Long-term arrhythmic prognosis in patients with biopsy-proven myocarditis, studied by cardiac magnetic resonance imaging and 3D-electroanatomic mapping

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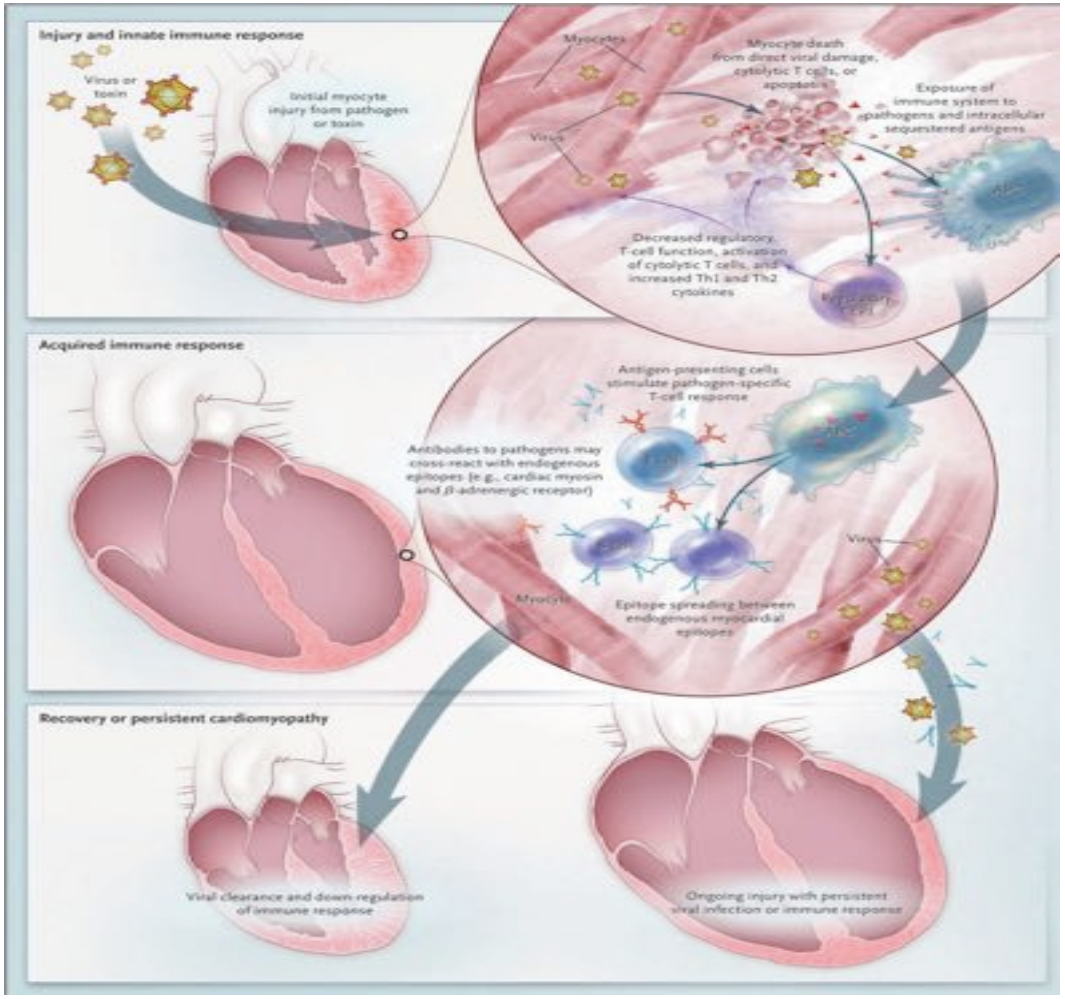
Disclosure

No disclosure to declare

Background

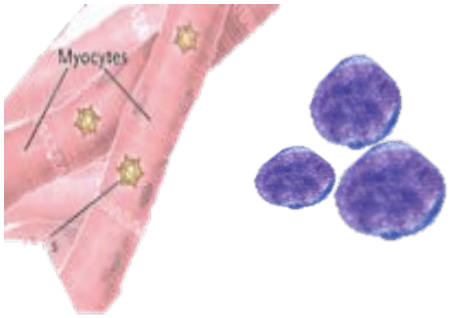
- ✓ Myocarditis represents an important cause of sudden cardiac death as reported in cases of post-mortem studies.
- ✓ In literature, the prevalence of myocarditis detected at necroscopy in subjects with sudden cardiac death and apparently normal heart ranged from 5 to 40%.



Cooper L.T. et al NEJM 2009

VT/VF Mechanisms in myocarditis

ACUTE MYOCARDITIS



"Fixed" substrate:

- Acute Inflammation

CHRONIC MYOCARDITIS

"Fixed" substrate:

- Fibrosis
- Inflammation

VT/FV

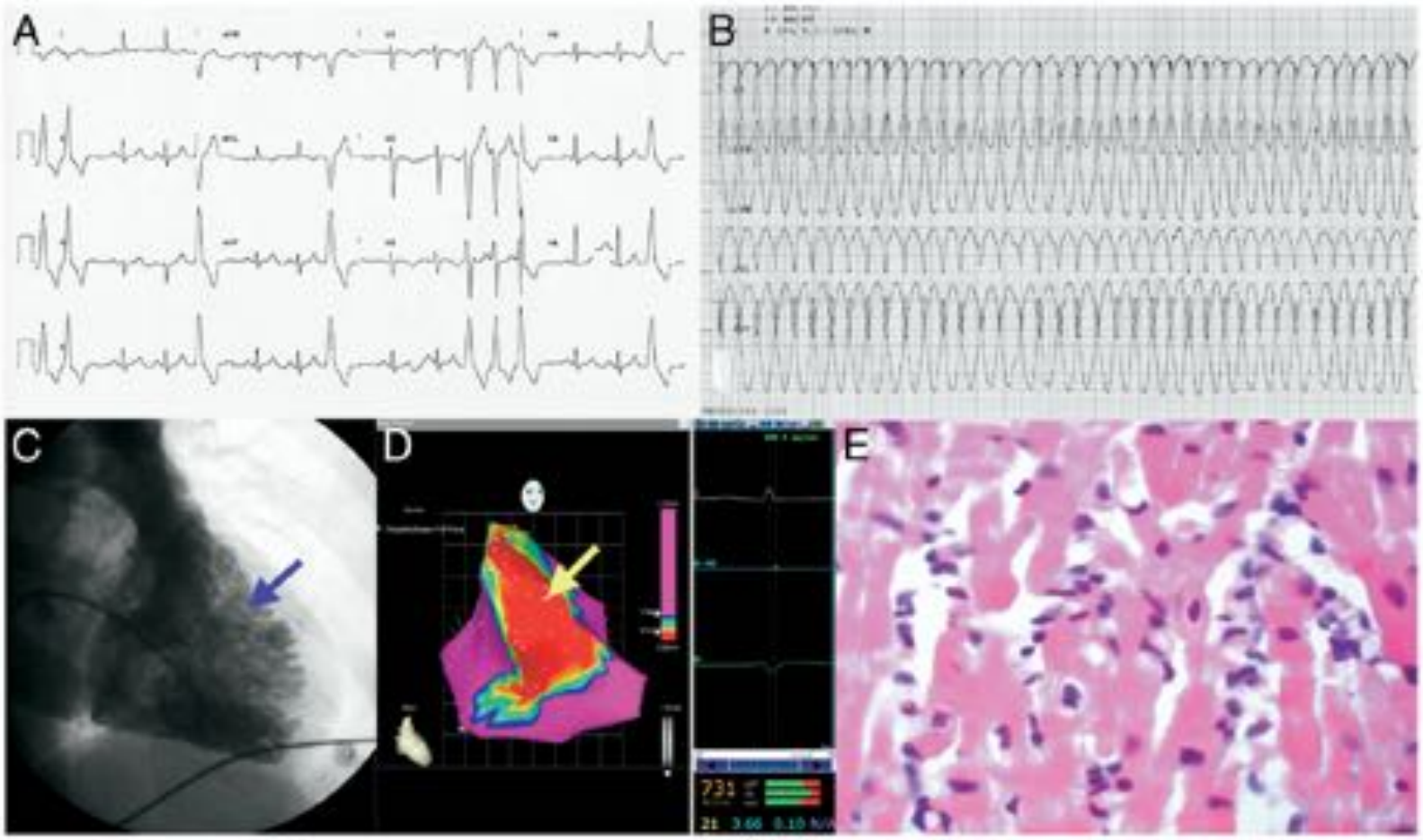
"Dynamic" substrate:

