use of ranolazine to treat an adult patient with TS type 2 and the p.(Gly402Ser) mutation was published by Shah et al.[5] in 2012. Here, we report a second case of the successful treatment of TS type 2 with ranolazine, with an 18-month follow-up period. We consider that ranolazine was effective because it suppressed all episodes of ventricular arrhythmia, even though we did not observe QTc shortening; this was also true for the case reported by Shah et al. The effects of therapeutic concentrations of ranolazine on cardiac ion currents include inhibition of I_{Kr}, late I_{Na} and late $I_{Ca,L}$ currents. Inhibition of I_{Kr} ranolazine prolongs the action potential duration (APD), whereas its inhibition of late I_{Na} and late $I_{Ca,L}$ shortens the APD. The net clinical impact of the inhibition of these ion channel currents is a modest increase in the mean QTc interval, as observed in the present case. The ability of ranolazine to produce multi-current inhibition (and particularly its ability to potently block the late I_{Na} current) probably underlies its ability to prolong QT without creating the substrate or trigger for the development of Torsade de Pointe. Indeed, this feature could contribute to the suppression of early after-depolarizations and a reduction in the spatial dispersion of repolarization (the substrate and trigger for Torsade de Pointe) and so might account for ranolazine's significant antiarrhythmic activity. The suppression of early after-depolarizations also results from the ranolazine-induced reduction in [Ca2+]i, which is known to modulate triggered activity.

Since there are no guidelines on the optimal dose for ranolazine in children, we monitored the blood concentration. This therapeutic drug monitoring prompted us to administer the drug once a day (rather than twice a day, as in adults), with clinical effectiveness.

The present case report is the first to describe the successful treatment of pediatric TS type 2 with ranolazine. Use of the drug has suppressed the need for appropriate shocks for the last 18 months.

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AUTHORS' CONTRIBUTIONS

Conceptualization, formal analysis, writing, review and editing, visualization: A. Hermida, and J. S. Hermida; methodology, validation: A. Hermida, G. Jedraszak, M. Kubala, and J. S. Hermida; investigation, data curation: A. Hermida, G. Jedraszak, M. Kubala, M. Bourgain, S. Bodeau, and J. S. Hermida; resources: A. Hermida, M. Kubala, S. Bodeau, and J. S. Hermida; writing, original draft: A. Hermida; supervision: J. S. Hermida.

CONFLICTS OF INTEREST

None declared.

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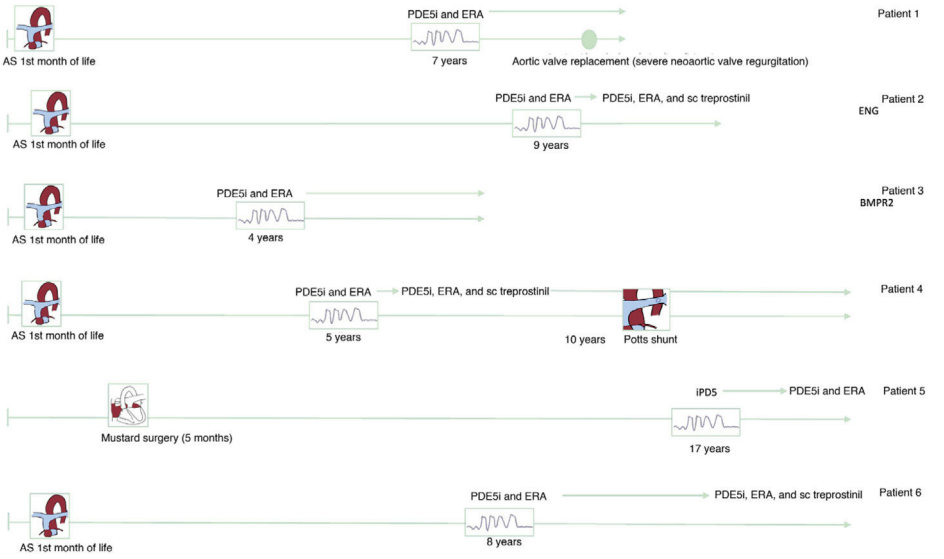
Prevalence of genetic variants in pediatric pulmonary arterial hypertension associated with corrected D-transposition of the great arteries. The REHIPED registry

Prevalencia de variantes genéticas en la hipertensión arterial pulmonar tras la reparación de D-transposición de grandes vasos. Registro REHIPED

