

proband's uncle since the proband was initially not available for mutation screening. The heterozygous ACTC1^{I289T} mutation was identified and cascade genetic studies were undertaken in the remaining relatives. No additional mutation was found in any of the other screened genes. The Table shows the results of the family study in affected (II:4, III:4, III:6 and IV:1) and nonaffected individuals (no additional family members were available for the study).

Gene sequencing yielded the presence of the heterozygous ACTC1^{I289T} mutation, not present in the National Center for Biotechnology list of single nucleotide polymorphisms in the ACTC1 gene. Although hundreds of variants have been identified in sarcomeric and desmosomal genes, only a few polymorphisms and < 30 mutations causing any kind of cardiomyopathy have been described in the ACTC1 gene, suggesting that changes in the ACTC1 gene are poorly tolerated. Actin is essential for cell morphology, adhesion, and migration. This novel variant alters a preserved amino acid residue (I289) in the protein, replacing a nonpolar (isoleucine) with another polar and noncharged (threonine) amino acid, thus causing moderate modifications in the physico-chemical properties related to the hydrophobicity, charge, polarity, and mass of the protein (Grantham distance 89 [0–215]). The prediction of *in silico* (SIFT [Sorting Intolerant from Tolerant], Polyphen-2, and Pmut) analyses neither confirmed nor ruled out its pathogenicity (inconclusive results with low confidence). The preserved I289 amino acid residue maps to subdomain 3, important for the stability and polymerization of the actin filaments⁶ and next to the myosin binding site, possibly disrupted by the presence of the ACTC1^{I289T} mutation. Furthermore, our ACTC1^{I289T} mutation cosegregated perfectly with the LVNC phenotype, with a 100% penetrance in the individuals available for the study.

We acknowledge that a more thorough genetic study could have included many other genes. Nonetheless, we considered it finished in terms of cost-effectiveness for three reasons: a) our results were consistent with a previous study linking LVNC and septal defects due to ACTC1 mutation⁴; b) the variant strongly cosegregated with the phenotype, and c) the molecular consequences of the variant were considered probably pathogenic. Further functional information obtained from animal models may be valuable to confirm the causal role of the ACTC1^{I289T} mutation.

In summary, we offer the phenotypical description of a family with LVNC caused by the highly penetrant, novel, heterozygous ACTC1^{I289T} mutation. Remarkably, in the literature this is the third ACTC1 mutation causing LVNC, and associated ostium secundum atrioseptal defect in some affected family members.

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Improvement in Hemodynamics and Contractility With Multipoint Left Ventricular Pacing in Cardiac Resynchronization Therapy



Mejoría hemodinámica y de la contractilidad con la estimulación multipunto del ventrículo izquierdo en la terapia de resincronización cardíaca

To the Editor,

Heart failure is a leading cause of morbidity and mortality in Western countries. Biventricular pacemakers have been used to treat heart failure since the 1990s.¹ Over the last decade,

randomized studies^{2,3} have demonstrated the benefit of cardiac resynchronization therapy (CRT) and helped to establish its indications. This therapy has been shown to increase survival and decrease hospitalizations in patients with heart failure, left ventricular (LV) dysfunction, and prolonged QRS, in particular in those with complete left bundle branch block.⁴ Unfortunately, a significant number of patients (30%–40%) have no response to CRT.⁵ This lack of response could be explained by inappropriate pacing site selection, suboptimal device programming, or absence of dyssynchronous basal LV contraction.⁵ Another limitation could be that pacing from a single LV point is incapable of generating a coordinated mechanical activation. Quadripolar electrodes would allow LV pacing from 2 points far

Table

Sample Characteristics (N = 8)

Women, %	3 (37.5)
Age, mean (SD), y	63 (8)
Underlying Heart Disease	
Dilated Cardiomyopathy	7 (87.5)
Ischemic Cardiomyopathy	1 (12.5)
CVRF	
HTN	4 (50)
Dyslipidemia	6 (75)
Diabetes mellitus	4 (50)
Smoking	4 (50)
LVEF, mean (SD), %	22.5 (8)
Treatment	
Loop diuretics	7 (87.5)
Beta-blockers	6 (75)
ACE-I/ARB	7 (87.5)
Aldosterone antagonists	6 (75)
Anti-arrhythmics	1 (12.5)
NYHA FC	
II	2 (25)
III	5 (62.5)
IV	1 (12.5)
Baseline ECG rhythm	
Sinus rhythm	7 (87.5)
Atrial fibrillation	1 (12.5)
QRS width, mean (SD), ms	162 (20)
Intraventricular Conduction	
CLBBB	6 (75)
Nonspecific abnormalities	1 (12.5)
Ventricular paced rhythm	1 (12.5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist (blocker); CLBBB, complete left bundle branch block; CVRF, cardiovascular risk factor; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NYHA FC, New York Heart Association functional class; SD, standard deviation. The values are expressed as N (%) or mean (standard deviation).

