utile nell'inquadramento eziologico dei pazienti sopravvissuti allo shock

Altered Desmosomal Proteins in Granulomatous Myocarditis and Potential Pathogenic Links to Arrhythmogenic Right Ventricular Cardiomyopathy

Angeliki Asimaki, PhD[1], **Harikrishna Tandri, MD**[2], **Elizabeth R. Duffy, MA**[3], **Jeffrey R. Winterfield, MD**[4], **Shannon Mackey-Bojack, MD**[5], **Maria M. Picken, MD, PhD**[6], **Leslie T. Cooper, MD**[7], **David J. Wilber, MD**[6], **Frank I. Marcus, MD**[8], **Cristina Basso, MD**[9], **Gaetano Thiene, MD**[9], **Adalena Tsatsopoulou, MD**[10], **Nikos Protonotarios, MD**[10], **William G. Stevenson, MD**[4], **William J. McKenna, MD**[11], **Shiva Gautam, PhD**[1], **Daniel G. Remick, MD**[3], **Hugh Calkins, MD**[2], and **Jeffrey E. Saffitz, MD, PhD**[1]

[1]Depts of Pathology (AA and JES), Medicine (SG) Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, MA

[2]Dept of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD

[3]Deptof Pathology, Boston University Medical Center, Boston, MA

[4]Dept of Medicine, Brigham and Women's Hospital & Harvard Medical School, Boston, MA

[5]Jesse E. Edwards Registry of Cardiovascular Diseases, St. Paul, MN

[6]Depts of Pathology (MMP), Medicine (DJW); Loyola University Health System, Maywood, IL

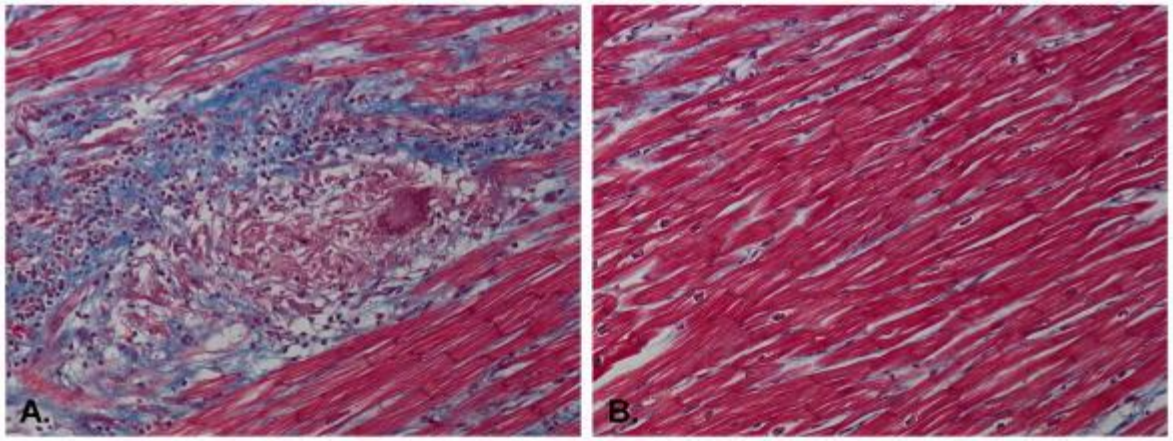
[7]Dept of Cardiovascular Diseases, Mayo Clinic, Rochester, MN