To the Editor,

Pulmonary arterial hypertension (PAH) occurring after correction of D-transposition of the great arteries (D-TGA) is a condition still under investigation. The pioneering technique for treating D-TGA was atrial switch (Mustard or Senning procedure) performed in the first 5 to 8 months of life. The reported incidence of PAH after this type of repair was 7%, attributed to cyanosis, endothelial injury, hyperoxia of the pulmonary arterial tree, and persistence of pulmonary-systemic shunts up to the time of surgery. Later, this treatment was replaced by anatomical correction or arterial switch performed in the first days of life. However, PAH still develops in some patients after arterial switch. Hence, other mechanisms have been proposed to explain this event: abnormal development of the pulmonary vascular tree during fetal growth (early closure of the fetal foramen ovale or pulmonary hypoxia), pulmonary embolic events during Rashkind atrial septostomy, and even certain genetic factors.[1]

Our aim was to analyze the prevalence of PAH-related genetic variants in a cohort of patients with repaired D-TGA and PAH, recorded in the REHIPED registry (Spanish Registry of Pediatric Pulmonary Arterial Hypertension).[2] Patients were diagnosed by right cardiac catheterization, with the exception of clinically unstable cases. Genetic analysis was caried out using an NGS panel



Gene	cDNA position	Protein position	Effect	Zygosity	AF	Pathogenicity		
						dbSNFP	CADD	ACMG
BMPR2	NM_001204.6:c.2598G>C	NP_001195.2:p.(Glu866Asp)	Missense	Heterozygosis	.	19/8	22.8999	VUS
ENG	NM_000118.2:c.79A>G	NP_000109.1:p.(Thr27Ala)	Missense	Heterozygosis	< 0,0001	0/27	14.75	PB

Figure 1. *In silico* analysis of candidate genes. The hg19 genome was used as a reference. The prediction used aggregated databases in *dbSNFP*, *CADD*, and *ACMG*. Allelic frequency was estimated based on multiple pseudo-control populations: gnomAD genomes (v2.1.1), gnomAD exomes (v2.1.1), Kaviar (version 160204-Public), Beacon (v2.0), 1000G, Phase III, and Bravo. AF, allelic frequency; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase 5 inhibitors; PB, probably benign; AS, arterial switch; VUS, variant of uncertain significance.

of 21 genes: *ABCC8, ACVRL1, BMPR1B, BMPR2, CAV1, CBLN2, CPS1, EIF2AK4, ENG, GDF2, KCNA5, KCNK3, MMACHC, NOTCH3, SARS2, SMAD1, SMAD4, SMAD5, SMAD9, TBX4,* and *TOPBP1*.[3] Variants were classified according to recommendations of the American College of Medical Genetics. Written informed consent was obtained from parents or legal guardians in all cases. The REHIPED registry was approved by the Medical Research Ethics Committees of the participating centers.

Between 2011 and 2020, 9 children with repaired D-TGA and PAH were candidates to participate, and 6 agreed to undergo a genetic study (4 male and 2 female individuals) were included. Five patients had undergone arterial switch and 1 (patient 5) had received Mustard surgery. Three participants (patients 2, 3, and 5) had a complete interventricular septum. Patient 1 was diagnosed at 7 years of age (mean pulmonary arterial pressure [mPAP], 34 mmHg; pulmonary vascular resistance index [PVRi], 4.3 UW/m^2) and has remained in functional class (FC) II with dual oral therapy. Although this patient had severe aortic regurgitation requiring aortic valve replacement at the age of 10 years, pulmonary capillary pressure (PCP) was found to be < 15 mmHg in successive catheterizations performed before surgery and at 1 year after. Patient 2 was diagnosed at 9 years of age (PAPm, 65 mmHg; PCP, 14 mmHg; PVRi, 30 UW/m^2), and is stable at 14 years with triple therapy that includes subcutaneous treprostinil. Patient 3 was diagnosed at 4 years of age (highly probable on transthoracic echocardiography findings, and right heart catheterization impossible because of clinical instability). She was started on dual oral therapy and 3 years later remains in FC II; on follow-up, right catheterization has been excluded due to a persistent, general low-risk situation. Patient 4 was diagnosed at 5 years of age (PAPm, 63 mmHg; PCP, 9 mmHg; PVRi, 17.4 UW/m^2). Despite triple therapy that included treprostinil, the patient required a Potts shunt at age 11 years. She is now in FC II at 21 years of age. In patient 5 (Mustard surgery at 5 months), PAH was confirmed at the age of 17 years (PAPm, 62 mmHg; PCP, 7 mmHg; PVRi, 12 UW/m^2). The patient is now 30 years old and remains in FC II with dual oral treatment. Patient 6 was 6 years old at the diagnosis (PAPm, 85 mmHg; PCP, 10 mmHg; RVPi, 17 UW/m^2) and remains in FC II with triple therapy including subcutaneous treprostinil (figure 1).

