Cardiac-only Timothy Syndrome (COTS): Peripartum Cardiomyopathy and Long QT Syndrome

Síndrome de Timothy exclusivamente cardiaco (COTS): miocardiopatía periparto y QT largo

To the Editor,

Long QT syndrome (LQTS) is characterized by a prolonged QT interval and ventricular arrhythmias.[1] The condition has been linked to more than 17 genes (encoding potassium, sodium, and calcium channels), with 75% of those affected having a *KCNQ1* (LQTS1), *KCNH2* (LQTS2), or *SCN5A* (LQTS3) mutation. In at least 1% to 5% of cases, mutations are detected in other genes such as *CACNA1C,* associated with Timothy syndrome or LQTS8.[1,2]

We report a case of Timothy syndrome that first presented as peripartum cardiomyopathy (PPCM), without any other extracardiac manifestations, an entity recently named cardiac-only Timothy syndrome (COTS).[1]

A 32-year-old woman presented with dyspnea 1 week after delivery. The patient had had another pregnancy a number of years previously, without complications. Although hemodynamically stable, she had signs of systemic and pulmonary congestion. Electrocardiography revealed generalized T-wave inversion with a Bazett-corrected QT interval (QTc) of 561 ms (Figure 1A). She had not received any QT-prolonging drugs and had no electrolyte abnormalities. Transthoracic echocardiography indicated a normal-size left ventricle, without hypertrophy, with moderate ventricular dysfunction (left ventricular ejection fraction [LVEF], 36%) and general hypokinesia. The global longitudinal strain was –8.2% (Figure 2A and B, Video 1 of the supplementary data). In-hospital telemetry found no extrasystoles or arrhythmias. After treatment with diuretics, bisoprolol, and enalapril, she progressively improved and was discharged after 7 days. However, the generalized T-wave inversion in V_1 to V_4 on electrocardiography persisted, as well as a QTc of 532 ms (Figure 1B).

The clinical course was satisfactory; transthoracic echocardiography at 6 months revealed a normal LVEF (68%) and a global longitudinal strain of –23% (Figure 2C, Video 2 of the supplementary data). Cardiac magnetic resonance indicated normal biventricular function and size, without delayed enhancement. The T-wave inversion was no longer visible on electrocardiography, but the QTc prolongation persisted (Figure 1C).

