

DISCLOSURES

A. Colli, A Beiras-Fernandez, von Bardeleben S, received travel grants from NeoChord, Inc. A. Beiras-Fernandez is proctor for NeoChord, Inc. S. von Bardeleben received travel grants from NeoChord Inc, Edwards Lifesciences, Carillon Contour system and Cardiac Dimensions.

CONFLICTS OF INTEREST

A. Colli received travel grants from NeoChord, Inc. A. Beiras-Fernández was a proctor for NeoChord, Inc. S. von Bardeleben received travel grants from NeoChord, Inc, Edwards Lifesciences and Cardiac Dimensions.

The other authors have nothing to disclose.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.rec.2019.04.003>.

Andrea Colli,^{a,*,*} Andres Beiras-Fernández,^b Tobias Ruf,^c Christian-Friedrich Vahl,^b Thomas Munzel,^c and Ralph Stephan Von Bardeleben^{b,◇}

^aCardiac Surgery Unit, Department of Cardiac, Thoracic, and Vascular Sciences, University of Padua, Padua, Italy

^bDepartment of Heart Surgery, Heart Center Mainz, University Medicine Mainz, Germany

^cDepartment of Cardiology I, Heart Center Mainz, University Medicine Mainz, Germany

* Corresponding author:

E-mail address: colli.andrea.bcn@gmail.com (A. Colli).

◇These authors equally contributed to the manuscript.

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REFERENCES

- Colli A, Manzan E, Besola L, et al. One-Year Outcomes After Transapical Echocardiography-Guided Mitral Valve Repair. *Circulation*. 2018;138:843–845.
- Colli A, Besola L, Montagner, et al. Prognostic impact of leaflet-to-annulus index in patients treated with transapical off-pump echo-guided mitral valve repair with NeoChord implantation. *Int J Cardiol*. 2018;257:235–237.
- Yoshida S, Fukushima S, Miyagawa S, et al. Mitral Valve Structure in Addition to Myocardial Viability Determines the Outcome of Functional Mitral Regurgitation After Coronary Artery Bypass Grafting. *Circ J*. 2017;81:1620–1627.
- Uchimuro T, Tabata M, Saito K, et al. Post-repair coaptation length and durability of mitral valve repair for posterior mitral valve prolapse. *Gen Thorac Cardiovasc Surg*. 2014;62:221–227.
- von Bardeleben RS, Colli A, Schulz E, et al. First in human transcatheter COMBO mitral valve repair with direct ring annuloplasty and neo-chord leaflet implantation to treat degenerative mitral regurgitation: feasibility of the simultaneous toolbox concept guided by 3D echo and computed tomography fusion imaging. *Eur Heart J*. 2018;39:1314–1315.

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Use of MitraClip in the Percutaneous Treatment of Severe Mitral Regurgitation in Heart Transplant Recipients



Implante de MitraClip en el tratamiento percutáneo de la insuficiencia mitral grave en pacientes con trasplante cardíaco

To the Editor,

The onset of mitral regurgitation (MR) after heart transplant (HT) is uncommon, but not rare, and appears in around 6% of cases. The condition has been associated with graft vascular disease and heart failure, and it has also been linked to increased mortality¹ in these patients. Traditional therapeutic options have been medical treatment and surgery, with the latter often posing a very high risk due to comorbidities, functional status, and the need for a new sternotomy. The MitraClip implant (Abbott Vascular, Menlo Park, California, United States) is a percutaneous alternative for which some scientific evidence is available.^{2,3} This technique may be useful in transplant recipients in whom further surgery would represent a high risk, although there is a paucity of published reports.^{4–6}

We describe 2 patients with severe MR following HT who underwent MitraClip implantation. Surgery for MR had been ruled

out in these patients, and both had clear worsening of their functional class related to MR.

