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Percutaneous Edge-to-Edge Mitral Valve Repair with the Mitraclip System in Barlow's Disease

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Percutaneous mitral valve repair (PMVR) with the Mitraclip system (Abbott Vascular, Santa Clara, CA) has evolved from a novel technology to a safe therapy for inoperable or high-risk patients with severe symptomatic mitral regurgitation (MR). However, patients with Barlow's disease were not enrolled in the pivotal randomized trial of Mitraclip (1). Different surgical techniques can be considered for the treatment of Barlow's disease, including annuloplasty, resection, sliding plasty or edge-to-edge repair, but conventional surgery still remains particularly burdensome in this condition due to several anatomical challenges (e.g., dilated annulus, excess myxomatous tissue, diffuse chordal elongation and/or isolated or multiple chordal rupture) (2). As a result, patients with Barlow's MR are mostly denied PMVR too and systematic clinical outcomes of treated patients in this setting are at their early stage.

Between August 2008 and June 2017, a total of 417 consecutive patients with moderate-to-severe or severe MR deemed to be at high surgical risk underwent PMVR with the Mitraclip system at our Institution. They were all included in the GRASP registry, whose details have been previously published (3). Among them, 81 patients (20%) presented with primary MR and 7 patients (8.6%) were treated for Barlow's MR. The decision to proceed with PMVR was discussed by a dedicated Heart Team, including interventional cardiologist, cardiac surgeon, anesthesiologist, clinical and echo cardiologist. All patients were deemed ineligible or at high risk for surgery according to the evaluation of STS score. Nevertheless, the correct definition of high-risk patients for PMVR can be very demanding, because, to date, there is a lack of specific tools for risk stratification. Consequently, therapeutic decision-making process included the assessment of comorbidities not contemplated in the STS score (i.e. autoimmune disease, porcelain aorta, chronic immunotherapy). All the patients

underwent transthoracic and transesophageal echocardiography in order to evaluate the typical features of Barlow's disease (4) and to assess the final eligibility for the procedure.

In all cases, a bi-leaflet prolapse - associated with excessive tissue, annular dilatation and leaflet thickening - was the main mechanism of MR. Baseline, procedural and follow-up data of the study population are described in Table 1. All outcomes were defined according to the Mitral Valve Academic Research Consortium definitions (5).

Technical success was achieved in all cases. Three patients were treated with 1 clip and 4 patients received 2 clips. Post procedural mean pressure gradient (3.4±2.7 mmHg) was acceptable in all cases, a part from one patient in which moderate mitral stenosis was encountered. No procedural mortality was recorded and no post-procedural complications occurred. No major device or procedure related major adverse events were recorded at 30 days, with consequent high rate of device success. The median follow up period was 57 months (interquartile range 4 to 61 months). Complete follow-up data at 12 months were available only in 5 patients and patient success was achieved in 4 of them. At the longest follow-up available, all patients but two (patient #1 and #5) experienced improvements NYHA class, if compared to the baseline. As regards major adverse events during the follow-up, patient #6 died at 4 months due to myocardial infarction. Patient #5 was re-hospitalized for heart failure due to recurrence of moderate-to-severe MR at six months and died fourteen months after PMVR, during urgent mitral valve surgery. Patient #1 underwent a repeat Mitraclip intervention due to recurrence of symptomatic MR sixty months after PMVR. However, despite the implantation of other 2 clips (three clips in total), early recurrence of MR occurred due to leaflet perforation and the patient underwent urgent mitral valve replacement.

We also compared results of the Barlow population with the patients with primary no-Barlow's disease (n=74) in the GRASP registry. Barlow patients were younger than no-Barlow population (58.7±13.8

vs. 77.08±10.06, respectively for Barlow and no-Barlow; p<0.001). No statistically significant differences regarding the estimated STS score (1.7±1.1 vs. 4.9±4.8, p=0.085) were encountered. Notwithstanding the more complex mitral valve anatomy of Barlow MR, significant differences regarding the rate of technical success (100% vs. 95.6%, p=0.232), device time (69.71 ±34.77 vs. 65.71± 36.45, p=0.772) and procedural time (132.49± 50.29 vs. 120.43 ±27.19, p= 0.535) between Barlow and no-Barlow's disease were not observed. No significant differences were detected in terms of length of hospital stay (4.7±4.5 vs. 3.7± 1.9 days, p=0.569). Patient success at 12 months was also comparable between the two-paired groups (p= 0.524).

The principal findings of this study could be summarized as follows:

a) PMVR in Barlow's disease in patients deemed ineligible for surgery by a dedicated Heart Team is feasible and effectively performed by expert operators in centers at high volume of MitraClip implantation

b) PMVR in Barlow's disease presents acceptable peri-procedural and 30-day results

c) Mid-term follow-up (i.e. one-year) is encouraging, although larger series and long-term follow-up are mandatory.

Patients with Barlow's disease have multi-segment prolapse, involving one or both leaflets, in a valve with excess tissue segments. In most of the cases, we tended to implant more than one clip in order to obtain a sufficient and stable grasping of the valve leaflets, without increasing the mean transvalvular pressure gradient **(Figure 1)**. Among patients who received just one clip, only one patient (#2) had a good midterm outcome, whereas the other two patients (#1 and #5) underwent repeat percutaneous or surgical mitral interventions for recurrent MR. In addition, we do recommend not undergoing PMVR in Barlow's patients with high baseline mitral valve gradient, because this event would prevent the implant of more than one clip, increasing the risk of MR recurrence at follow up.

The present analysis has two main limitations: firstly, the comparison between Barlow and primary non-Barlow's disease was not included in our preliminary protocol. Secondly, a small sample size with limited follow-up was included, thus our results should be reproduced in a larger cohort with longer follow-up. Moreover, the procedures hereby described were performed in a high-volume center for MitraClip, therefore our results should not be generalized.