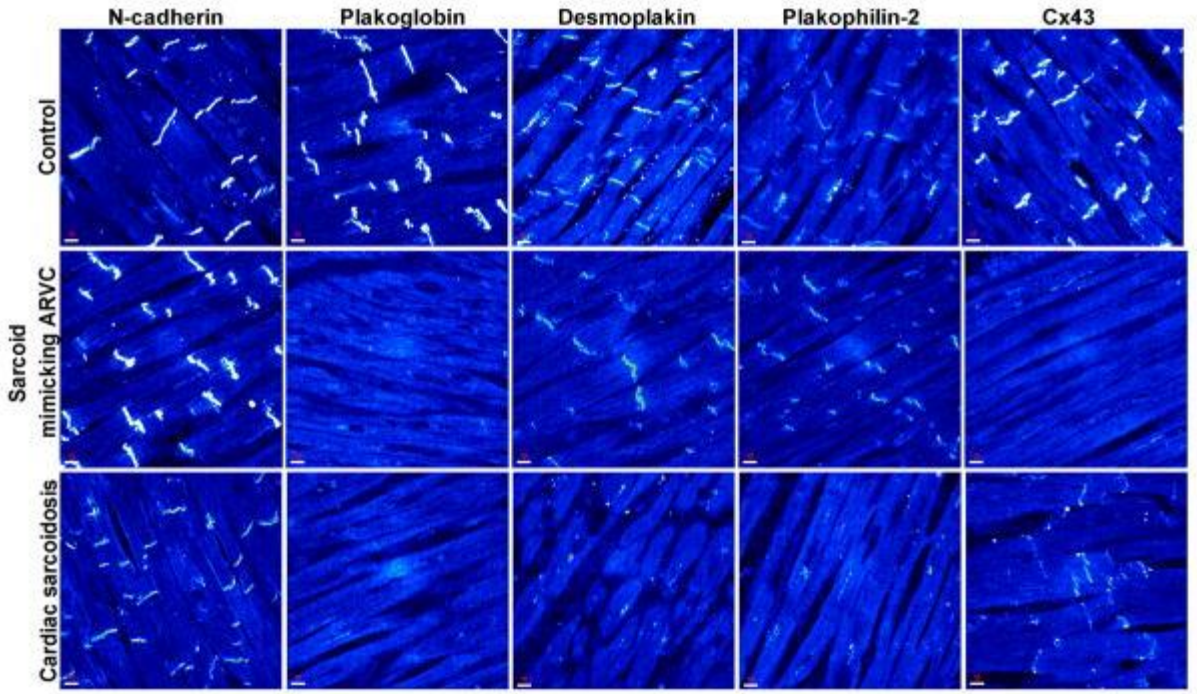
[8]Dept of Medicine, University of Arizona, Tucson, AZ

[9]Dept of Medico-Diagnostic Sciences & Special Therapies, University of Padua, Padua, Italy

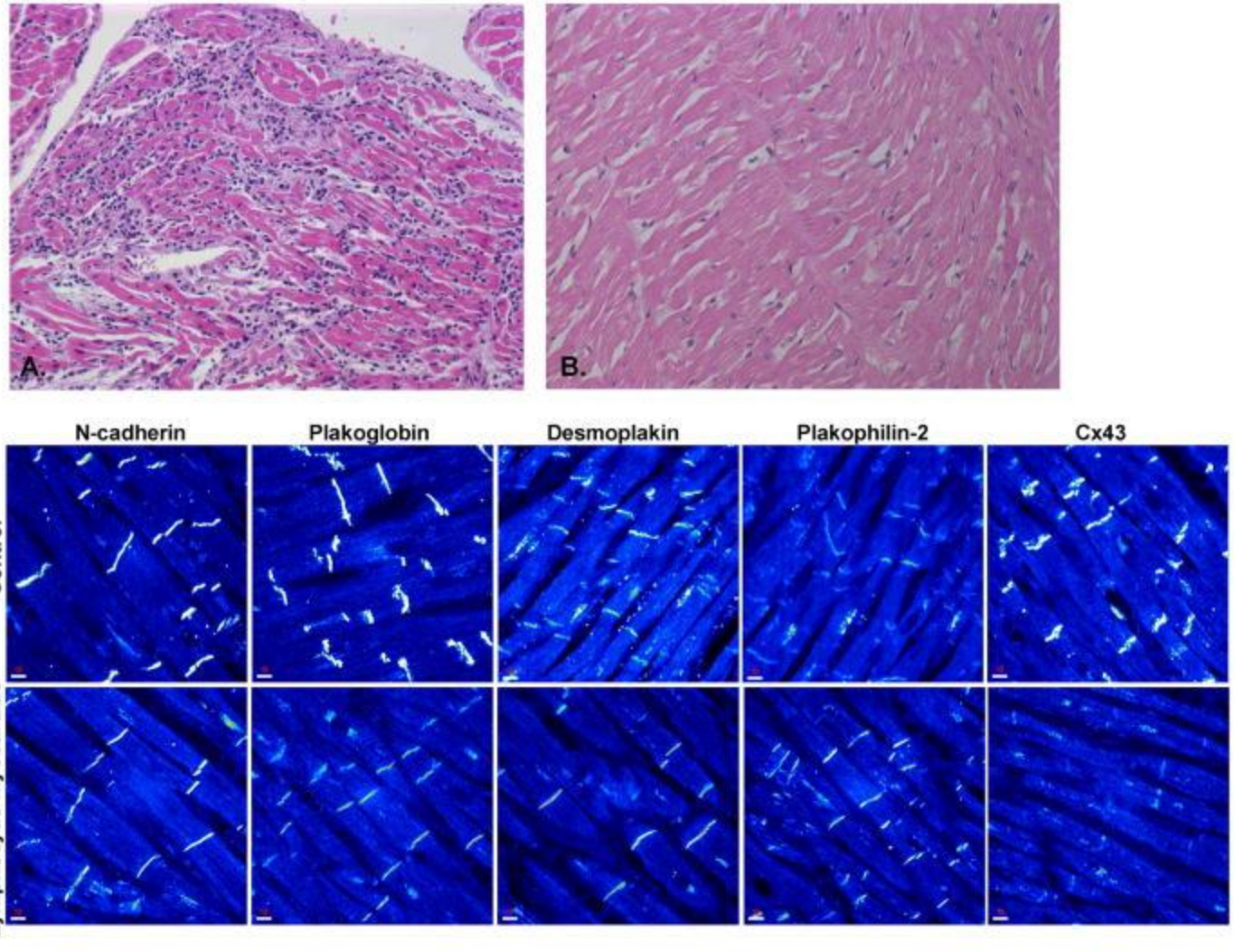
[10]Yiannis Protonotarios Medical Center, Naxos, Greece