- Autonomic tone
- Metabolic/Ionic abnormalities
- Haemodynamics
- Hypoxia/Ischemia

Triggers:

- PVCs
- Pauses

Endomyocardial Biopsy and 3D-Electroanatomic Mapping in Myocarditis



Pieroni M et al, JACC 2009

Casella M et al, Circulation Arrhythmias 2015

Aims of the study

- To characterize arrhythmic substrate in patients with ventricular arrhythmias and biopsy-proven myocarditis, using cardiac magnetic resonance (CMR), electrophysiological study (EPS) and 3D-electroanatomic mapping (EAM)

- To evaluate predictors of sustained ventricular arrhythmias (VA) at follow-up in patients with ventricular arrhythmias as first clinical presentation of myocarditis

Methods

Patients with ventricular arrhythmias and clinical suspect of myocarditis (enrolled between 2009 and 2014)

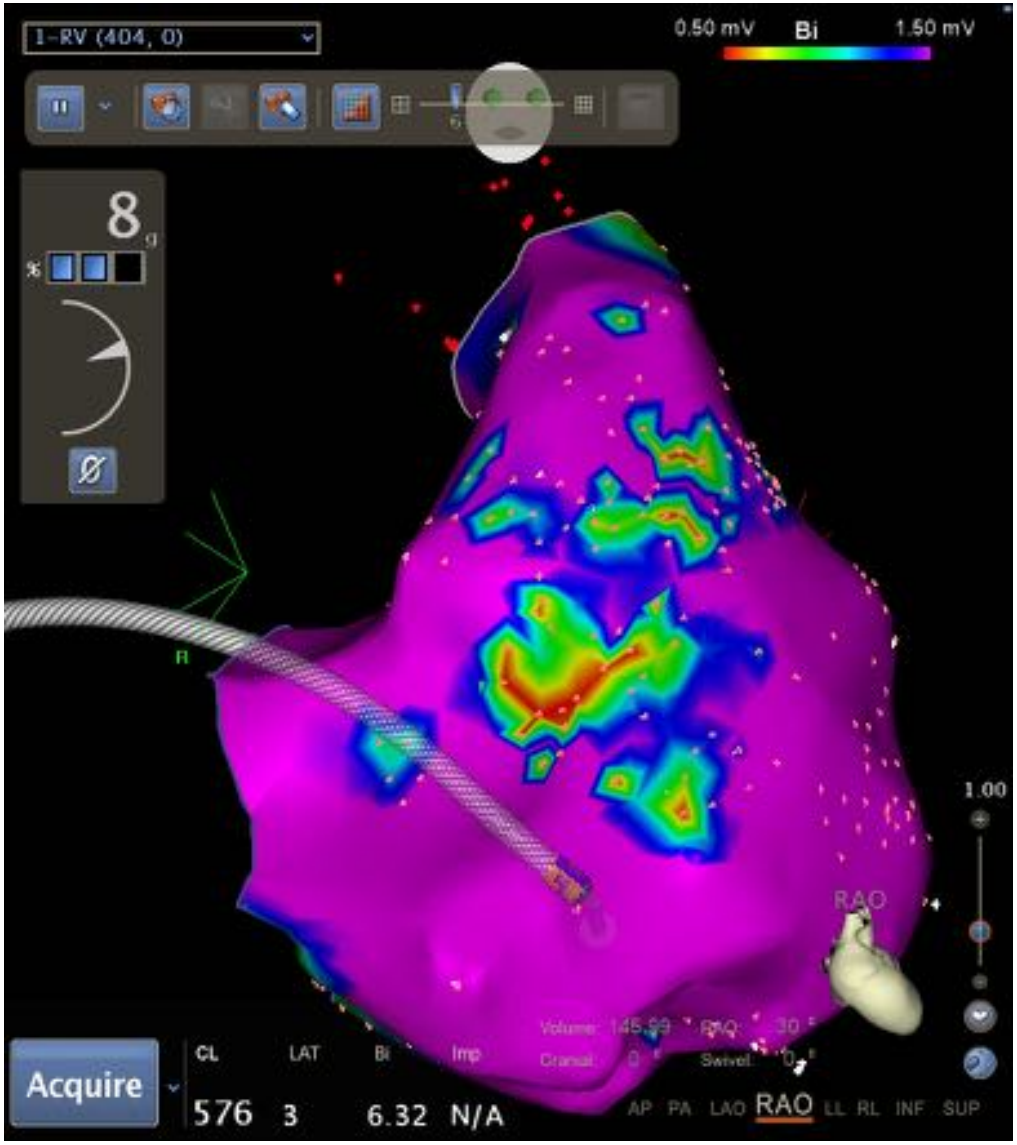
- 2D Echocardiography (ECHO)
- Cardiac Magnetic Resonance Imaging (cMRI)
- Coronary Angiography
- Electrophysiological study (EPS)
- 3D Electroanatomical Mapping (EAM)
- Endomyocardial Biopsy (EMB) guided by EAM

Group M1
Biopsy-proven myocarditis
(active or borderline)

Group M0
No Biopsy-proven myocarditis (aspecific alterations)

Exclusion criteria: Patients with coronary artery disease, valvular diseases, hypertrophic cardiomyopathy, ARVD.

Endocardial Bipolar mapping



DEFINITION - Bipolar Voltages:

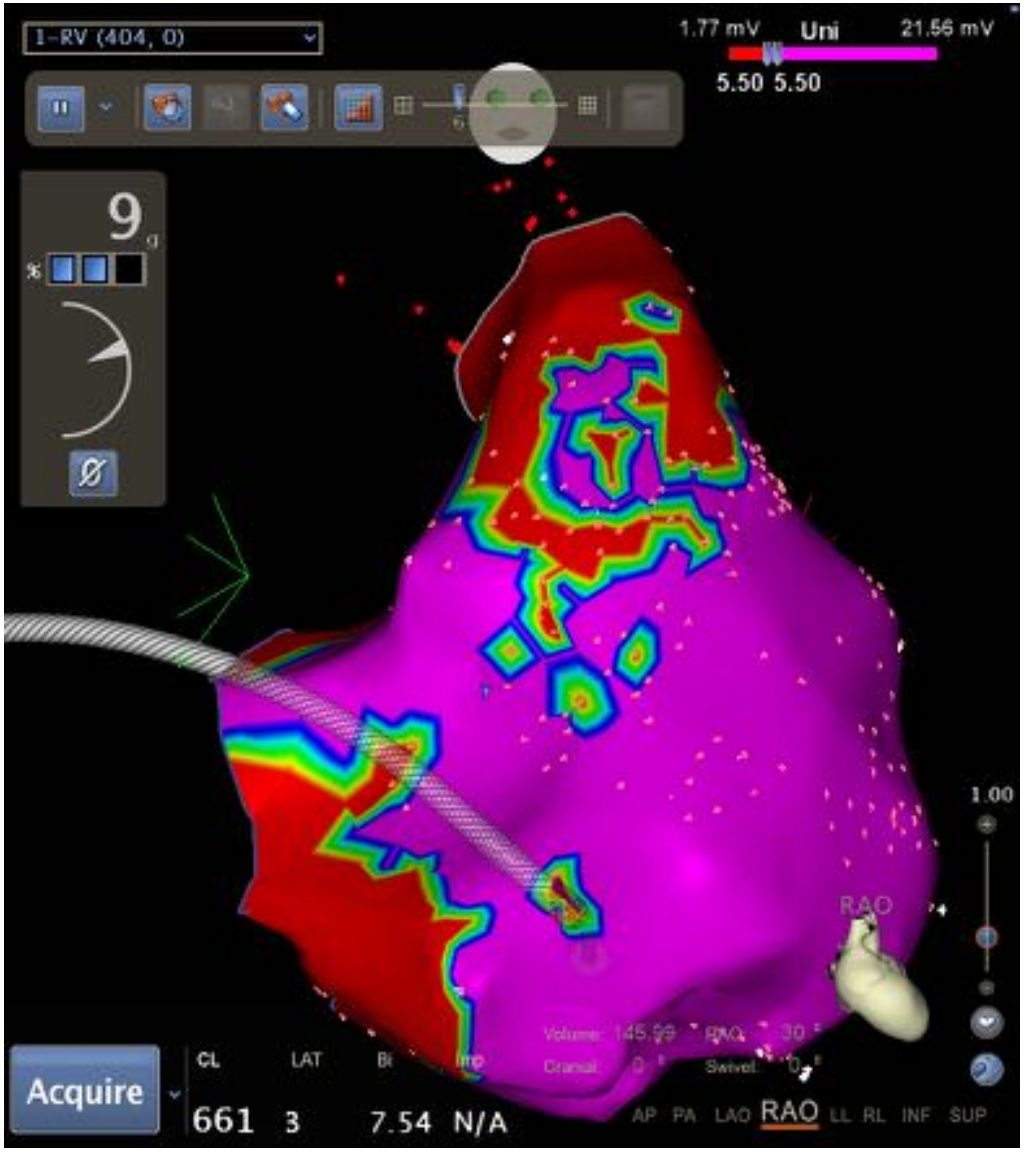
- Normal myocardium >1.5 mV
- Borderzone 0.5-1.5 mV
- Scar Area <0.5 mV

