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Transcatheter mitral valve repair may increase eligibility for heart transplant listing in patients with end-stage heart failure and severe secondary mitral regurgitation

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ABSTRACT

Background: Heart transplantation remains the gold standard for treatment of patients with end-stage heart failure and severely reduced ejection fraction (HFrEF). An increased pulmonary vascular resistance (PVR), which is often prevalent in HFrEF patients with secondary mitral regurgitation (SMR), limits the eligibility for transplantation. Therefore, we evaluated whether transcatheter mitral valve repair (TMVr) improves pulmonary circulatory hemodynamics and increases the eligibility for transplantation in end-stage HFrEF patients with severe SMR.
Methods: We retrospectively analysed the hemodynamics by right heart catheterization (RHC) as well as laboratory and clinical outcomes of end-stage HFrEF patients with SMR that underwent TMVr.
Results: Seventeen patients (age: 55 ± 10 yrs) underwent TMVr and repeat RHC at a mean follow-up of 5.7 ± 7.9 months. TMVr decreased PVR (3.5 ± 2.2 to 2.3 ± 1.2 wood units, $p = 0.02$) and systolic pulmonary artery pressure (55.4 ± 15 mmHg to 45.6 ± 9.8 mmHg, $p = 0.02$) from baseline to follow-up, respectively, while cardiac output was increased (3.7 ± 0.9 l/min to 4.6 ± 1.3 l/min, $p = 0.02$). In addition, transpulmonary gradient decreased significantly (12.0 ± 7.5 mmHg to 9.7 ± 5.3 mmHg, $p = 0.04$). The prevalence of New York Heart Association functional class ≥III at follow-up was reduced from 88% (15/17 patients) to 47% (8/17 patients, $p = 0.01$). All five patients with initially too high PVR (>3.5 WU) showed a significant decrease in PVR and three of them became potential candidates for heart transplantation after TMVr.
Conclusion: TMVr is associated with reduction in PVR which may increase eligibility for transplantation in some HFrEF patients with severe SMR.

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) is a major public health challenge (1,2) with a prevalence of over 5.8 million patients in the USA and over 26 million worldwide (3,4). Already in 1997, HFrEF was singled out as an emerging epidemic (5) and in 2017 it was a contributing cause of 1 out of 8 deaths in the US (6). In this context patients with end-stage HFrEF have an estimated 1-year survival of approximately 50% (7). Despite up-titrated medical treatment, the therapeutic options are highly limited (8). Although assist-device implantation is a therapeutic option for some patients, heart transplantation remains the gold standard for the treatment of HFrEF patients (9). The evaluation of eligibility for heart transplantation includes a careful workup of a series of parameters that must be met in order to select patients with promising outcomes after transplantation.

Left ventricular dilatation and consecutive mitral annulus dilatation cause restriction of valve leaflets leading to secondary MR (SMR) in HFrEF patients (10–13). Thus, end-stage HFrEF is often accompanied by moderate to severe SMR in nearly 30% of patients, which contributes to worse prognosis (14–16). These pathologic changes favour the development of pulmonary hypertension and an increased PVR which in turn might preclude listing for heart transplantation (17–19). Therefore, the purpose of this study was to investigate whether transcatheter edge-to-

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edge mitral valve repair (TMVr) improves right heart hemodynamics, which may increase the eligibility for heart transplantation in selected HFrEF patients with severe SMR.

2. Methods

2.1. Study design

Patients with severe SMR and end-stage heart failure that underwent TMVr between 2011 and 2019 at our centre have been retrospectively screened for pre procedural right heart catheterization (RHC). Data collected in clinical routine were retrieved from the EVERY-VALVE-registry, which was approved by the local ethics committee. Heart failure medication was optimized in each patient prior to the evaluation of further therapies. If indicated cardiac resynchronization therapy was provided. Despite optimized medical therapy, 31 patients suffered from end-stage heart failure with an ejection fraction (HFrEF) of ≤30% and severe SMR. These patients were all evaluated by the local heart transplant committee for potential heart transplantation or assist device implantation. All 31 patients underwent TMVR and finally, 17 out of these patients with end-stage HFrEF underwent another invasive hemodynamic assessment after TMVR. These 17 patients were retrospectively analysed and clinical outcomes were assessed.