enough apart to reduce activation time and LV dyssynchrony. A newly-marketed device (QUADRA ASSURA, St. Jude Medical) achieves multipoint LV pacing using a quadripolar lead. Compared with conventional CRT, initial results of multipoint

pacing have shown an additional hemodynamic benefit.⁶ Our aim was to describe the first use of multipoint pacing in Spain, and evaluate its benefit over conventional CRT, using echocardiography.

Following informed consent, 8 patients with indications for conventional CRT were enrolled and underwent device implantation between November 2013 and March 2014. A St. Jude Medical automatic implantable CRT-defibrillator was used, capable of pacing from multiple poles with the left ventricular lead. We compared baseline situation (no ventricular pacing), pacing from 1 LV point (conventional group), and pacing from 2 LV points (Multipoint Pacing [MPP] group). We used an anatomical configuration for multipoint pacing, from the distal and proximal poles of the LV lead (47 mm apart), with the goal of capturing the maximum myocardial mass possible. The device was programmed in AAI at 90 bpm (baseline group) and DDD at 90 bpm (conventional group and MPP group) to avoid the effect of cardiac frequency on cardiac output variation. Hemodynamic evaluation was performed using transthoracic echocardiography (IE33, Philips®) at least 1 month post-implant, by an echocardiographer blinded to the device program. The same operator repeated the measurements masked, to determine variability. Ejection fraction was calculated using the Simpson method, and cardiac output using the time-volume integral. Descriptive statistics were calculated. To determine intra-observer variability, an intraclass correlation coefficient was used. The Kolmogorov-Smirnov normality test was performed due to small sample size. Normally distributed variables were analyzed using ANOVA (with Bonferroni correction for multiple comparisons); those with non-normal distribution were compared using the Kruskal-Wallis test. We performed the statistical analysis using IBM SPSS Statistics 18, defining significance as a *P*-value of < 0.05. Patient characteristics are summarized in the Table. There were no complications during implantation, and no subsequent electrode dislocation. Echocardiographic calculations showed low variability (intra-class correlation coefficient 0.965). Seven patients (88%) showed hemodynamic improvement with resynchronization activation. Of those patients, 6 (86%) achieved greater improvement with multipoint pacing. Mean cardiac output (SD) was 4.8 L/min (0.8), 5.3 L/min (0.9), and 5.6 L/min (1.2) in the baseline, conventional and MPP groups, respectively. We studied the relative increase in cardiac output in the CRT patients, and found greater increases in the MPP group (16.7%), compared with the conventional group (10.4%), but the difference was not statistically significant

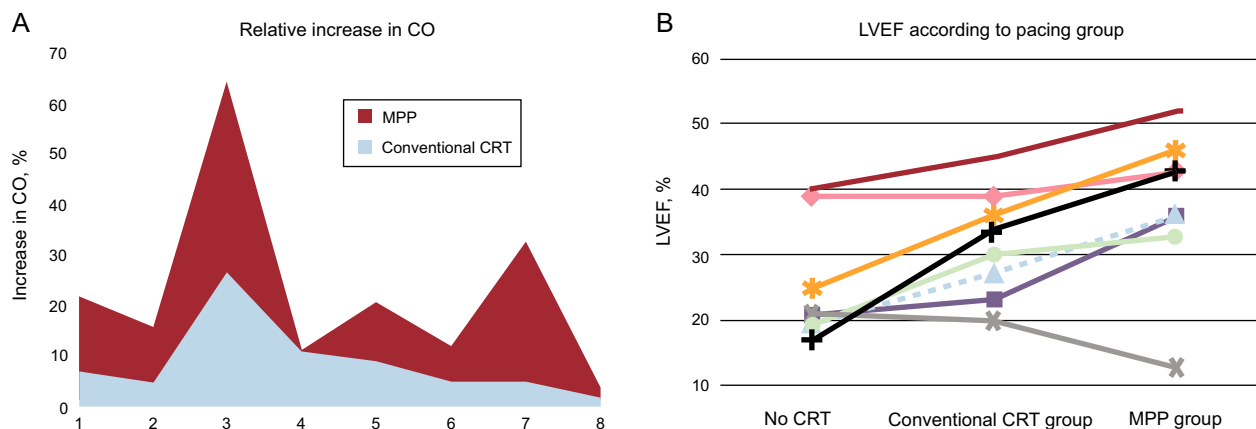


Figure. A: Increase in cardiac output by type of pacing. B: Change in LVEF according to pacing group. CO, cardiac output; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; MPP multipoint pacing.