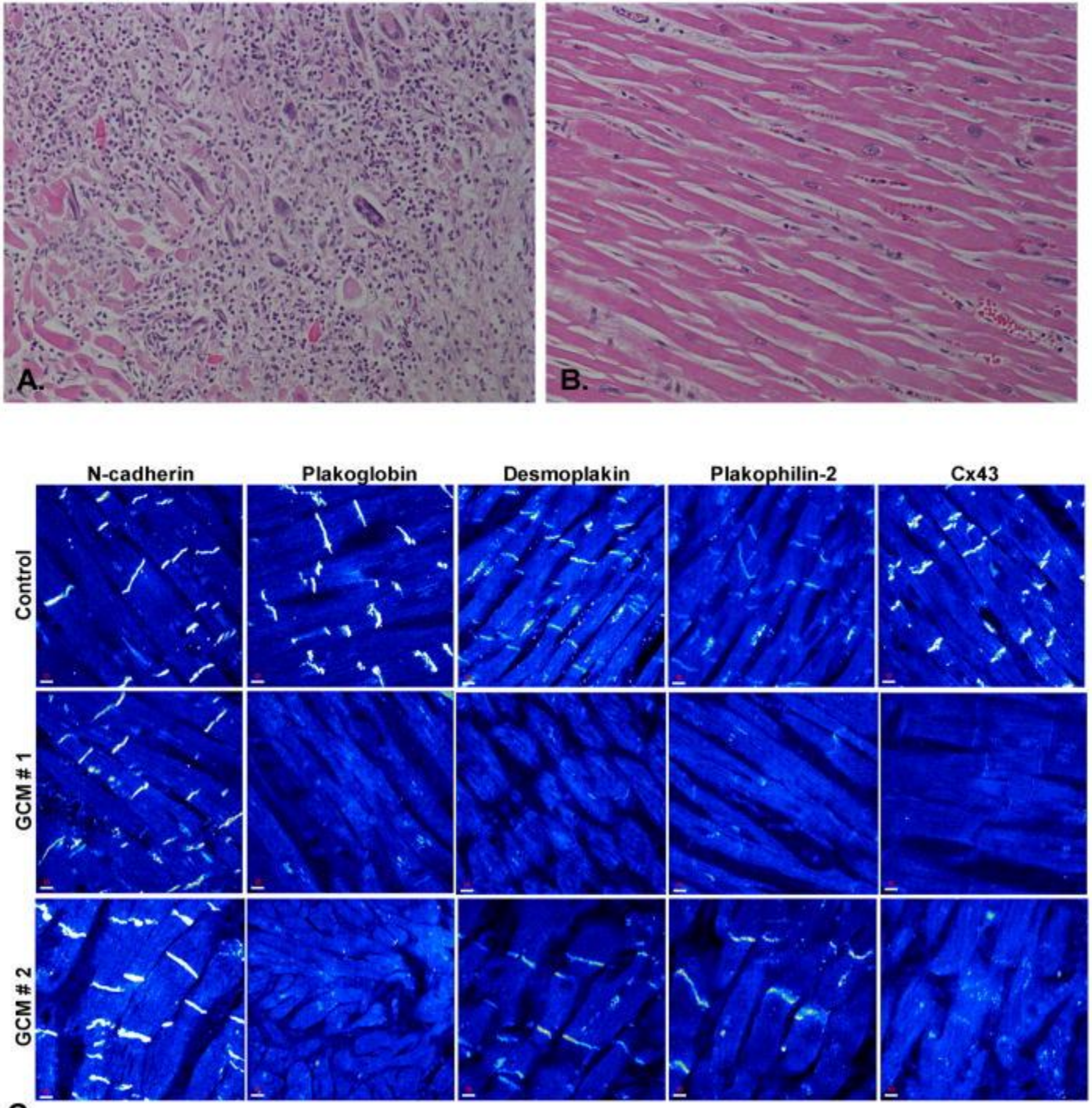
[11]The Heart Hospital, University College London, London, United Kingdom


