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Percutaneous mitral valve repair: The last chance for symptoms improvement in advanced refractory chronic heart failure?

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ABSTRACT

Background: The role of percutaneous mitral valve repair (PMVR) in patients with end-stage heart failure (HF) and functional mitral regurgitation (FMR) is unclear.
Methods: Seventy-five consecutive patients with FMR grade ≥ 3+ and severe HF symptoms despite optimal medical therapy and resynchronization therapy underwent PMVR with the MitraClip system (Abbott, Abbott Park, IL, USA) at 3 centers. Clinical evaluation, echocardiography and pro-BNP measurement were performed at baseline and at 6-month.
Results: Mean age was 67 ± 11 years, logistic EuroSCORE = 23 ± 18%, left ventricle ejection fraction (LVEF) 30 ± 9%. In 6 patients (8%) PMVR was performed as a bridge to heart transplant; many patients were dependent from iv diuretics and/or inotropes. Rate of serious adverse in-hospital events was 1.3% (1 patient who died after conversion to cardiac surgery). Sixty-three patients (84%) were discharged with MR ≤ 2+. At 6-month, 4 patients died (5%), 80% had MR ≤ 2+ and 75% were in New York Heart Association class ≤II. Median pro-BNP decreased from 4395 pg/ml to 2594 pg/ml ($p = 0.04$). There were no significant changes in LV end-diastolic volume (222 ± 75 ml vs. 217 ± 79, $p = 0.19$), end-systolic volume (LVESV, 154 ± 66 ml vs. 156 ± 69, $p = 0.54$) and LVEF (30 ± 9% vs. 30 ± 12%, $p = 0.86$). Significant reverse remodeling (reduction of LVESV ≥ 10%) was observed in 25%, without apparent association with baseline characteristics. The number of hospitalizations for HF in comparison with the 6 months before PMVR were reduced from 1.1 ± 0.8 to 0.3 ± 0.6 ($p < 0.001$).
Conclusions: In extreme risk HF patients with FMR, PMVR improved symptoms and reduced re-hospitalization and pro-BNP levels at 6 months, despite the lack of LV reverse remodeling.

1. Introduction

Significant functional mitral regurgitation (FMR) is common in heart failure (HF) patients with increased left ventricular (LV) volumes and depressed LV ejection fraction (EF) and has been associated with a ominous prognosis [1,2]. Additionally, perioperative mortality after surgery for FMR is not negligible, and a large number of patients with FMR are judged inoperable or at high surgical risk because of severe LV dysfunction and/or comorbidities [3,4].

Percutaneous mitral valve repair (PMVR) with the MitraClip™ device (Abbott, Abbott Park, IL, USA) has recently evolved as a therapeutic alternative for patients with significant MR, of both degenerative and functional origin, whose surgical risk is considered very high or prohibitive [5–7]. Although less effective than surgery in reducing mitral regurgitation, PMVR has been demonstrated to be safe and capable of leading to significant improvement in clinical outcomes. Additionally, reverse cardiac remodeling at mid-term follow-up has been reported after successful PMVR in patients with left ventricular dysfunction [8–10]. However, few data are currently available on ventricular and neurohormonal changes in patients with FMR due to severe LV

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dysfunction and refractory, advanced heart failure, otherwise destined to heart transplant or death [11].

The aim of this multicenter study was to assess and compare the effects of PMVR therapy on clinical outcomes, LV remodeling and neurohormonal changes in inoperable end-stage patients with chronically symptomatic FMR despite optimal medical/electrical therapy and severe LV dysfunction.

2. Methods

2.1. Patient selection

Patients were enrolled at 3 third-level Italian centers: University Hospital St. Orsola-Malpighi of Bologna, University Hospital of Trieste, University Hospital of Pavia. Clinical and echocardiographic data of consecutive patients with advanced HF and moderate to severe FMR who underwent PMVR therapy at participating centers for significant symptoms not responding to optimal medical therapy and cardiac resynchronization therapy (CRT). All patients had been judged inoperable by the local heart team on the basis of extreme cardiac remodeling and/or the presence of several comorbidities. Candidates for PMVR were selected and proposed by the respective advanced heart failure departments, and all followed within a comprehensive program which included CRT, left ventricular assist device and heart transplant. When applicable, CRT had to be performed first, and PMVR was considered only after ≥6 months of CRT with persisting New York Heart Association (NYHA) functional class III or IV despite pharmacological optimization [8].