Low Voltage Area: Scar+ Borderzone

VARIABLES:

- Localization of Low Voltage areas (<1.5 mV)
- Low voltage Area measurement (cm^2, %)
- Localization of SCAR (<0.5 mV)
- SCAR Area measurement (cm^2, %)

Endocardial Unipolar mapping



DEFINITION - Unipolar Voltages:

Right Ventricle

- Scar Area <5.5 mV

Left Ventricle

- Scar Area <8.0 mV

VARIABLES:

- Localization of Scar (<0.5 mV)
- Scar Area measurement (cm^2, %)

Hutchinson MD Circ Arrhythm Electrophysiol 2011

Endomyocardial biopsy

HISTOLOGY

Routine hematoxylin and eosin stained serial sections have been evaluated for the presence of:

- **inflammatory infiltrate**
- **myocyte damage type: myocytolysis, apoptosis, or other myocyte alteration**
- **fibrosis**

IMMUNOHISTOCHEMISTRY

Principal antibodies for immunophenotype characterization: CD45, CD45RO, CD3, CD20, CD4, CD8, and CD68/ PGM1.

Consensus statement on endomyocardial biopsy; Cardiovasc Pathol 2011

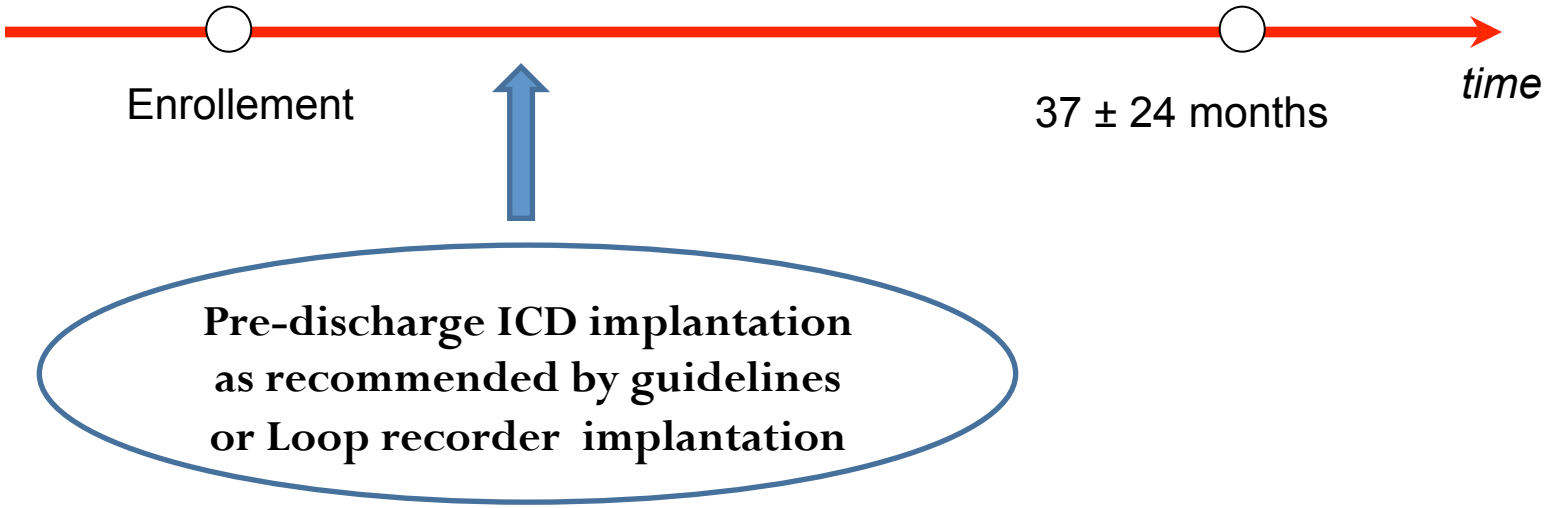
Myocardial necrosis or degeneration

\+ **Active myocarditis**

\- **Borderline myocarditis**

Angelini A et al, Heart 2002

Follow-up



END-POINT :

- Sustained Ventricular Tachycardia (SVT) or Ventricular Fibrillation (VF)
- Appropiate ICD shocks
- Appropriate ICD Therapy (ATP)

Clinical data

	Group M1 N= 50 patients (82%)	Group M0 N=11 patients (18%)	P*
Age (years)	41.0 ± 14.6	42.3 ± 12.7	0.79†
Gender M/F	29/21	7 /4	0.73
Clinical History			
Previous myocarditis/pericarditis	7 (14.0%)	2 (18.2%)	0.72
Familiar History of SCD	5 (10.0%)	3 (27.3%)	0.12
Clinical Presentation			
Resuscitated SCD	3 (6.0%)	2 (18.2%)	0.18
Electrical storm (ES)	1 (2.0%)	0 (0%)	0.63
Syncope	6 (12.0%)	2 (18.2%)	0.58
Palpitation	24 (48.0%)	3 (36.4%)	0.48
Dyspnea	6 (12.0%)	1 (9.1%)	0.78
QRS duration at sinus rhythm ECG	106.5 ± 24.4	108.3 ± 21.8	0.82†
ECG findings at admission			
VF	3 (6.0%)	2 (18.2%)	0.18
SVT	10 (20.0%)	1 (9.1%)	0.39
PVCs/NSVT	37 (74.0%)	8 (72.7%)	0.82

*= p from Chi-quadro test ; † = p from unpaired t-test

Imaging and Histological data

	Group M1	Group M0	P*
Echocardiography	**(n=50)**	**(n=11)**	
LVEF <50%	15 (30.0%)	4 (36.4%)	0.68
LVEF (%)	51.6 ± 11.8	54.0 ± 10.7	0.55†
Abnormalities in RV	11 (35.5%)	3 (27.3%)	0.62
Abnormalities in LV	19 (61.3%)	3 (27.3%)	0.06
Cardiac MRI	**(n=37)**	**(n=11)**	
Evidence of Delayed Enhancement (DE)	19 (51.4%)	4 (36.4%)	0.38
LVEF (%)	52.8 ± 12.5	51.6 ± 13.4	0.78†
RVEF (%)	53.7 ± 10.8	54.1 ± 8.5	0.92†
RV alteration(akinetic segments/dilatation)	18 (56.2%)	3 (30.0%)	0.15
LV alteration (akinetic segments/dilatation)	12 (42.9%)	4 (44.4%)	0.93
Endomyocardial Biopsy	**(n=50)**	**(n=11)**	
Active Myocarditis	20 (40.0%)	-	
Borderline Myocarditis	30 (60.0%)	-	