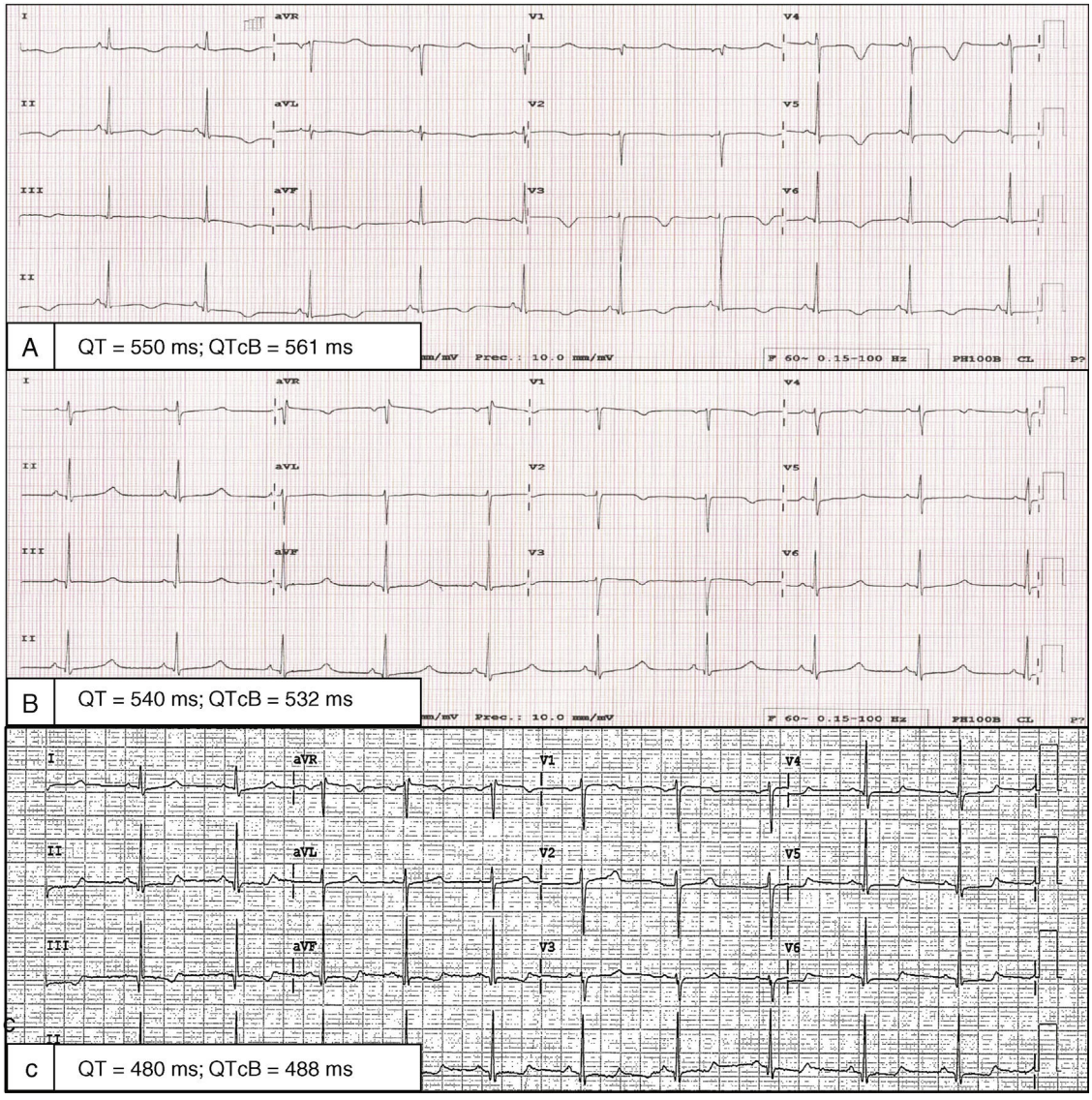

Figure 1. Electrocardiogram: at admission (A), at hospital discharge (B), and 6 months later (C). QTcB, QT interval corrected with Bazett formula.

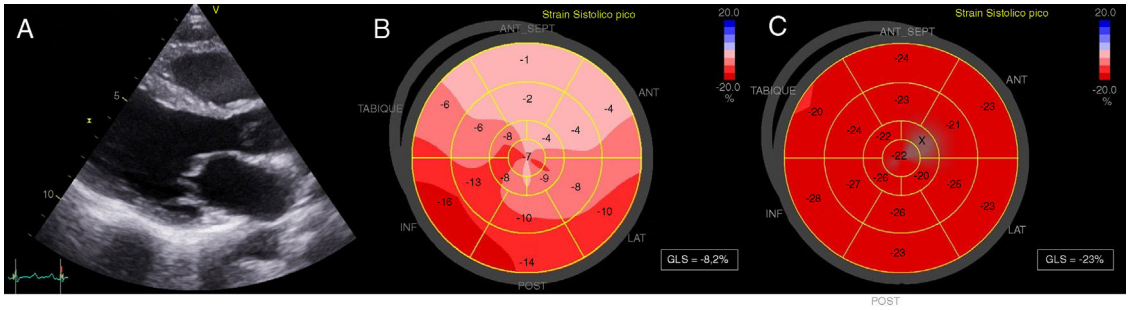

Figure 2. Echocardiogram: normal size of the left ventricle (A) and a greatly decreased global longitudinal strain (GLS) (B), which normalized after 6 months (C).