A.
B.

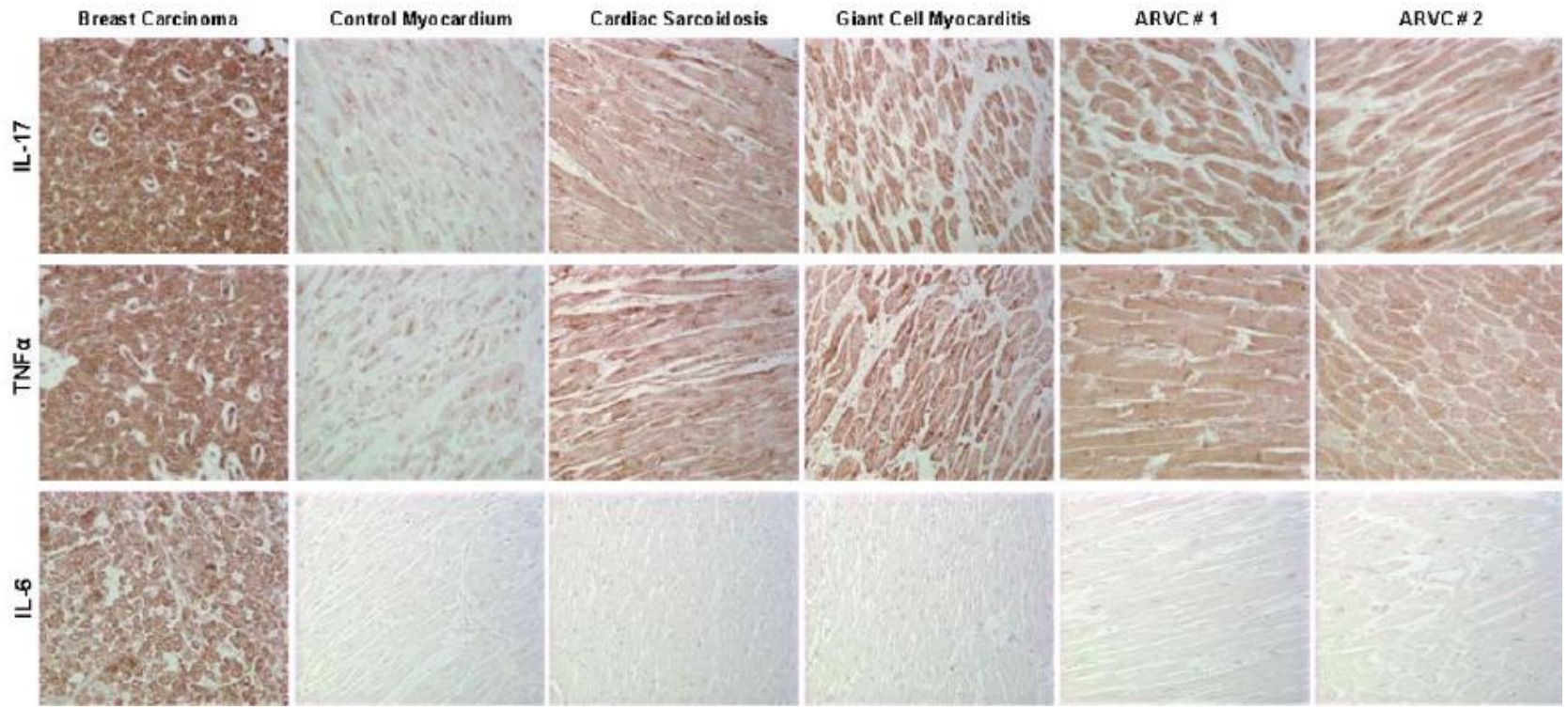

N-cadherin
Plakoglobin
Desmoplakin
Plakophilin-2
Cx43
Control
Sarcoid mimicking ARVC
Cardiac sarcoidosis

C.