The first patient was a 64-year-old man with a Killip IV acute myocardial infarction in 1993 who required emergency HT using the Lower and Shumway biatrial suture technique, with very good clinical progress. In 2012 (19 years post-HT), echocardiography revealed severe MR, which subsequently remained stable with medical therapy until 2018 (25 years post-HT), when he required multiple hospitalizations due to decompensated heart failure and pleural effusion. Echocardiography showed severe (grade III-IV) MR in relation to mitral valve prolapse, predominantly of leaflets A2 and A3, with normal coaptation and cusp mobility, a regurgitant orifice of 0.89 cm², ejection fraction of 64%, and a nondilated left ventricle.

The second patient was a 57-year-old man who underwent HT in 2003 with the bicaval atrial suture technique due to dilated cardiomyopathy of ischemic etiology. The patient had several episodes of acute cell rejection in 2006, 2007, and 2008 that were resolved with corticosteroid treatment. He experienced progressive development of graft vascular disease, leading to a loss of ventricular function and requiring the implantation of multiple drug-eluting stents in the anterior descending, obtuse marginal, and right coronary arteries. He also had complete atrioventricular

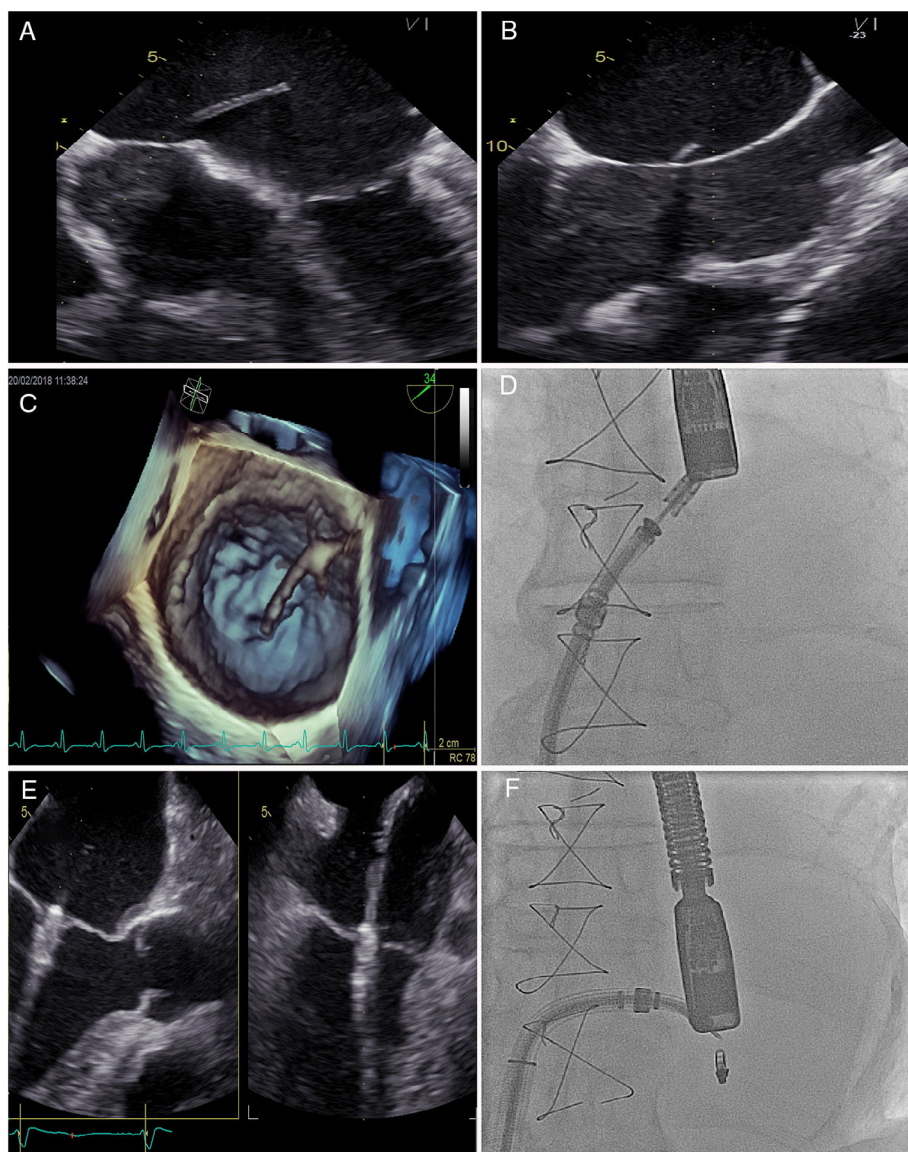


Figure 1. MitraClip implantation in a heart transplant recipient (biatrial suture technique). A and B: echocardiographic images of the transseptal puncture, in which the sheath was advanced while avoiding the more fibrous areas. C: 3 D echocardiography showing the advance of the transseptal puncture catheter to the left atrium. D: fluoroscopy image of clip introduction into the left atrium. E: echocardiography of clip placement in the mitral valve. F: final fluoroscopy image of the implanted clip.