*= p from Chi-quadro test ; † = p from unpaired t-test

Electrophysiological data

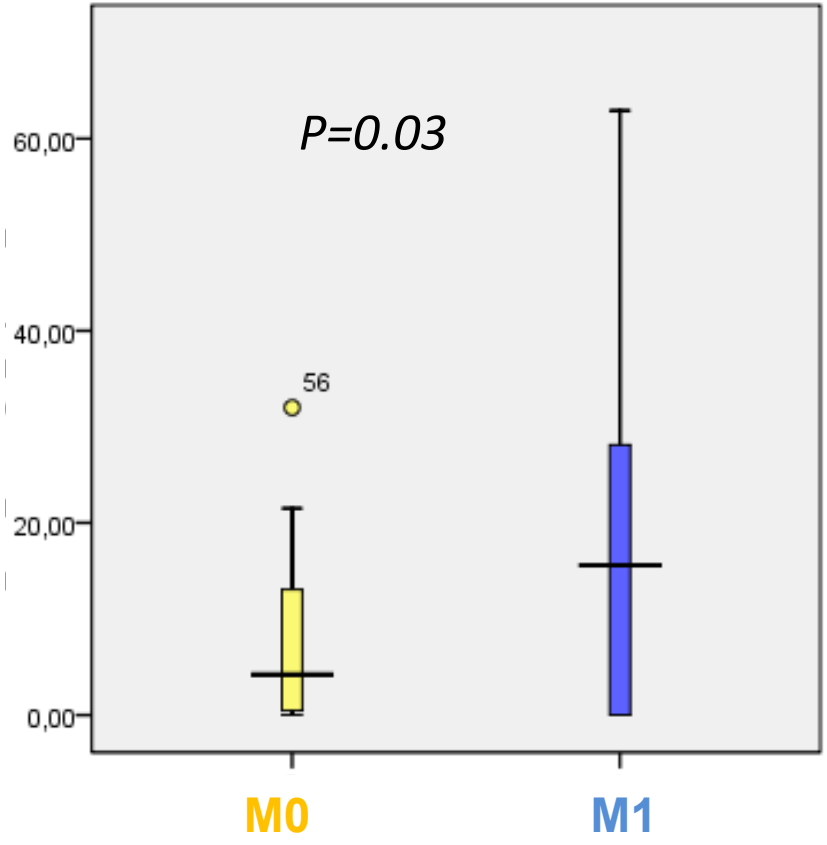
	Group M1	Group M0	P*
Electrophysiological Study (EPS)	**(n=48)**	**(n=11)**	
Inducible VT/VF	14 (29.2%)	2 (18.2%)	0.46
Electroanatomic Mapping (EAM)			
RV total Area (cm2)	211.3 ± 34.1	165.8 ± 47.7	0.02†
RV total Volume (ml)	142.0 ± 33.4	101.5 ± 55.2	0.05†
LV total Area (cm2)	239.9 ± 83.5	225.0 ± 51.0	0.69†
LV total Volume (ml)	192.8 ± 95.0	154.0 ± 40.1	0.41†

*= p from Chi-quadro test ; † = p from unpaired t-test

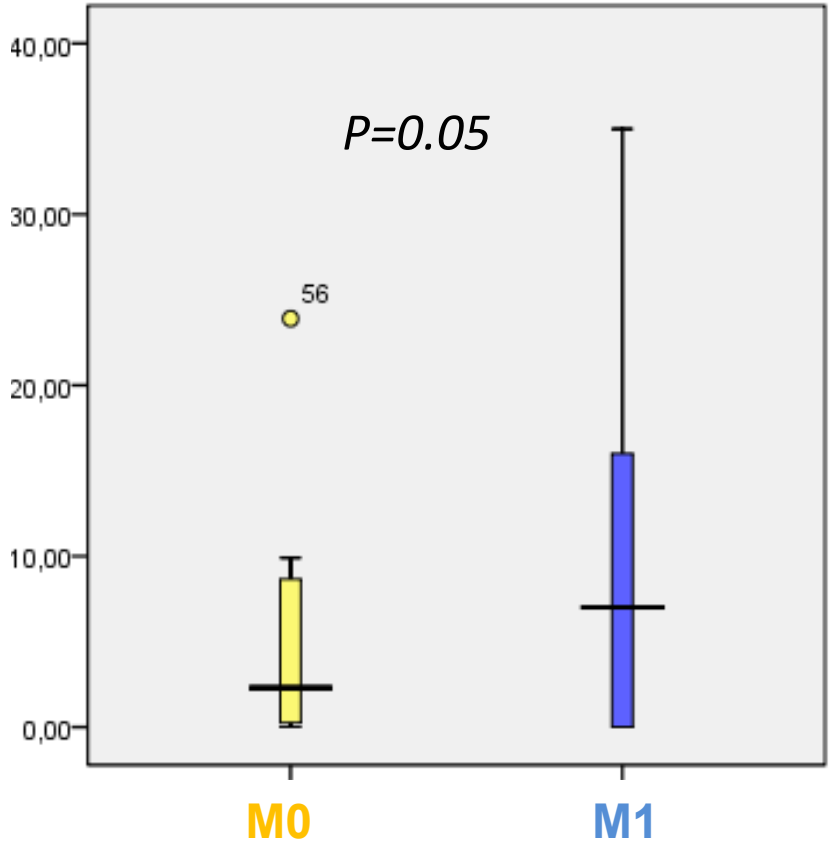
Endocardial Bipolar mapping

Total (RV+ LV) Low-Voltage Bipolar Area

Total Low-Voltage Bipolar Area (cm2)