A.
B.
N-cadherin
Plakoglobin
Desmoplakin
Plakophilin-2
Cx43
Control
Lymphocytic myocarditis
C.


A.
B.
N-cadherin
Plakoglobin
Desmoplakin
Plakophilin-2
Cx43
Control
GCM # 1
GCM # 2
C.

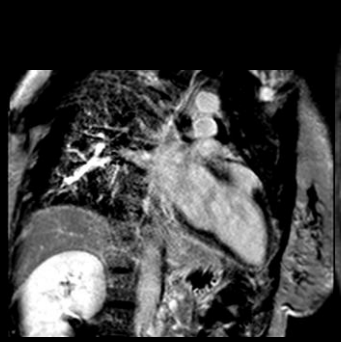
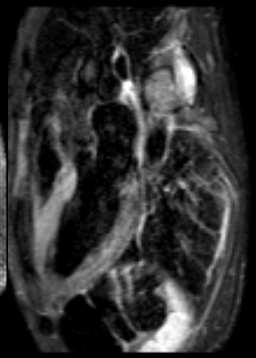
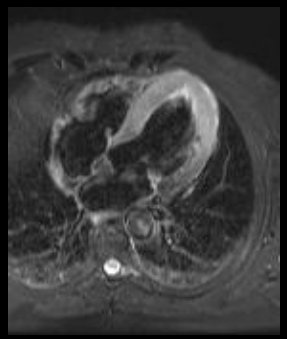
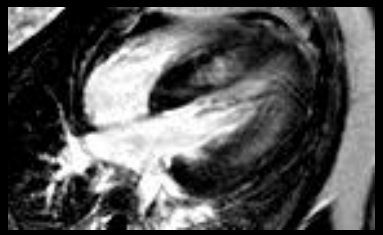
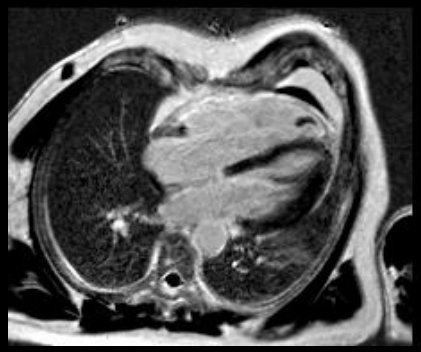
Evidence of immunoreactive signal (brown staining) for IL-17, TNF but not for IL6 cytokine



CMR and aethiology orientation in acute myocarditis

PHENOCOPIES

SARCOID PHEO MYOCARDITIS HCMO ARVC

CONCLUSIONI 1.

- **L'eco è la metodica di imaging prima scelta nella miocardite per accessibilita' e costo**
- **La RM cardiaca non ha un ruolo nei pazienti ad esordio più grave ma è importante nell'inquadramento eziologico dei sopravvissuti**
- **Il ruolo dell'imaging nell'individuazione dei pazienti a prognosi severa è ridotto per la rapidità dell'evoluzione del quadro clinico e per la mancanza di predittori specifici**

CONCLUSIONI 2.

- la RM cardiaca rappresenta lo standard diagnostico non invasivo in grado di confermare il sospetto diagnostico di miocardite dei casi più frequenti e ad esordio meno grave

- la possibilita' di evidenziare edema/flogosi e fibrosi miocardica consente una accurata definizione del timing della malattia

- Il significato prognostico della fibrosi miocardica residua e' ancora indefinito

- La complessa patogenesi di alcune cardiomiopatie ad interessamento desmosomiale si manifesta con quadri RMC simili (fenocopie)

- L'integrazione dei dati di imaging, di amplificazione virale, di tipizzazione immunoistochimica ed istologica consentirà una più accurata valutazione eziologica e prognostica