($P = .2$) (Figure A). Lastly, we studied the influence of multipoint pacing on LV ejection fraction, comparing the conventional, baseline and MPP groups [25.1% (3.2), 31.8% (3.0), and 37.8% (4.2) respectively]. Compared with the baseline group, the mean increase in LV ejection fraction was greater in the MPP group than in the conventional group: 12.7% ($P = .055$) vs 6.7% ($P = .58$) (Figure B).

This prospective single-center study describes the first use of multipoint pacing in Spain. The hemodynamic data obtained from multipoint pacing are promising, because they show an improvement on the outcome of traditional resynchronization. Use of simultaneous stimulation from multiple points of the LV could lead to a reduction in the rate of non-responders and further improvement for those who do respond.

The main limitation of the study is the small sample size, and therefore further validation is required with larger-scale studies. Also, the study used acute hemodynamic data, so medium- and long-term follow-up is required to assess the clinical benefit of multipoint pacing.

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Nonsyndromic Familial Aortic Disease: an Underdiagnosed Entity



Enfermedad aórtica familiar no sindrómica: una entidad infradiagnosticada

To the Editor,

We report the case of a 55-year-old woman with no remarkable history who had a type B aortic dissection in August 2008. Computed tomography showed a large dissection opening after the exit of the left subclavian artery and extending to the iliac bifurcation. The descending thoracic aorta was dilated (60 mm) with partial thrombosis of the false lumen. The aortic valve was trileaflet and showed normal function, and the ascending aorta was of normal size. In the absence of acute complications, treatment with beta-blockers was chosen and endovascular treatment was deferred. Since the aortic arch had an acute angle, and the distance between the subclavian artery and the left carotid was short, there was insufficient neck for proximal stent implantation, and consequently a 2-pronged intervention was indicated: an aortobicarotid bypass followed by endovascular treatment. In February 2010, we proceeded with the aortobicarotid bypass, which was complicated by retrograde dissection of the ascending aorta from the clamp point and so the middle and distal ascending aorta were replaced with a Hemashield 28 vascular prosthesis. Follow-up showed progressive dilation of the descending thoracic aorta (Figure 1), despite which the patient refused all intervention.

In August 2011, the patient reported that the 38-year-old son of a second cousin had experienced a type B aortic dissection. This relative, who had no previous history, had been admitted to another hospital for aortic dissection originating after the exit of the left subclavian artery and progressing to the iliac bifurcation. At the time of the dissection, there was a slight dilation of the

descending thoracic aorta (39 mm), with a trileaflet and normally functioning aortic valve and without dilatation of the remaining aortic segments. The diagnostic approach then shifted to familial aortic disease; a thorough physical examination of both patients was performed, which showed no signs of Marfan or Loeys-Dietz syndrome, and a genetic analysis of the *ACTA2* gene (encoding isoform 2 of alpha actin in vascular smooth muscle cells) in the second patient was requested. The analysis showed a novel heterozygous mutation (c.253G>A) resulting in an amino acid change (p.Glu85Lys). The same mutation was also detected in the index case and in the father, paternal uncle and the daughter of the second case, and in the sister, paternal aunt, daughters, and niece of the index case (Figure 2). None of the *ACTA2* mutation carriers had *iris flocculi* or *livedo reticularis*, characteristics that have previously been described in the context of mutations in this gene.¹ Considering the familial aortic disease and aortic fragility observed during surgery, it was decided to avoid endovascular treatment and the patient underwent open surgery to replace the descending thoracic aorta with a tube graft with reimplantation of the visceral vessels.

Although most type B aortic dissections occur in middle-aged patients with hypertension and/or atherosclerosis, a considerable proportion of patients show early presentation with a likely, but not well-understood, genetic basis. In the absence of an identifiable syndrome, up to 21.5% of patients with aortic aneurysms have a family history; genetic mutations are identified in 20%,² the most common being the mutation in *ACTA2* (10–14%).³ This mutation is associated with aortic disease with 48% penetrance and variable expressivity, most often in the form of type A aortic dissections, even with nonsignificantly dilated aortic diameters, and isolated cases of type B⁴ dissections; it has also been associated with premature coronary artery and cerebrovascular disease.¹

Although family screening with imaging of the first-degree relatives of patients with premature aortic disease may be reasonable, indications for genetic analysis are not well established.