block, leading to implantation of a dual-chamber pacemaker in June 2018. After these procedures, the patient continued to have symptoms of heart failure in New York Heart Association (NYHA) functional class III-IV, and echocardiography revealed severe (grade III-IV) functional MR with cusps showing no organic involvement, regurgitant volume of 69 mL, and slightly dilated left ventricle (end-diastolic diameter, 62 mm) with ejection fraction of 50%. Once the patients were confirmed to have suitable anatomy for percutaneous treatment with the MitraClip implant, the procedure was indicated.

In the first patient (Figure 1), transseptal puncture was undertaken with special care because it should be performed at the ideal height and because patients with biatrial anastomosis by the Lower and Shumway technique have an interatrial septal

suture containing fibrous tissue, making this puncture more difficult.

Both procedures were performed without complications, and both reduced MR from grade III-IV to grade I-II following MitraClip implantation (1 device in patient 1; 2 devices in patient 2) (Figure 2). Neither patient had significantly elevated gradient or antegrade velocity. Following good clinical progress and improvement to NYHA functional class II, the patients were discharged.

Follow-up at 6 months showed persistence of NYHA II, as well as grade II MR on echocardiography.

Although there are only a few case reports in the literature, patients with severe MR post-HT are good candidates for percutaneous treatment, in view of their high surgical risk and the excellent outcomes reported.