All potential candidates underwent transthoracic (TTE) and transesophageal Doppler echocardiography (TEE). Anatomic feasibility for PMVR was largely based on the Endovascular Valve Edge-to-Edge REpair Study (EVEREST) criteria for FMR. Surgical risk was estimated using the Society of Thoracic Surgeons (STS) score and the logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), although additional clinical and instrumental parameters were taken into account. The decision whether to proceed with MitraClip procedure was always taken by a multidisciplinary team composed by clinical cardiologist, interventional cardiologist, expert echocardiographer, cardiac surgeon and cardiac anesthesiologist. In particular, patients with criteria beyond the EVEREST recommendations were the object of an in depth collegial discussion [12].

2.2. Echocardiographic examination

The severity of FMR at baseline was graded according to the American Society of Echocardiography guidelines [13] as: mild 1+, moderate 2+, moderate-to-severe 3+ and severe 4+. In addition, the vena contracta width at the narrowest portion of the regurgitant jet was measured [10].

Measurement of LV volumes and EF were performed according to the biplane Simpson's method [14]. The mitral valve orifice area, when feasible, was assessed using the pressure half-time method [15]. Systolic pulmonary artery pressure was measured using the gradient derived from the maximal velocity of tricuspid regurgitation, adding 5 mm Hg if the inferior vena cava had a normal diameter (<21 mm), 10 mm Hg if the vena cava was dilated with reduced respiratory excursions, 15 mm Hg when the vena cava was dilated without respiratory excursions. Right ventricular dimensions and contractile function were also evaluated according to standardized criteria [16].

2.3. Device and procedure

The MitraClip system has been previously described in details [5,12]. Briefly, it is a catheter-based system designed to perform a double orifice repair of the mitral valve. The system includes a clip, a steerable guide catheter, and a clip delivery system that enables positioning and placement of the clip on the mitral valve leaflets, resulting in permanent leaflet approximation. The procedure was performed under general anesthesia under TEE and fluoroscopic guidance. Live real-time 3-D echocardiography was used to improve the conduct of the implantation. When necessary, more than a clip was implanted. Procedural success was defined as the implantation of at least 1 clip and reduction of severity of mitral regurgitation of at least 1 grade.

2.4. Study objectives and follow-up

The aim of this study was to assess the effect of PMVR on cardiac remodeling, clinical status and neurohormonal profile (pro-BNP plasma levels measurement) at 6 months after procedure in patients with severe FMR and severe LV dysfunction for whom risk of surgical repair/replacement of the mitral valve was prohibitive.

Clinical evaluation was performed before MitraClip treatment, after 30 days, 3 months and 6 months, or more frequently if clinically-indicated. We assessed the incidence of death, myocardial infarction, stroke, conversion to conventional surgical mitral valve replacement and re-admission for heart failure. In-hospital outcomes included also bleeding, need for inotropic drugs and acute kidney injury. Bleeding was classified as life-threatening (fatal bleeding, bleeding in a critical organ, bleeding with severe hemodynamic consequences, drop in hemoglobin ≥5 g/dL or need for red blood cells transfusion ≥4 units), major bleeding (overt bleeding with drop in hemoglobin ≥3 g/dl or requiring transfusion or causing hospitalization or permanent injury, or requiring surgery), and minor bleeding (all other bleedings). Acute kidney injury was defined as increase in serum creatinine ≥0.3 mg/dl compared with baseline. Trans-thoracic echocardiography was performed at baseline, after PMVR and planned every 6 months thereafter. Main parameters of interest were LVEF, LV end-diastolic volume (EDV), LV end systolic volume (ESV) and gradation of FMR. A subgroup of patients, i.e. those enrolled in the hospital of Bologna, received pro-brain-natriuretic-peptide (NTproBNP) plasma level measurements before the procedure and at 6 months.

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages and compared with the Chi squared test. Paired Student *t*-tests were utilized to assess the differences in the means of continuous variables before and after procedures. Comparison test between proportions were utilized to assess the differences in the categorical variables before and after procedure. The Wilcoxon matched pairs signed-ranks test was utilized for comparison of pro-BNP value before and after procedure. A P value < 0.05 was considered statistically significant. Univariate logistic regression analyses were performed to evaluate the effect of single vs. multiple clip procedure on residual MR and LV remodeling at six-month follow up, and results given as Odds Ratio (OR) and 95% Confidence Interval (95% CI). Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

3. Results

3.1. Baseline characteristics of patient population

Between June 2013 and April 2015, 75 consecutive patients with advanced HF and severe FMR (59% ischaemic etiology; 41% idiopathic dilated cardiomyopathy) underwent PMVR at the 3 participating centers and were enrolled in the study. Baseline patients' characteristics are listed in Table 1. The study population included 77% men with a mean age of 67 ± 11 years. All patients were in NYHA functional class III/IV before the procedure. In six cases, PMVR had been performed as a bridge to