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SUPPLEMENTARY MATERIAL

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Long-term Follow-up of Symptomatic Adult Patients With Noncompaction Cardiomyopathy



Seguimiento a largo plazo de pacientes sintomáticos adultos con miocardiopatía no compactada

To the Editor,

Noncompaction cardiomyopathy (NCC) is thought to arise due to an arrest of the normal myocardial compaction process during intrauterine life.¹ Clinical manifestations include heart failure, embolic events, and arrhythmias.² Its prognosis varies considerably between studies and remains largely unknown.

Our aim was to better define the outcomes of symptomatic adult patients (defined as those > 18 years old, presenting with heart failure, atrial or ventricular arrhythmias, or embolic events) with NCC and compare them with those of a contemporary cohort of patients with idiopathic dilated cardiomyopathy (IDC).

This retrospective study included all consecutive patients who fulfilled echocardiographic criteria of NCC,³ managed at 2 tertiary centers from 2001 to 2015. As a comparison group, we included all consecutive symptomatic patients with IDC managed at the Heart Failure Program of one of the participating centers from 2008 to 2015. We collected adverse events during follow-up, defined as sustained ventricular arrhythmias, cardioembolic events, cardiovascular death, or heart transplant. The study was approved by the clinical research ethics committees of both centers. Comparative analysis between the groups were performed with the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Survival analyses were performed with Kaplan-Meier curves and differences were tested using the log-rank test. To evaluate whether NCC predicted outcomes compared with IDC, we performed a backward step multivariate Cox proportional hazard analysis.

The Table shows the patients' baseline characteristics and treatment. Seventy-five patients with NCC fulfilled the inclusion criteria. In 65 (86.7%) patients, heart failure was the index complaint, whereas 9 (12%) had arrhythmias (6 atrial in origin and 3 ventricular tachycardia [2 sustained VT with

hemodynamic stability and 1 with frequent runs of symptomatic nonsustained VT]) and 1 (1.3%) presented with an embolic event (stroke); 17% of the patients with NCC had a known family history of cardiomyopathy at diagnosis (but had not previously undergone family screening).

Patients with IDC were older and showed larger left ventricular end-diastolic diameters, as well as lower ejection fraction.

The patients were followed up for a median of 5 (2.4–6.7) years. During follow-up, 14 (18.7%) patients in the NCC group had a first adverse event (5 ventricular arrhythmias, 3 cardiovascular deaths, 4 cerebrovascular embolic events, and 2 heart transplants), whereas 35 (26.7%) patients had a first adverse event in the IDC group (13 ventricular arrhythmias, 12 cardiovascular deaths, 3 cerebrovascular embolic events, and 7 heart transplants). None of the patients with cerebrovascular events were under anticoagulant treatment prior to the event.

In the NCC group, 19 (25.3%) patients underwent an ICD placement, 12 as primary prevention and 7 as secondary prevention. In the IDC group, 48 patients (36.6%) underwent an ICD placement, 24 as primary prevention and 24 as secondary prevention. No statistically significant differences were found in terms of the ICD implantation rate between groups. Only patients in whom the indication was secondary prevention showed ICD therapies during follow-up.

The Figure shows the Kaplan-Meier survival curves free from a first event and free from cardiovascular death or heart transplant in both groups. Having an NCC did not predict a different outcome free from a first event compared with IDC (HR, 1.01; 95%CI, 0.49–2.10; $P = .98$) after multivariate adjustment for age, left ventricular end-diastolic diameter, ejection fraction, and serum creatinine.

Our main finding is that symptomatic adult patients with NCC had a similar incidence of adverse events and survival compared with patients with IDC. The annual incidence of thromboembolic events was 1.06 percent per year in the NCC group and 0.62 percent per year in the IDC group. Interestingly, both groups showed a high incidence of anticoagulation therapy, even in sinus rhythm, but a diagnosis of NCC was not an indication for the use of anticoagulants. The low rate of thromboembolic events was probably related to this