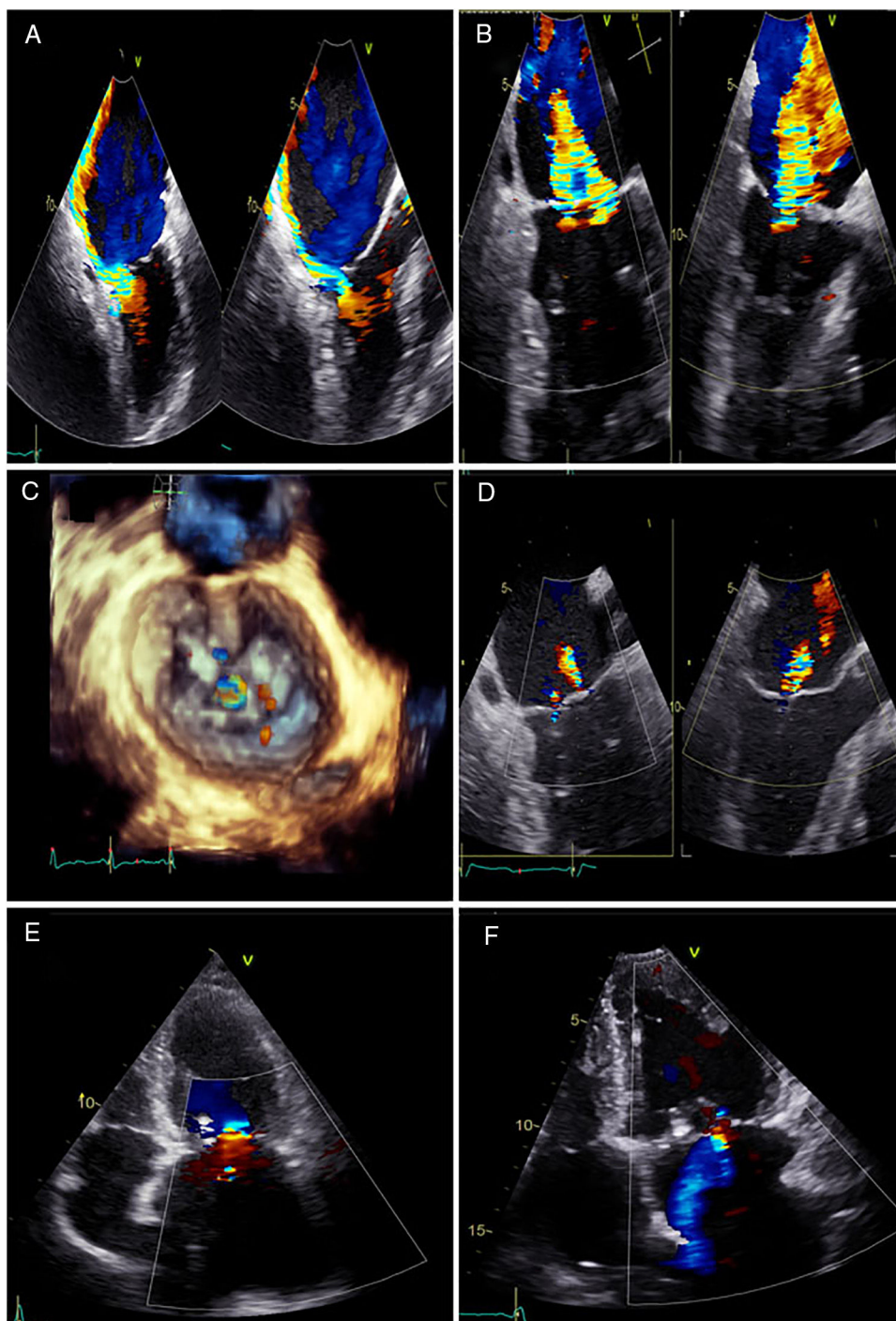


Figure 2. Final outcome following clip implant. A: image of severe preclip eccentric mitral regurgitation in the patient with heart transplantation by biatrial technique. B: image of severe preclip mitral regurgitation in the patient with heart transplant by bicaval technique. C: 3 D image of the final outcome of the 1-clip implant in the patient with heart transplant by biatrial technique. D: final outcome following implantation of 2 clips in the patient with heart transplant by bicaval suture. E: transthoracic echocardiography in the patient with heart transplant by biatrial technique 3 months after the procedure, showing mild mitral regurgitation. F: transthoracic echocardiography in the patient with heart transplant by bicaval technique 3 months after the procedure, showing 2 clips and mild-to-moderate mitral regurgitation.

Miguel Salas,^a Gerard Roura,^{a,*} Dabit Arzamendi,^b Javier Berdejo,^a Nicolás Manito,^a and Joan Antoni Gómez-Hospital^a

^aServicio de Cardiología, Hospital Universitario de Bellvitge, IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

^bServicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

* Corresponding author:

E-mail address: groura@bellvitgehospital.cat (G. Roura).

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REFERENCES

1. Roig E, Jacobo A, Sitges M, et al. Clinical implications of late mitral valve regurgitation appearance in the follow-up of heart transplantation. *Transplant Proc.* 2007;39:2379–2381.

- Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307–2318.
- Cid Álvarez AB, Rodríguez Leor O, Moreno R, Pérez de Prado A. Spanish Cardiac Catheterization and Coronary Intervention Registry. 27th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990–2017). *Rev Esp Cardiol.* 2018;71:1036–1046.
- Raza F, Grayburn P, Choi J. Use of a MitraClip for severe mitral regurgitation in a cardiac transplant patient. *Proc (Bayl Univ Med Cent).* 2017;30:226–227.
- Iorio A, Di Nora C, Abate E, et al. MitraClip after heart transplantation: A case report. *Int J Cardiol.* 2015;196:143–144.
- Ferraro P, Biondi-Zoccai G, Giordano A. Transcatheter mitral valve repair with MitraClip for significant mitral regurgitation long after heart transplantation. *Catheter Cardiovasc Interv.* 2016;88:144–149.