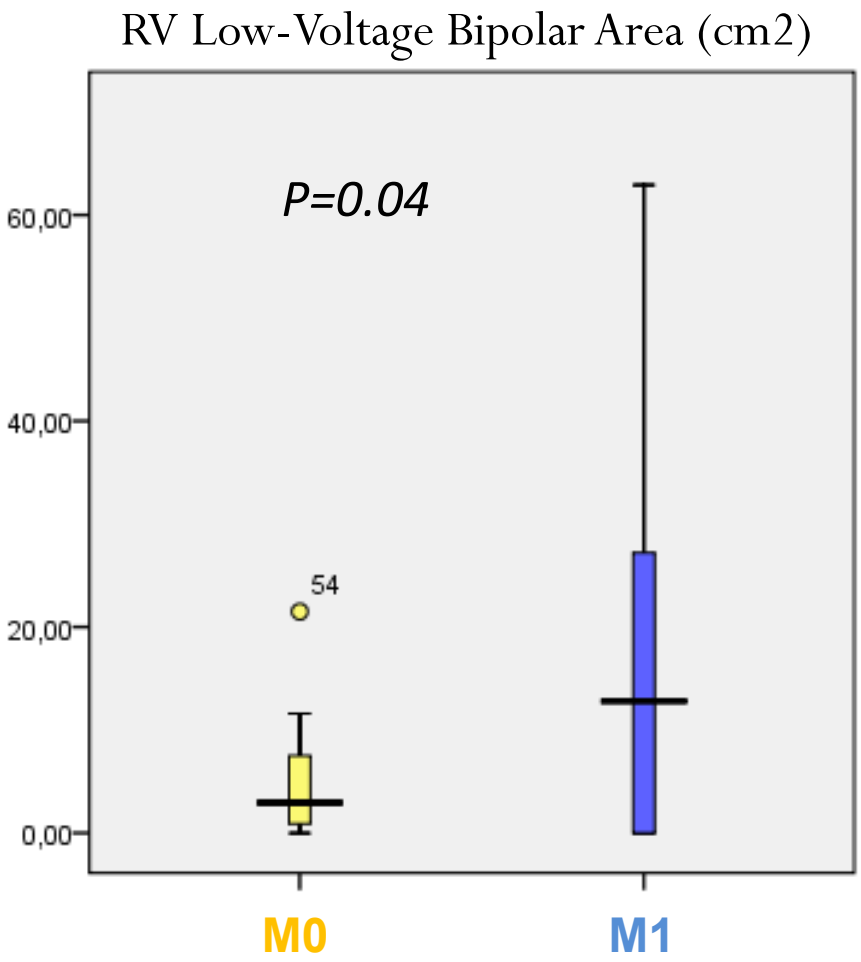


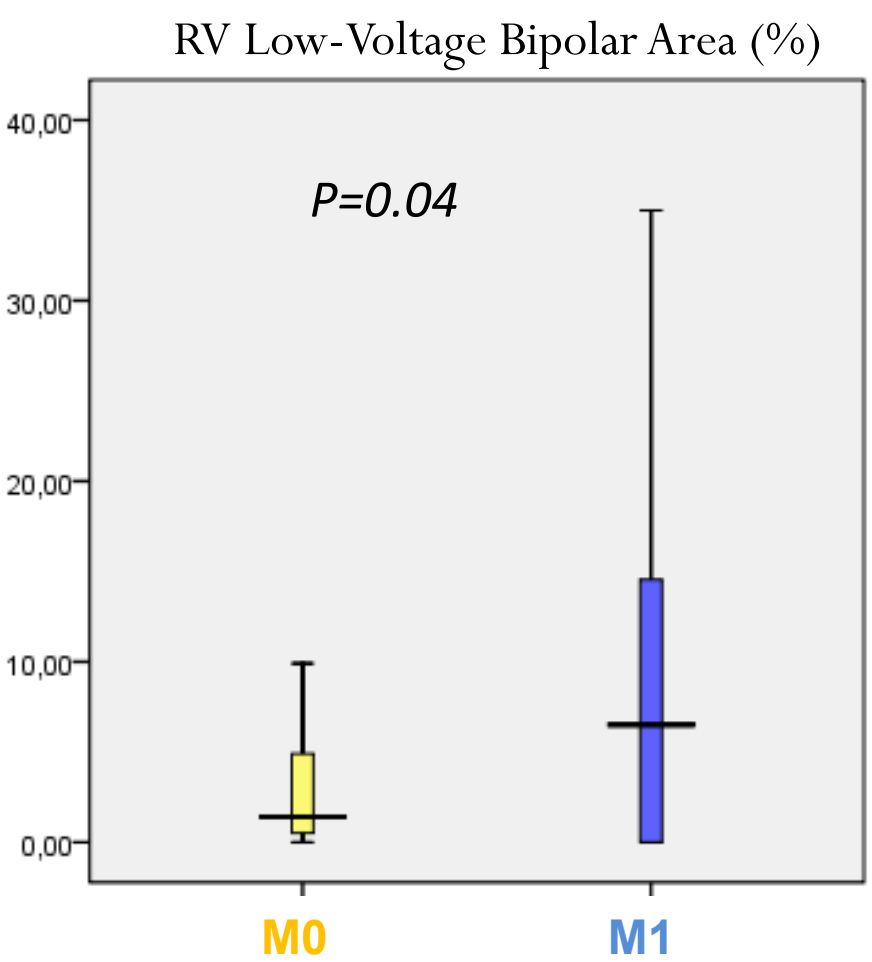
Total Low-Voltage Bipolar Area (%)



Endocardial Bipolar mapping

Right Ventricle Low-Voltage Bipolar Area

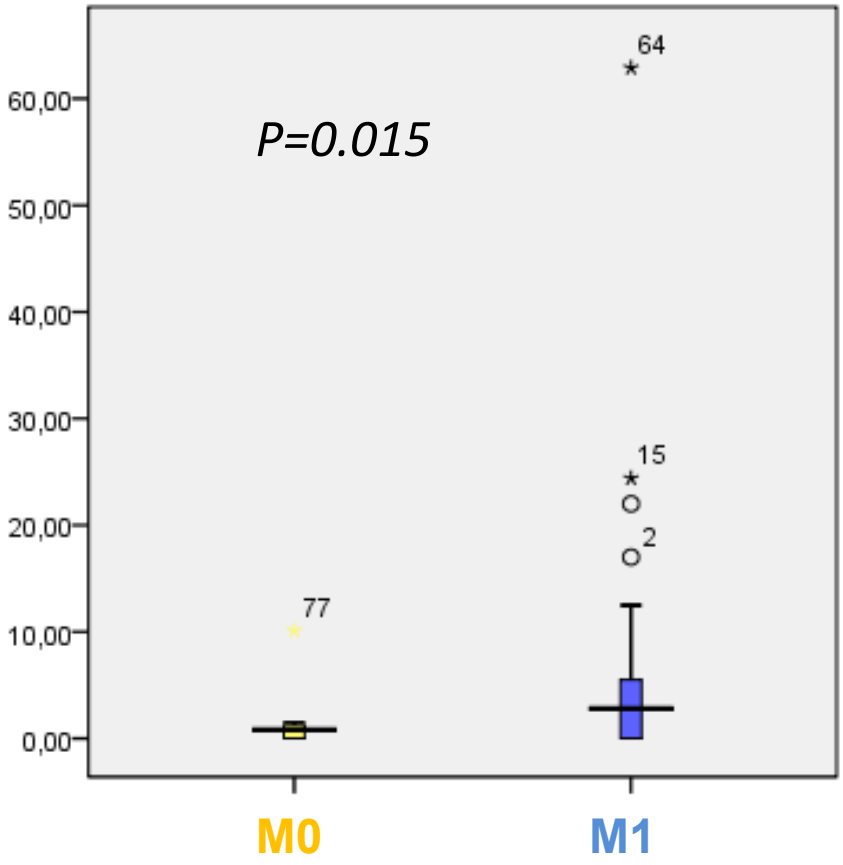




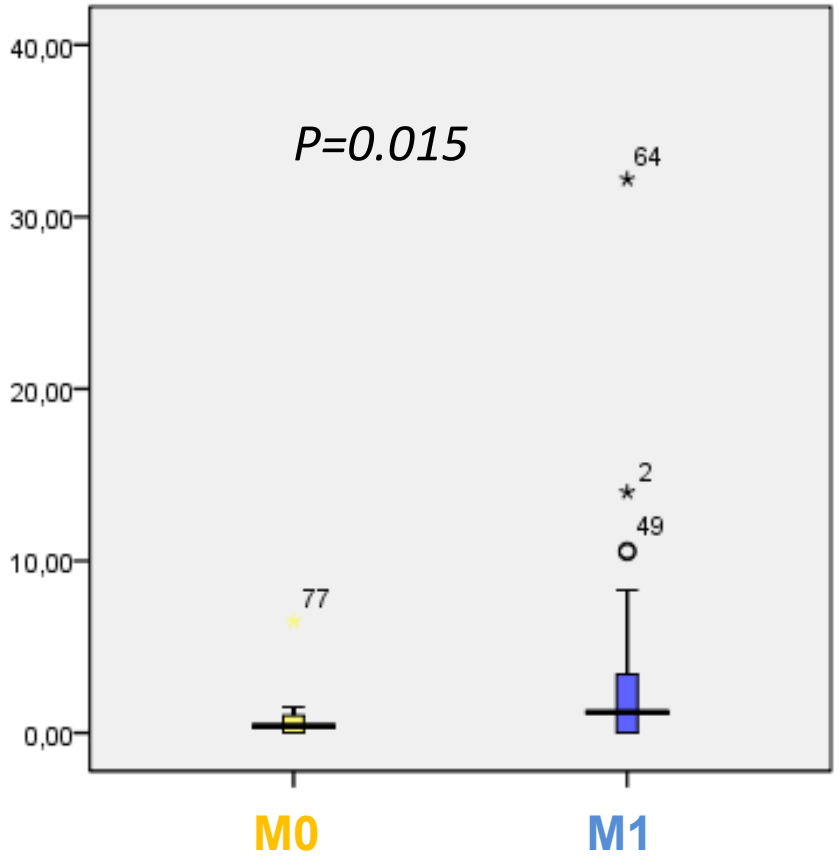
Endocardial Bipolar mapping

Right Ventricle Scar Bipolar Area

RV Scar Bipolar Area (cm2)