Table
Baseline Characteristics

Variable	NCC (n = 75)	IDC (n = 131)	P
Sex			.293
Male, %	51 (68)	98 (74.8)	
Female, %	24 (32)	33 (25.2)	
Age	50.4 (14.8)	57.2 (11.9)	.0005
Hypertension, %	24 (32)	45 (34.3)	.731
Diabetes mellitus, %	14 (18)	24 (18.3)	.951
Dyslipidemia, %	19 (25.3)	43 (32.8)	.260
Known family history of cardiomyopathy	13 (17.3)	-	-
LVEDD, mm	63.8 (9.1)	68.3 (9.2)	.001
Ejection fraction, %	32 [29-34]	27 [21-32]	.001
Left atrium diameter, mm	46.2 ± 9	44.8 ± 6	.225
Biventricular involvement, %	23 (30.7)	50 (38.1)	.279
Functional class, %			.96
I	10 (13.3)	21 (16)	
II	39 (52)	66 (50.4)	
III	25 (33.3)	42 (32.1)	
IV	1 (1.3)	2 (1.5)	
Serum creatinine, μmol/L	92.2 [85-99]	93 [78-109]	.057
NT-proBNP, ng/L	2150 [1115-2786]	1115 [343-2574]	.345
History of atrial fibrillation/flutter,* %	29 (38.7)	40 (30.5)	.51
LBBB	33 (44)	46 (35.1)	.29
Beta-blockers, %	70 (93.3)	121 (92.3)	1
ACE inhibitors/ARBs, %	71 (94.7)	127 (97)	.47
Aldosterone antagonists, %	45 (60)	87 (68)	.28
Digoxin	21 (28)	50 (38)	.17
Oral anticoagulants, %	40 (53.3)	58 (44)	.245
Antiplatelet therapy	12 (16)	24 (18)	.848
Diuretics	65 (86.6)	110 (84)	.602
Implantable cardioverter-defibrillator	19 (25.3)	49 (38)	.096

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; LBBB, left bundle branch block; LVEDD, left ventricle end-diastolic diameter; NCC, noncompaction cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

The data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

* History of atrial fibrillation or flutter (including prior to the beginning of follow-up).

high incidence, and anticoagulation with a tight control of the therapeutic range may benefit patients with left ventricular dysfunction in sinus rhythm.⁴ The prevalence of ventricular arrhythmias and rates of ICD implants did not differ significantly between the 2 groups.

This study has several limitations. First, this is a retrospective study with limited statistical power. A major limitation is that only echocardiography was used as a method of diagnosing patients with NCC and this could overestimate the real number of patients, given the limitations of the echocardiographic diagnostic criteria.⁵ Even

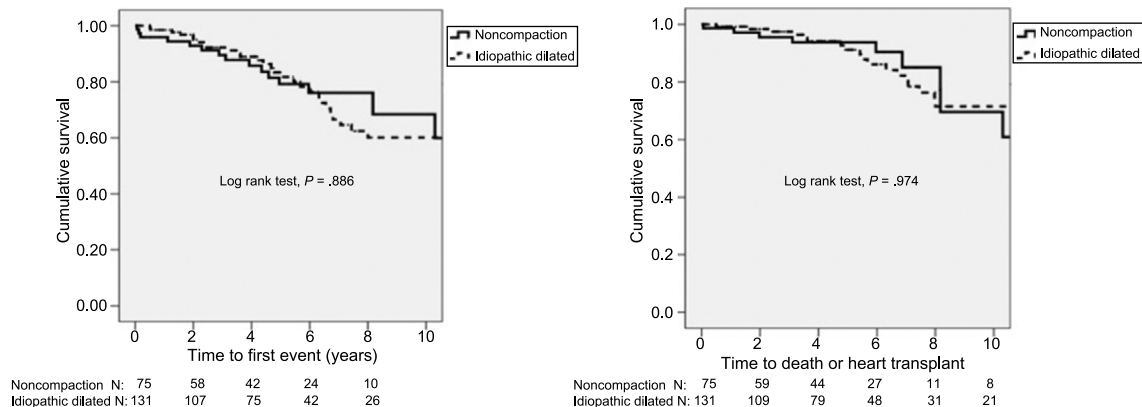


Figure. Kaplan-Meier survival curves free from a first event and free from death or heart transplant in patients with noncompaction cardiomyopathy and idiopathic dilated cardiomyopathy.

though 50 patients (66.6%) with echocardiographic NCC underwent cardiac magnetic resonance imaging to complete the study, the use of this technique was uneven across the cohort. Of note, NCC was confirmed in all the patients who underwent magnetic resonance imaging. Importantly, only a minority of our patients underwent genetic testing. Finally, the presence of neuromuscular disorders was not evaluated and all patients came from and were followed up at heart failure units; this may have created a possible selection bias which could influence the observed outcomes.