Genetic study identified a probably benign variant in the *ENG* (endoglin) gene and a variant of uncertain significance in *BMPR2*. Although *in silico* analysis initially classified the *ENG* variant as having uncertain significance, presence of the varient in the patient's asymptomatic father led to its reclassification as probably benign. In patient 3, *in silico* analysis initially classified the variant as probably pathogenic, but it was reclassified as having uncertain significance after it was confirmed in the patient's father, who was also asymptomatic.

This is the first study investigating the possible influence of PAH-related genetic variants on the development of this condition following D-TGA correction. Although the variants found are not considered pathologically significant, their potential role cannot be excluded in the presence of D-TGA. Because of the small sample size and analysis limited to currently known PAH-related genes, the genetic hypothesis in the development of PAH cannot be ruled out. A recent genome-wide association study (GWAS) in a cohort of 133 patients with D-TGA found a relationship between certain genetic polymorphisms and an improvement in the prognosis following arterial switch.[4] New studies are needed to bring to light possible genetic factors involved in the development of PAH in D-TGA patients. It may be necessary to use techniques such as GWAS to search for new implicated genomic regions.[4]

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AUTHORS' CONTRIBUTIONS

All authors have contributed to the design, writing, and critical analysis of the article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest related to this article.

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An unusual case of *Brucella* endocarditis involving a prosthetic pulmonary valve

Un caso inusual de endocarditis por Brucella que afecta a una válvula pulmonar protésica

To the Editor,

Brucella is one of the most important zoonotic infections worldwide caused by the intracellular Gram-negative bacteria *Brucella*, which is transmitted to humans either through contaminated food or via direct contact with infected animals.[1] *Brucella* endocarditis (BE) is one of the most feared complication of brucellosis today since it can be life-threatening.

Brucella is endemic in animals and humans within the Middle East region, including Lebanon. Of note, the fifth largest world outbreak of *Brucella* occurred in Lebanon beginning in 2017 with a total of 1180 cases.[2] According to the World Health Organization Eastern Mediterranean Regional Office (EMRO), the annual incidence of brucellosis in Lebanon was between 3.5 and 9 cases per 100 000 inhabitants from 1997 to October 2009.[3] Due to its endemicity, it is common in clinical practice in Lebanon to include brucellosis in the differential diagnosis when working up a patient with fever of unknown origin.

There are only a few case reports in the literature about BE due to infrequent recognition of the disease. The organism appears to have a predilection for invading damaged endocardial tissue and tends to cause aortic and mitral valve endocarditis.[4] While some case reports describe BE involving the mitral and aortic valves, cases of BE involving the pulmonary valve are exceedingly rare in the literature. We herein present such a case.

A 41-year-old woman presented to the clinic for a 1-month history of intermittent fever reaching 39 °C and occasional cough. She also complained of fatigue and persistent nausea during the last month. Her past medical history was significant for Tetralogy of Fallot, for which she underwent 2 surgical corrections at 3 and 9 years of age. She also had pulmonary valve replacement and patch repair of her ventricular septal defect 10 years previously. She denied any exposure to pets or intravenous drug use. At her initial presentation, all her vital signs, including temperature, were within the reference range. Physical examination did not yield any significant findings except a systolic ejection murmur on the left sternal border. Initial blood tests revealed mild leukopenia with a white blood cell count (WBC) of 3300/cu.mm (reference range 4000-11 000/cu.mm) and mildly elevated transaminase enzymes (serum glutamic-oxaloacetic transaminase of 62 units/L and serum glutamic pyruvic transaminase of 57 units/L). The patient also had elevated lactate dehydrogenase of 288 units/L. C-reactive protein and erythrocyte sedimentation rate were elevated at values of 29.6 mg/L and 50 mm/h, respectively. *Brucella* serology was ordered and both direct and indirect titers were positive at 1:320. She was therefore treated with doxycycline and trimethoprim-sulfamethoxazole for 6 weeks and improved significantly. However, 2 months later, her symptoms recurred. Blood culture was positive for *Brucella* and antibody titers were unchanged. Transthoracic echocardiography showed severe right ventricular dilation and 2 masses consistent with vegetations on the pulmonary valve, the larger of the 2 measuring 12 mm in length. Transesophageal echocardiography showed moderate regurgitation of the pulmonary valve prosthesis with accompanying vegetations and no abscess, in addition to the presence of a hypermobile oscillating mass in the pulmonary artery with no evidence of abscess formation (figure 1). All the other valves were normal.

Medical treatment was initiated and the patient was started on streptomycin 1 g intramuscularly daily, doxycycline 100 mg orally