In conclusion, MR due to Barlow's disease is a challenge for both cardiac surgeons and interventional cardiologists (6). Surgical mitral valve repair remains the gold standard for these patients, with good mid- and long-term results. However, in our initial experience, the Mitraclip system resulted to be an effective therapeutic option in selected patients with Barlow's disease considered inoperable by the Heart Team. The development of new technologies as Mitraclip XTR (7) and the PASCAL systems (8), because of their higher dimensions with improved grippers and span, may facilitate edge-to-edge PMVR in this extremely complex anatomical and clinical scenario.

Disclosure statement

Dr. Carmelo Grasso is a proctor physician for Abbott vascular. Davide Capodanno received consulting honoraria from Abbott Vascular. Corrado Tamburino received speaker's honoraria from Abbott Vascular. All other authors have no conflicts of interest to declare.

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Table1. Patients Baseline Characteristics, Peri-procedural Outcome and Follow-up Data

Variable	Patient#1	Patient#2	Patient#3	Patient#4	Patient#5	Patient#6	Patient#7
Age (yrs)	54	51	75	79	45	62	45
Sex	Male	Female	Male	Female	Female	Male	Male
STS -PROM, (%)	1	1.2	2.5	3.7	2.3	1.3	0.3
Comorbidities	Autoimmune Disease, previous TIA, CKD	Autoimmune Disease	Porcelain Aorta, CKD, PH	Recent major Stroke, CKD, LL	Autoimmune Disease, CKD, PH	Marfan and Raynaud Syndrome	Ongoing Solid Tumor
NYHA class (baseline)	3	3	3	4	4	3	3
Pre-procedural							
Rhythm	SR	SR	AF	AF	SR	SR	SR
MR	4	3	3	4	3	4	4
Mean Gradient (mmHg)	3	1.9	3	2	8	1	3
Mitral Valve area (cm^2)	3.8	4.7	3.8	4.1	3.1	5	3.9
LVEF (%)	58	60	56	55	64	30	57
sPAP (mmHg)	45	40	60	35	70	50	30
Primary Lesion							
Bi-leaflet Prolapse	Yes (A2-P2-P3)	Yes (A2-P2-P3)	Yes (A1-A2-P2)	Yes (A2-P2-P3)	Yes (A2-P2-P3)	Yes (A2-P2-P3)	Yes (A1-A2-P2)
Excess Leaflet Tissue	Yes	Yes	Yes	Yes	No	No	Yes
Leaflet Thickening	No	No	No	No	Yes	Yes	No
Chordal Elongation	No	No	No	No	Yes	No	No
Chordal Rupture							

Secondary Lesion	No	No	Yes	No	No	No	Yes
Annular Dilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calcification	No	No	No	No	Yes	No	No
Procedure							
Technical Success	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Device Time (min)	50	35	135	90	55	65	30
Number of clip(s)	1	1	2	2	1	2	2
Type of Mitraclip	G1	G1	G1	G1	G1	G1	G1
Post-Procedure							
MR	2	1	2	<1	<1	<1	<1
Mean Gradient (mmHg)	3	2	2	2	10	3	2
Mitral Valve area (cm^2)	3.8	3.3	2.4	1.6	1.5	2	2.1
LVEF (%)	55	60	56	55	64	35	55
sPAP (mmHg)	48	40	48	33	68	35	27
30-Day Follow-up							
Procedural Success	Yes	Yes	Yes	Yes	No	Yes	Yes
Device Success	Yes Acceptable	Yes Acceptable	Yes Acceptable	Yes Optimal	No*	Yes Optimal	Yes Optimal
Twelve-month Follow-up							
Patient success	Yes	Yes	Yes	Yes	No	No	N/A
MR	2	2	2	<1	3	N/A	N/A
Mean Gradient (mmHg)	2.7	1.3	2.5	2.4	11	N/A	N/A
Mitral Valve Area (cm^2)	3.5	3.3	3	2.2	1.6	N/A	N/A
LVEF (%)	60	55	60	58	50	N/A	N/A
NYHA	2	1	2	1	4	N/A	N/A
Last Follow-up							
Follow-up (months)	60	52	63	61	14	4	2
MR	3	2	2	1	N/A	1	1
Mean Gradient (mmHg)	2.4	1.4	2.5	2.4	N/A	4	2.8
Mitral Valve Area (cm^2)	3.9	3.1	3.4	2.7	N/A	2.1	2.2
LVEF (%)	60	55	60	58	N/A	35	57
NYHA	3	1	2	1	N/A	1	1
Percutaneous/Surgical Redo	Yes	No	No	No	Yes	No	No

Abbreviations: STS-PROM, Society of Thoracic Surgeons-Predicted Risk of Mortality; TIA, Transient Ischemic Attack; CKD, Chronic Kidney Disease; PH, Pulmonary Hypertension; LL, Lymphocytic Leukemia; NYHA, New York Heart Association; SR, Sinus Rhythm; AF, Atrial Fibrillation; G1, First Generation; MR, Mitral Regurgitation; LVEF, Left Ventricle Ejection Fraction; sPAP, Systolic Pulmonary Artery Pressure.

* Baseline mean gradient was 8 mmHg but a real mitral stenosis was excluded by the assessment of mitral valve area with 3D echocardiography.

Figure legend

Figure 1. Intra-procedural transesophageal echocardiography (Patient#7)

A) Baseline echocardiography showing prolapse of both leaflets **B-C)** Severe mitral regurgitation with two jets along the coaptation zone **D)** After placing the first clip, residual moderate-to-severe MR was still encountered **E)** A second clip was then positioned laterally in order to reduce MR and stabilize the first clip **F)** Optimal final result after 2 clips implanted