A genetic study was performed via massively parallel sequencing with a panel of 218 genes linked to channelopathies and cardiomyopathies. The p.Arg518Cys variant was detected in the *CACNA1C* gene (exon 12), which is classified as pathogenic according to current criteria.[1,3,4] It can be considered a *de novo* mutation because the patient has no family history of sudden cardiac death or cardiomyopathy and her parents and child have a normal QTc, without structural heart disease, and are not carriers of the variant.

She is currently asymptomatic and maintains a QTc < 500 ms by taking beta-blockers and avoiding QT-prolonging agents.

The *CACNA1C* gene encodes the alpha-1 subunit of the voltage-dependent L-type calcium channel; it consists of 4 interconnected homologous domains (DI–DIV), each containing 6 transmembrane segments (S1–S6). It is essential for cell excitability, myocyte contraction, regulation of gene expression, and the plateau phase of the action potential.[1] Pathogenic variants resulting in loss of channel function have been linked to J-wave syndromes, whereas gain of function variants have been associated with 4 different phenotypes[1,2]:

a) Timothy syndrome: characterized by LQTS, syndactyly, cardiac abnormalities, facial dysmorphisms, and autism spectrum disorders. It presents in childhood and is associated with a high risk of sudden cardiac death. All of the variants described are *de novo* in the different S6 transmembrane segments.[1,2]

b) Isolated LQTS: caused by variants localized to the cytoplasmic linkers and the extreme N and C termini.[2]

c) Syndactyly, psychomotor retardation, and pulmonary hypertension without LQTS: has recently been linked to the p.Arg1024Gly variant.[5]

d) COTS (cardiac-only Timothy syndrome): has been described in 3 families (12 cases) who have one of the following phenotypes from 20 years of age, without extracardiac manifestations: LQTS, hypertrophic cardiomyopathy (HCM), septal defects, and sudden cardiac death.[1] p.Arg518Cys and p.Arg518His variants have been identified in the DI–DII linker. There is cosegregation, with complete penetrance and variable expressivity, and none was *de novo*. An index case, a carrier of the same variant found in our patient, first showed PPCM and LQTS at 25 years of age, had a ventricular septal defect, and developed HCM 7 years later,[1] which our patient does not currently have. Recently, another family was described to have HCM, LQTS, and the same variant.[4] Functional studies (whole-cell patch clamp) revealed a combination of loss and gain of channel function, with lower global current density and an increased late current and window.[1] In addition, there are defects in channel traffic and lower channel concentration in the cell membrane.[1] Because this channel is essential for muscular excitation-contraction coupling,[1] we consider that it can cause hypertrophy or transient ventricular dysfunction due to poor calcium management.

PPCM is characterized by ventricular dysfunction before or after delivery. Although its cause is unknown, evidence suggests that dilated cardiomyopathy and PPCM patients show a similar prevalence of truncating variants, with truncations in the gene encoding titin the most frequent genetic predisposition in both entities, although other variants are involved as well.[6]

Our patient showed an association of PPCM and LQTS as the first manifestation of COTS. The presence of a LQTS together with PPCM or HCM should alert physicians to the possible presence of pathogenic variants of *CACNA1C*.

CONFLICTS OF INTEREST

I. Cárdenas-Reyes is an employee of Health in Code SL. L. Monserrat-Iglesias is a shareholder in Health in Code SL.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2019.01.017.

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Long-term Survival After Surgery Versus Transcatheter Technique to Treat Degenerated Aortic Bioprostheses

Supervivencia a largo plazo tras el tratamiento quirúrgico frente al percutáneo de prótesis aórticas degeneradas

To the Editor,

Currently, biological prostheses account for more than 80% of valves implanted by surgery. The possibility of transcatheter aortic valve implantation (TAVI) to replace a degenerated biological valve often tilts the balance towards the use of a bioprosthesis. This type of intervention is less invasive than open surgery. A meta-analysis found that hospital mortality rates were similar for TAVI and surgery.[1] However, there is a lack of long-term results. When a bioprosthesis degenerates, this lack is sometimes used as an indication for open surgery on a hostile mediastinum that has already undergone intervention.