The primary outcome measure was defined as reduction of pulmonary vascular resistance (PVR) after TMVr at the time of the last available follow-up. Secondary outcome measures were defined as changes in cardiac output (CO), cardiac index (CI), mean and systolic pulmonary artery pressure (mPAP, sPAP), pulmonary capillary wedge pressure (PCWP), central venous oxygen saturation as well as grade of SMR. In addition, clinical improvement according to New York Heart Association (NYHA)-classification as well as laboratory parameters including NT-proBNP, glomerular filtration rate (GFR), Bilirubin, Gamma-glutamyl transferase (GGT), Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels were analysed. Long-term clinical improvement defined as persistent NYHA functional class ≤II was assessed by telephone calls. Finally, long-term survival as well as the destination therapy were assessed.

2.2. Procedural techniques and echocardiography

The TMVr procedure was performed under general anesthesia with two- and three-dimensional transesophageal echocardiography as well as fluoroscopic guidance as previously described (20). Sixteen patients were treated using the MitraClip system (Abbott Vascular, USA) and one patient was treated using the PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, CA, USA).

RHC was performed as a separate invasive procedure without sedation prior to TMVr. Cardiac output was determined using the method of Fick or the thermodilution-method and standard hemodynamic parameters were documented accordingly. Severity of mitral regurgitation was quantified using transthoracic echocardiography and graded from 1+ to 4+ according to current guidelines (21).

2.3. Statistical analysis

For the purpose of descriptive statistics all numerical continuous data are presented as means or medians with standard deviation (SD) and interquartile ranges (IQR) depending on the dispersion of the data. Categorical data are presented in the form of proportions, frequencies or percentages. Concerning all primary and secondary outcome measures, invasive and clinical measurements were compared between time of pre-procedural and post-procedural RHC. Normality of data distribution was assessed graphically and using the Shapiro-Wilk test. For comparison of continuous outcomes within one subject, *t*-test or Wilcoxon rank-sum test was performed according to the data distribution. *P*-values are reported with two decimal points; all our tests yield 2-sided *p*-values with a level of significance $\alpha < 0.05$ to determine statistical significance. Missing data are treated as missing completely at random. The statistical software applied for data analysis and visualization was R (Version 1.2.5019, The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We analysed a total of 17 HFrEF patients with a median age of 55 ± 10.3 years that underwent TMVr for SMR. Forty-seven percent of patients suffered from ischemic cardiomyopathy. The etiology of MR in this study cohort was predominantly secondary (94.1%) due to left ventricular dilatation (mean LVEDV = 230 ml ± 99.2) and consecutive leaflet teathering. Mean LVEF was 22% ± 6.6. RV-function was reduced as expressed by a mean TAPSE of 15.3 mm ± 3.3. Patients received maximally tolerated doses of guideline-directed medical therapy. All baseline characteristics are summarized in Table 1. Initial RHC was performed 29 (7–49) days before TMVR. Procedural success (post procedural MR ≤ 2+) was achieved in 100% of patients. Twelve out of 17 patients (70.6%) showed post procedural MR ≤ 1+. Reduction of MR remained stable at follow-up (MR ≤ 2+ in 88.2% of patients). MR quantitative parameters are shown in Table S1.

Mean follow-up including RHC was available 5.7 ± 7.9 months following TMVr. Overall heart failure medication remained stable over time (Table S2). TMVr was associated with a significant decrease in PVR from 3.5 ± 2.2 wood units (WU) at baseline to 2.3 ± 1.2 WU at follow-up ($p = 0.02$, Table 2, Fig. 1A). CO and CI increased after TMVr (CO: 3.7 l/min at baseline vs. 4.6 l/min at follow-up; CI: 1.8 l/min/m^2 at baseline vs. 2.2 l/min/m^2 at follow-up; $p = 0.02$ and $p = 0.08$, respectively, Fig. 1B), while sPAP decreased (55.4 ± 15.6 mmHg at baseline vs.

Table 1
Clinical characteristics.