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Two Novel Cases of Autosomal Recessive Noonan Syndrome Associated With *LZTR1* Variants



Dos nuevos casos autosómicos recesivos del síndrome de Noonan asociados con variantes del gen *LZTR1*

To the Editor,

Noonan syndrome (NS, OMIM 163950) is a genetic multisystem condition with a relatively high estimated incidence of about 1 in 1000 to 1 in 2500 live births.¹

This syndrome constitutes the most common syndromic cause of congenital heart disease after Down syndrome.¹ The diagnosis of NS depends mainly on the identification of characteristic clinical features, such as a distinctive facial appearance, short stature, and congenital heart disease.¹ Cardiovascular abnormalities occur in 50% to 90% of individuals with NS, with pulmonary valve stenosis being the most common. Hypertrophic cardiomyopathy (HCM), found in 20% to 30% of individuals, usually develops early in life. Other cardiovascular abnormalities described in NS include atrial and ventricular septal defects, coarctation of the aorta, partial atrioventricular canal, and tetralogy of Fallot.¹

NS has been classically considered an autosomal dominant disorder; however, an autosomal recessive pattern of inheritance related to biallelic variants in the leucine-zipper-like transcriptional regulator 1 (*LZTR1*) has been very recently described.² Here we present 2 novel NS cases with autosomal recessive inheritance.

Case 1. A male patient was diagnosed at birth with severe HCM and mild pulmonary valve stenosis. He had the characteristic facies of NS, with broad forehead, hypertelorism, downward-slanting palpebral fissures, posteriorly rotated ears with a thickened helix, and broad thorax with webbed neck. Electrocardiogram (ECG) showed broad QRS complexes for his age (above 0.10 seconds at age 4 years), right bundle branch block, left axis deviation, and a striking negative pattern in the left precordial leads (Figure 1A). A genetic test for RASopathies by next-generation sequencing (NGS; 18 genes panel) was requested, which identified 2 novel variants in *LZTR1* (p.Arg362* and c.1149 + 1G >T).

Case 2. This male patient was diagnosed at birth with severe HCM without obstruction. The ECG was typical of NS, with broad

QRS complexes for his age, left axis deviation, and a negative pattern in the precordial leads (Figure 1B). He presented with severe feeding problems, needing a nasogastric tube and a gastrostomy. Genetic testing with the same RASopathies panel was performed and identified 2 novel variants in *LZTR1* (p.Val579-Met and c.2070-2A >G).

Genotyping of healthy nonconsanguineous parents confirmed genetic segregation in both clinical cases with biallelic variants.

Clinical and genetic analyses allowed classification of the 4 variants found in *LZTR1* in the 2 probands presented here as likely pathogenic (Table 1). One of the variant identified in case 1, c.1149 + 1G >T, has not been previously described in the literature, but the same splice site has been described as being affected in compound heterozygosity in a patient with an AR form of NS². The other mutation identified in case 1, c.1084C >T (p.Arg362*), introduces a stop signal that leads to an aberrant transcript and would therefore not be translated. As for case 2, c.2070-2A >G affects the canonical splice site in the intronic region of the gene. Finally, the other variant identified in case 2, p.Val579Met, is located in the BACK I domain, where other pathogenic missense mutations have been identified. Future functional studies are needed to definitely confirm their pathogenicity.

The 2 cases presented here are of special interest for clinical diagnosis and genetic counselling.

First of all, we report 2 novel clinical cases of an autosomal recessive form of NS. This pattern of inheritance was suggested 5 decades ago by Dieckman et al.,³ who described 2 brothers and a sister with clinical features of NS consisting of HCM and pterygium colli, with both parents being unaffected. However, it was not until very recently that clinical and genetic data confirmed the existence of a form of NS inherited following an autosomal recessive pattern, when Johnston et al.² described biallelic pathogenic variants in *LZTR1* in 23 children with clinical NS and with heterozygous, clinically-unaffected parents. *LZTR1* germline mutations associated with autosomal dominant NS with a highly variable expressivity had been previously described.⁴ These data suggest that *LZTR1* germline variants could be cause dominant or recessive NS.

Another aspect worth highlighting about the reported cases is that the 2 patients presented with ECG features that had been