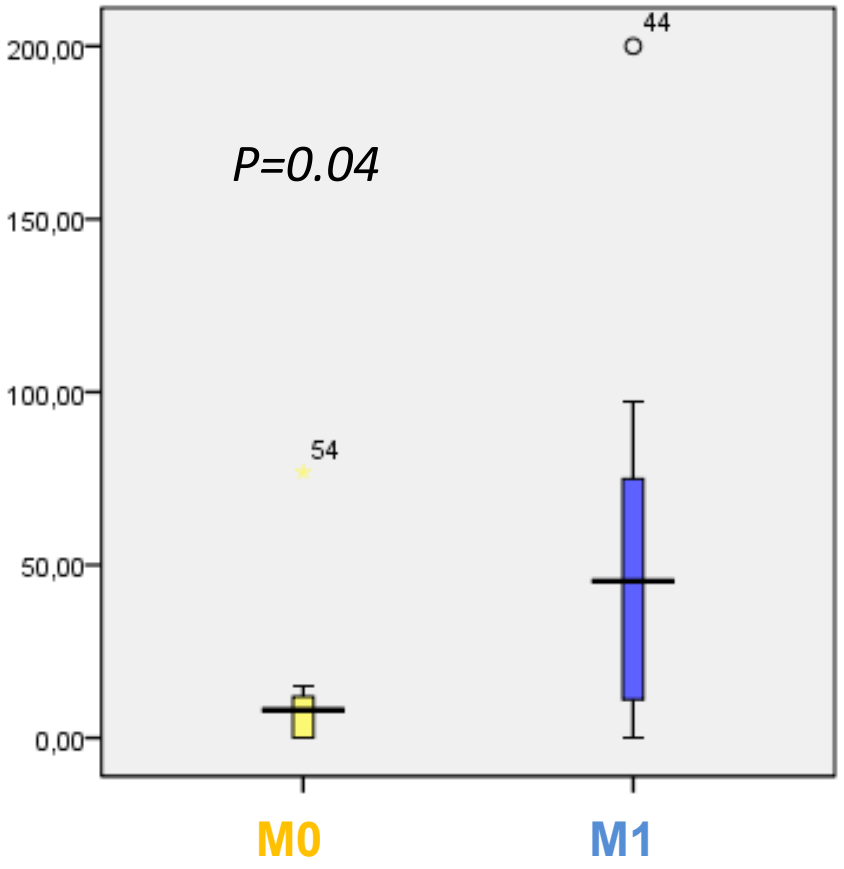
RV Scar Bipolar Area (%)



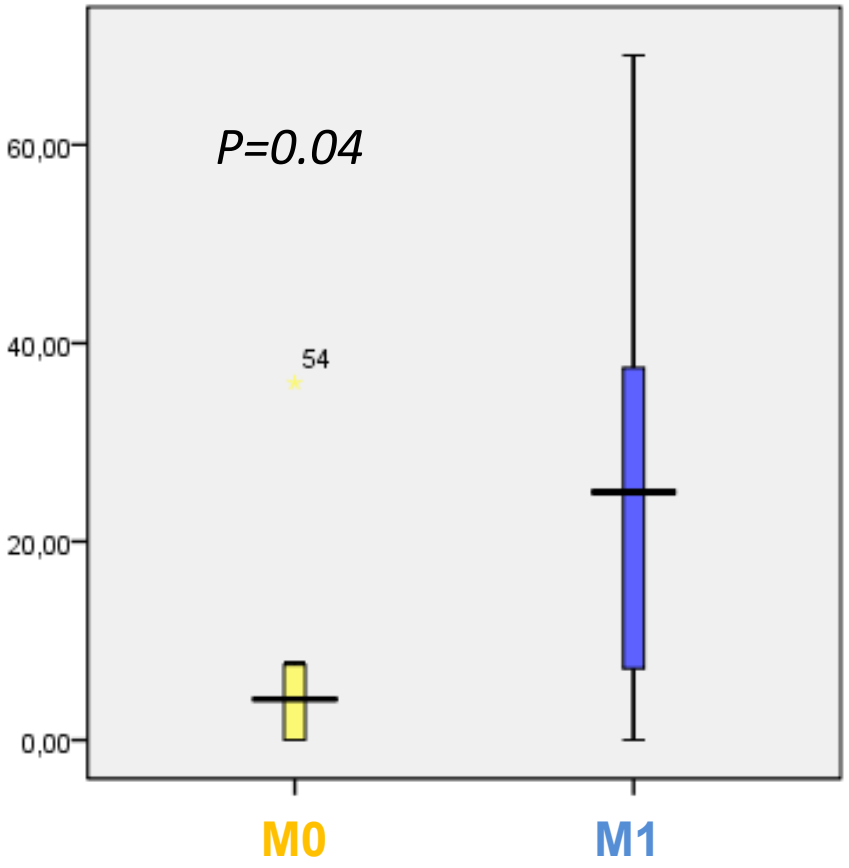
Endocardial Unipolar mapping

Right Ventricle Scar Unipolar Area

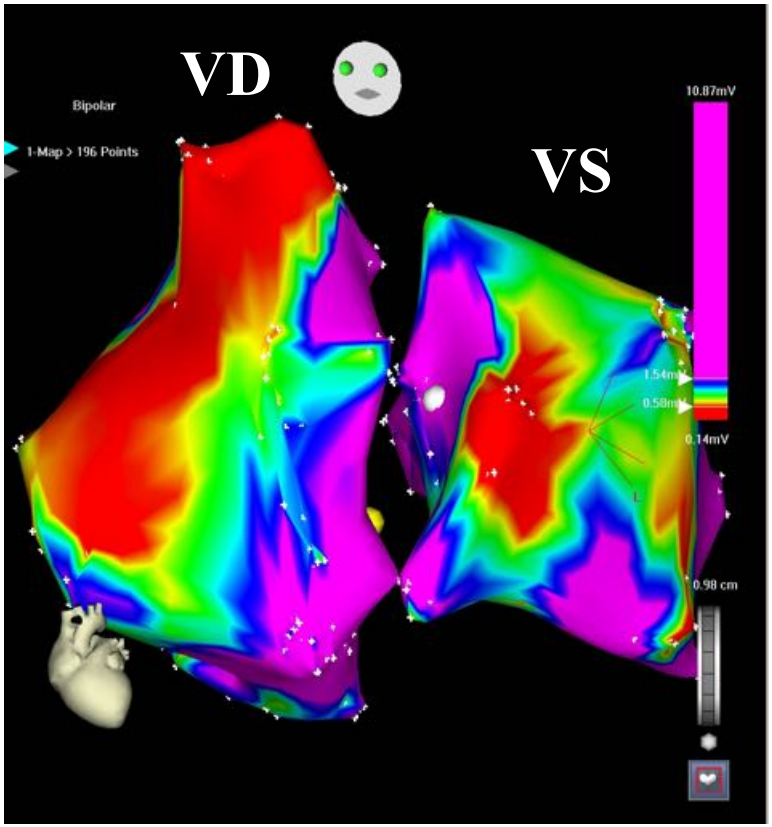
RV Scar Unipolar Area (cm2)



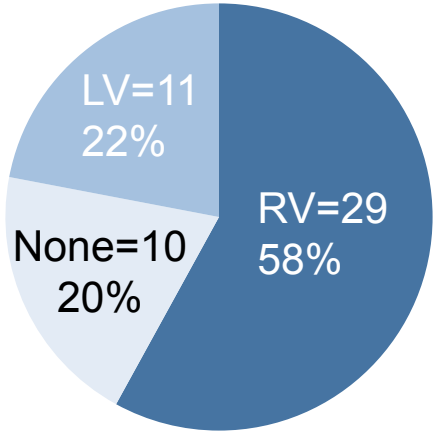
RV Scar Unipolar Area (%)