In conclusion, our study shows a nonsignificant effect of NCC on mortality compared with IDC in symptomatic adult patients being followed up at specialized heart failure units.

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Nanotechnology Applied to Preserve Extracellular Matrix as Teranostic Tool in Acute Myocardial Infarction



Nanotecnología aplicada a conservar la matriz extracelular como herramienta teranóstica en el infarto agudo de miocardio

To the Editor,

Hyperoxygenation after coronary reperfusion causes reperfusion injury, partly as a result of macrophage infiltration contributing to activation of extracellular matrix metalloproteinases (MMP), the main effectors of ventricular necrosis.¹ Extracellular-matrix-metalloproteinase-inducer (EMMPRIN) is an essential activation factor.² A murine coronary ischemia-reperfusion (IR) model has shown the importance of EMMPRIN as a target for the treatment of acute myocardial infarction,¹ and more recently, the use of EMMPRIN-targeted magnetic nanoparticles (Figure 1) has been shown to be a potential therapeutic tool for preventing necrosis.³ Before they are studied in a clinical setting, we aimed to evaluate the effectiveness of a porcine coronary IR model.

The study included 15 female Yorkshire albino pigs. Five of these were infarct-free. The remaining animals were anesthetized with intravenous administration of propofol 2 mL/kg/h and phentanyl 50 mg/kg/h and submitted to 45minutes of occlusion of the anterior descending artery by balloon inflation. The animals were then injected with 10mg/kg of nanoprobe NAP9 (containing EMMPRIN binding peptide AP9) or NAPSC (containing scramble peptide) as control (Figure 1A).³ Myocardial function was assessed before and 7 days after infarction by echocardiography. Tissue samples were examined for the presence of nanoparticles (confocal microscopy), myocardial integrity (histological staining with hematoxylin-eosin), necrotized area (staining with triphenyl tetrazolium), and EMMPRIN, MMP-9, and MMP-13 as necrosis markers.

Cytotoxicity was studied by injecting NAP9 at 0, 10, 50mg/kg and measuring serum concentrations of aspartate transaminase and alanine transaminase as markers of hepatic injury, creatinine as a renal marker, and creatine kinase MB isoenzyme as a marker of cardiac necrosis. Total absence of cytotoxicity occurred at a dose of 10mg/kg (Figure 1B). Biodistribution was analyzed by confocal microscopy of sections of heart, liver, kidney, pancreas, spleen, lung, bladder, and intestine after 7 days of IR (IR7); the heart and lung were the tissues with highest NAP9 uptake (Figure 1C).

The effect of NAP9 on progression of acute myocardial infarction was studied by injecting 10mg/kg of NAP9 or NPASC after 15minutes of reperfusion of the anterior descending artery. It was found that left ventricular ejection fraction (estimated in B mode by the Simpson biplane method and in M mode [Teichholz method], with similar results) of the pigs injected with NAP9 was significantly greater than in control animals (NAP9 IR7 vs control IR7, 51.7% [3.5%] vs 45.2% [2.2%]; $P < .05$) (Figure 2A). In contrast, the extent of the necrotized area, expressed as a percentage of the total surface of the left ventricle (control vs NAP9, 28.05% [3.68%] vs 16.08% [4.96%]; $P < .0003$) (Figure 2B) and expression of MMP-9 and MMP-13 (Figure 2C), indicative of necrosis due to extracellular matrix degradation, decreased in pigs treated with NAP9.

Nanotechnology applied to the treatment and prevention of reperfusion injury is an approach with promising clinical results.^{4,5} In conclusion, the extension of infarction was significantly reduced in the pigs that underwent coronary IR and received NAP9, and therefore ventricular function was at least improved through reduction of necrosis associated with degradation of the extracellular matrix. Before studying the approach in clinical trials, and bearing in mind the limitation of using echocardiography compared with magnetic resonance imaging for functional assessment of contractility, it would be necessary to increase the sample size of the study and, depending on the visibility of NAP9 in magnetic resonance imaging, complement the results by