The aim of the present study was to compare long-term survival after TAVI vs open surgery for the treatment of degenerated aortic bioprostheses.

The study was a retrospective cohort study using prospective data collection from a digital database. Between January 2012 and November 2018, we selected all patients undergoing TAVI or open surgery in our hospital for degenerated bioprosthetic aortic valves. We excluded patients undergoing other valvular or concomitant proximal aortic surgery.

The primary objective was to compare long-term survival after the application of the 2 techniques. The secondary objective was to determine the combined survival rates and hospital readmission rates for cardiovascular causes.

Continuous variables are expressed as medians [interquartile range]. Patients were matched on propensity scores (PS) to minimize the bias inherent to observational studies. This score was calculated using logistic regression in which the dependent variable was TAVI or surgery. In line with expert recommendations, we selected as independent variables those theoretically related to survival.[2] After we obtained the PS, open-surgery patients with a PS similar to that of the TAVI group were selected according to the nearest-neighbor method with replacement. The final balance between the 2 groups was verified using several statistical methods.

Once the pairs were created, Kaplan-Meier survival curves were compared using a stratified log-rank test.

The characteristics of the patients and the implanted prostheses are shown in Table 1. The analyzed cohort was at high surgical risk, with a EuroSCORE II of 7.1 [5.6-9.7] for TAVI and 8.6 [4.9-10.8] for surgery.

After 57 matched pairs were created, in-hospital mortality from surgery and TAVI were 2 (3.5%) and 4 (7%), respectively, with no significant difference ($P = 0.68$). Median follow-up was 33.9 [6.5-50.7] months and there were no losses. The Figure 1 shows the Kaplan-Meier survival curves. Survival in the surgery group vs the TAVI group at 1, 3, and 5 years was 77.2% (95% confidence interval [95%CI] 64.0%-86.1%), 77.2% (95%CI, 64.0%-86.1%), and 67.5% (95%CI, 51.45-79.3%) vs 94.6% (95%CI, 84.1%-98.2%), 79.9% (95%CI, 57.9%-91.3%), and 74.5% (95%CI, 50.9%-87.9%), respectively. As shown in the Figure 1, the log-rank test did not reach significance for survival ($P = .25$) or for the combined objective ($P = .67$).

The study included a total of 114 matched patients who underwent TAVI or surgery for degenerated bioprosthetic aortic valves. To the best of our knowledge, this series of high-risk patients is the largest comparative series with the longest follow-up time published to date.

The superposition of the confidence intervals shows that the survival curves in both groups are comparable. At 3 and 5 years of follow-up, survival rates approach 80% and 70%, respectively. These results are similar to those of Ejiofor et al.[3] who recently compared the 3-year survival of 22 matched pairs. The authors of that retrospective study suggested that hospital mortality was similar and that the survival rate was slightly more than 75% in both groups at 3 years.

Around 70% to 90% of patients with degenerated biological prostheses do not undergo reoperation and this degeneration increases the risk of death by 4.5.[4] This study shows that TAVI achieves at least the same 5-year survival rate as surgery and could reduce the percentage of patients with nonintervened degenerated bioprosthetic valves who die.

The main limitation of this study is the sample size, which made it difficult to achieve perfect matching and showed standardized mean differences of more than 10%. Other potentially relevant variables, such as the presence of coronary artery disease, the number of vessels, and the number of aortocoronary grafts, could not even be included in the creation of the PSs, despite the differences between the 2 groups. In addition, this study is an observational single-center retrospective study and was therefore subject to the possible biases and limitations inherent to this methodological design. However, given that it is the largest comparative series published to date, it can be considered to be a pilot study and a hypothesis generator.

Therefore, in the absence of multicenter studies with large sample sizes, the present series suggests that the 5-year survival rate could be the same in both groups.