Low Voltage Areas localization at Bipolar EAM

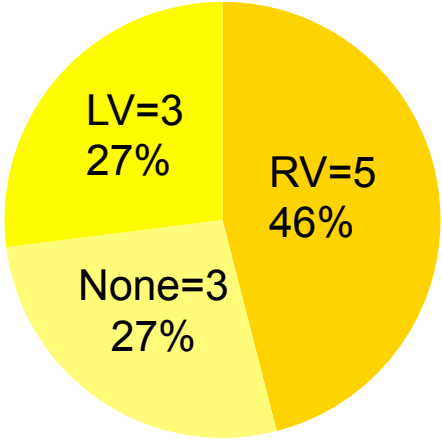


Low voltage areas in M1 (40/50 pts: 80%)

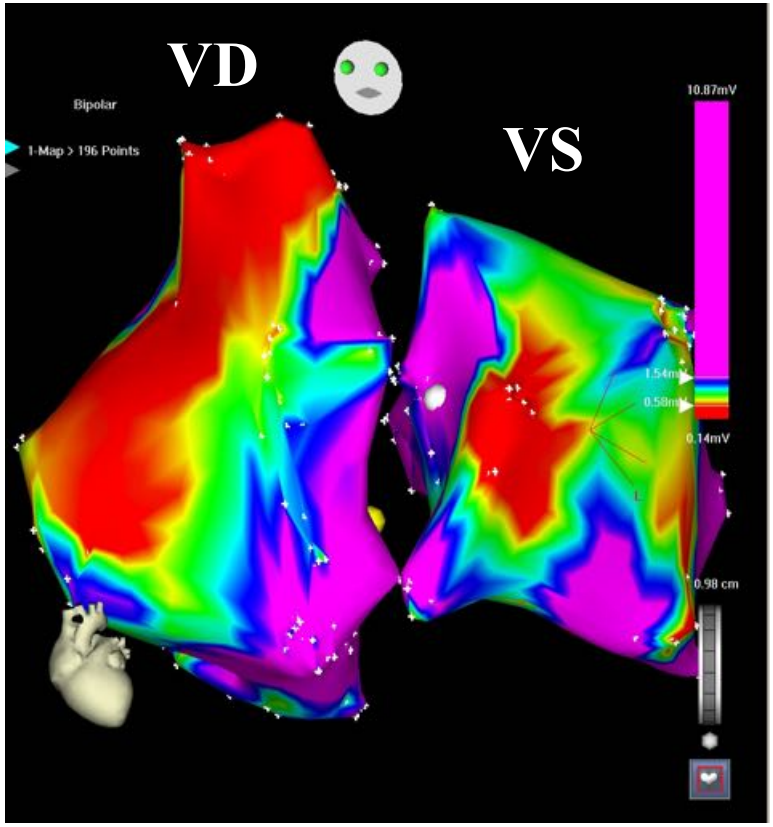


P=0.31

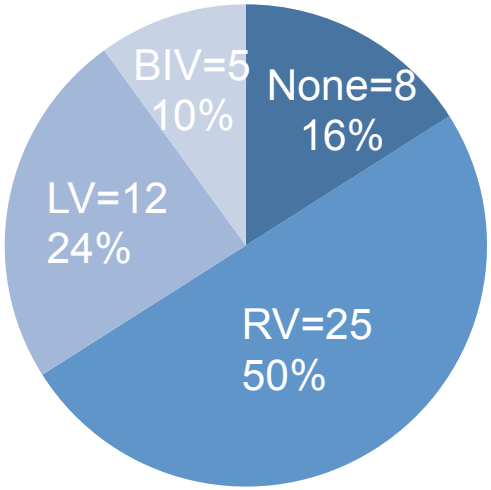
Low voltage areas in M0 (8/11 pts: 72%)



Scar localization at Unipolar EAM

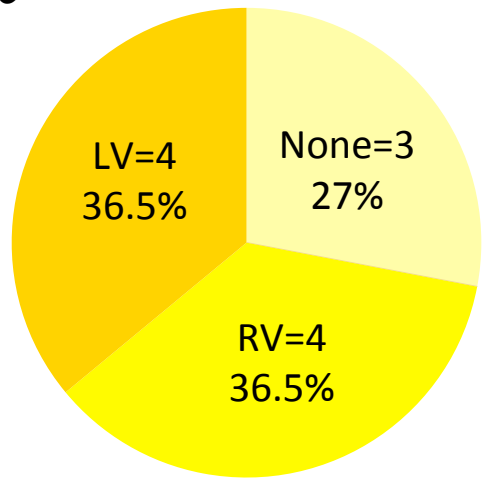


Scar in M1
(42/50 pts : 84%)



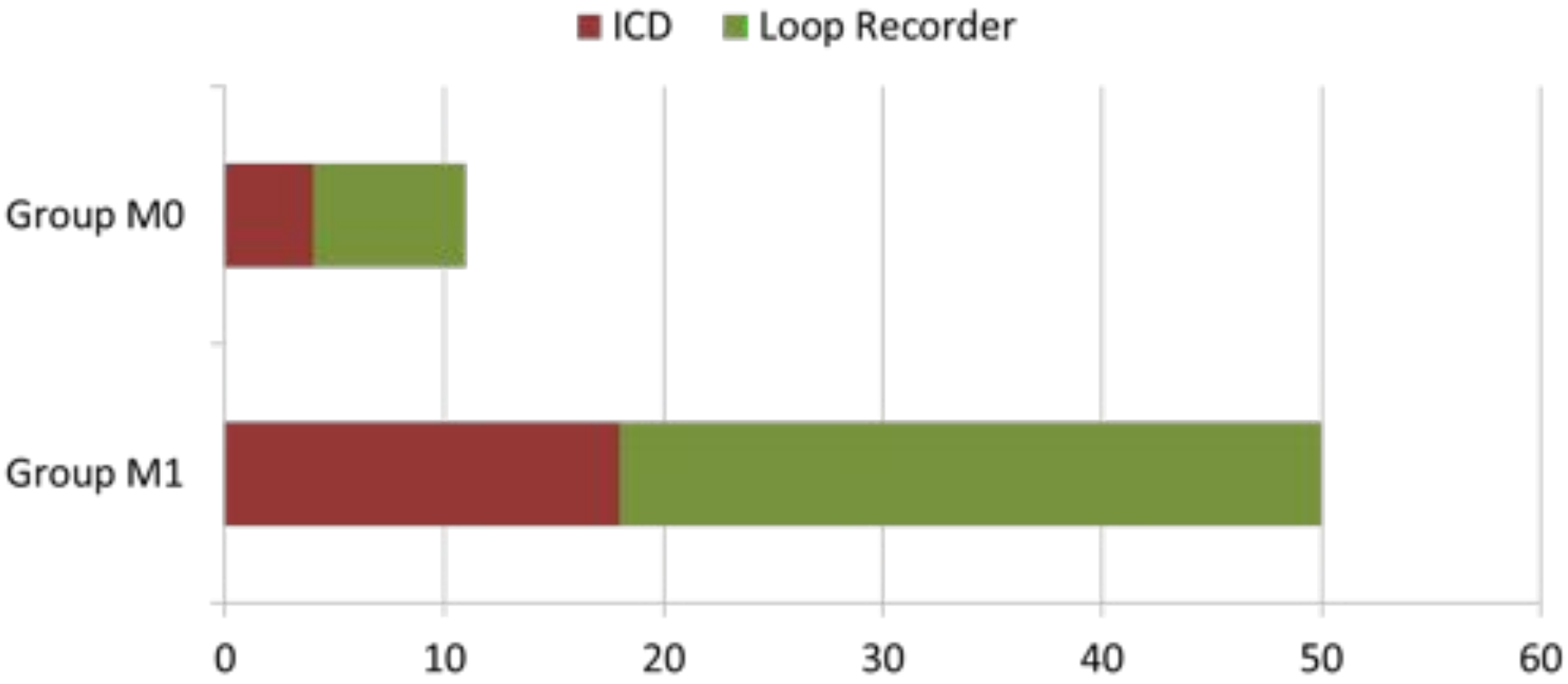
P=0.40

Scar in M0
(8/11 pts : 72%)



ICD and Loop Recorder Implantation

- Group M0: ICD implantation in 4/11 patients (36%)
- Group M1: ICD implantation in 18/50 patients (36%)

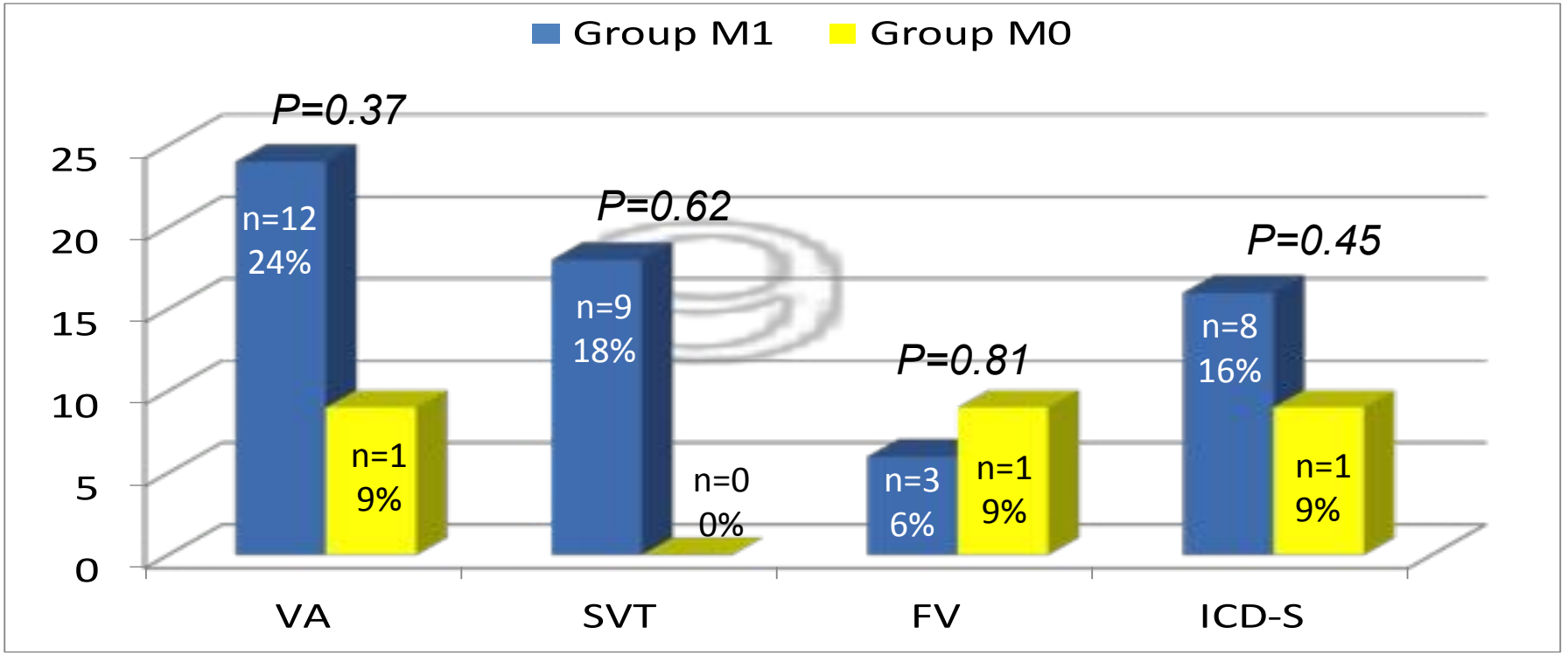


Follow-up and Events

Mean Follow-up: 37 ± 24 months

Events: Ventricular Arrhythmias (VA) defined as

- Sustained Ventricular Tachycardia (SVT) or Ventricular Fibrillation (VF)
- Appropiate ICD shocks (ICD-S) o Appropriate ICD Therapy (ATP)



Predictors of VA at follow-up
Univariate Analysis

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
Diagnosis of Myocarditis at EBM	0.50 (0.05-4.73)	0.55
Active myocarditis	0.73 (0.20-2.58)	0.62
Familial History of SCD	0.71 (0.09-5.53)	0.74
Presentation Electrical storm (ES)	4.63 (0.56-38.35)	0.15
Presentation VF	4.98 (0.98-25.45)	0.05
Presentation Syncope	2.87 (0.76-10.87)	0.12
Presentation Palpitation	0.57 (0.18-1.82)	0.57
Presentation VT	4.87 (1.52-15.77)	0.008
LVEF < 50%	3.02 (0.95-9.59)	0.06
LVEF < 35%	10.75 (2.61-44.19)	0.001
DE at cardiac MRI	1.15 (0.22-6.00)	0.87
VT Inducibility	5.63 (1.62-19.64)	0.007

Predictors of VA at follow-up
Univariate Analysis

Group M1

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
Active myocarditis	0.83 (0.21-3.29)	0.80
Familial History of SCD	0.82 (0.10-6.45)	0.85
Presentation Electrical storm (ES)	5.03 (0.59-42.44)	0.14
Presentation VF	3.01 (0.37-26.09)	0.29
Presentation Syncope	2.05 (0.43-9.67)	0.36
Presentation Palpitation	0.65 (0.19-2.14)	0.47
Presentation TV	5.78 (1.66-20.15)	0.006
LVEF < 50%	3.54 (1.06-11.88)	0.04
LVEF < 35%	13.85 (2.98-64.31)	0.001
DE at cardiac MRI	1.45 (0.23-9.19)	0.69
VT Inducibility by PVS	7.48 (1.89-29.59)	0.004

Predictors of VA at follow-up
Univariate Analysis

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
Total Low Voltage at Bipolar EAM	0.99 (0.95-1.04)	0.77
Total Scar at Bipolar EAM	1.03 (0.98-1.08)	0.18
Total Scar at Unipolar EAM	1.09 (0.99-1.02)	0.11
RV Low Voltage at Bipolar EAM	0.99 (0.95-1.04)	0.86
RV Scar at Bipolar EAM	1.03 (0.98-1.09)	0.23
RV Scar at Unipolar EAM	1.01 (0.99-1.02)	0.17
LV Low Voltage at Bipolar EAM	1.07 (0.89-1.13)	0.91
LV Scar at Bipolar EAM	1.26 (0.97-1.54)	0.08
LV Scar at Unipolar EAM	1.04 (0.98-1.02)	0.67

Predictors of VA at follow-up
Multivariate Analysis

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
LVEF < 35%	7.95 (1.51 - 41.76)	0.014
VT Inducibility by PVS	4.25 (1.17 – 15.40)	0.03

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
LVEF < 35%	10.40 (2.42 – 44.79)	0.002
Presentation VT	4.43 (1.36 – 14.38)	0.013

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
VT Inducibility by PVS	7.42 (1.88 – 29.31)	0.004
Presentation VF	12.08 (1.01 – 144.28)	0.05

Predictors of VA at Follow-up	Hazard Ratio (IC 95%)	P
Presentation VT	7.49 (1.90 – 29.50)	0.004
Presentation VF	11.42 (1.78 – 73.43)	0.01

Multivariate survival analysis using Cox's regression model

Conclusions

- A higher degree of unipolar and bipolar alterations involving the RV was observed in patients with biopsy-proven myocarditis compared with patients with no histological diagnosis of myocarditis, confirming that substrate alteration at EAM reflects histological abnormalities in these patients.

- At cardiac MRI, there were no statistical significant differences in term of imaging data between group M1 and M0. In both groups, we demonstrated a moderate degree of DE and ventricular involvement.

Conclusions

- Patients presenting with VA in a clinical setting of myocarditis had a rate of VA recurrence at follow-up of 21%.

- Indipendent predictors of arrhythmic events at follow-up were: VT inducibility, clinical presentation with VF/VT, and a significant dysfunction of LV (LVEF<35%).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