Characteristic	Overall
n	17
Age, years	55.4 (±10.3)
Gender (male)	14 (82.4)
Height, cm	174.5 (±10.1)
Weight, kg	77.6 (±17.4)
BMI, kg/m^2	25.3 (±3.8)
HTN (%)	7 (41.2)
Diabetes (%)	3 (17.6)
Smoking (%)	7 (41.2)
COPD (%)	17 (100.0)
Dyslipidemia (%)	6 (35.3)
IHD (%)	8 (47.1)
No. of vessels (%)	
0	9 (52.9)
1	5 (29.4)
3	3 (17.6)
Hist. of PCI (%)	8 (47.1)
CABG (%)	2 (11.8)
LVEF (%)	22.1 (6.6)
TAPSE, mm	15.3 (±3.2)
LVEDV, ml	230.0 (±99.2)
LVEDD, mm	7.0 (±1.2)
EROA, qcm	0.29 (±0.14)
ICD/CRT (%)	13 (76.5)
AFIB (%)	11 (64.7)
Concomitant treatment of TR (%)	1 (5.9)
History of stroke (%)	3 (17.6)
NYHA level (%)	
III–IV	15 (88.2)
ACE-Inhibitors/AT1-Antagonists (%)	13 (76.5)
Neprilysin-Inhibitor (%)	3 (17.6)
Betablockers (%)	15 (88.2)
Aldosterone-Antagonists (%)	15 (88.2)

Table 2
Hemodynamic data of patients undergoing TMVR.

Outcome	n	Baseline	Follow-up	Mean difference (95% CI)	*P* value
PVR, WU	14	3.5 (±2.2)	2.3 (±1.2)	−1.0 (0.4 to 2.5)	**0.02**
Cardiac output (CO), l/min	14	3.7 (±0.9)	4.6 (±1.3)	0.9 (−2.1 to −0.4)	**0.02**
Cardiac index (CI), l/min/m^2	14	1.8 (±0.5)	2.2 (±0.5)	0.4 (−1.0 to 0.06)	0.08
mPCWP, mmHg	17	24.1 (±9.0)	22.7 (±5.8)	−1.4 (−4.0 to 6.0)	0.52
mPAP, mmHg	17	36.1 (±12.0)	31.4 (±8.4)	−4.7 (−1.0 to 10.0)	0.14
sPAP, mmHg	17	55.4 (±15.6)	45.6 (±9.8)	−9.8 (2.5 to 19.0)	**0.02**
TPG, mmHg	17	12.0 (±7.5)	9.7 (±5.3)	−2.3 (0.5 to 7.0)	**0.04**
SVO2, %	7	55.5 (±8.9)	62.6 (±6.3)	7.1 (−22.5 to 0.7)	0.07

Bold values signifies p ≤ 0.05.

45.6 ± 9.8 mmHg at follow-up, p = 0.02, Fig. 1C). In addition, TPG decreased from 12.0 ± 7.5 at baseline to 9.7 ± 5.3 at follow-up ($p = 0.04$).

A subgroup of five patients was initially not eligible for heart transplantation based on a baseline PVR > 3.5 WU. Therefore, we further analysed the hemodynamic effects of TMVr in these patients (Table 3). In this subgroup, hemodynamic parameters revealed major improvements in all five individuals. Mean PVR decreased significantly after successful TMVr (6.1 WU at baseline vs. 2.9 WU at follow-up, $p = 0.01$, Fig. 2A). There was also a notable increase in CO (3.3 l/min at baseline vs. 4.4 l/min at follow-up, $p = 0.01$) and CI (1.6 l/min/m^2 at baseline vs. 2.3 l/min/m^2 at follow-up, $p = 0.1$). Furthermore, sPAP significantly decreased from 67 mmHg at baseline to 48 mmHg at follow-up ($p = 0.05$, Fig. 2C). In addition, TPG significantly decreased following TMVr from 20.2 mmHg at baseline to 13.4 mmHg at follow-up ($p = 0.03$). While all individuals showed notable PVR reduction after successful TMVR, PVR was successfully reduced to ≤3.5 WU in three out of these five patients.

The reduction of MR and concomitant improvement in hemodynamic parameters was associated with clinical improvement in the majority of the 17 patients analysed. The prevalence of patients with NYHA III or IV was reduced from 88% (15/17 patients) to 47% (8/17 patients) at the time of post-procedural RHC ($p = 0.01$). Additionally, six-minute

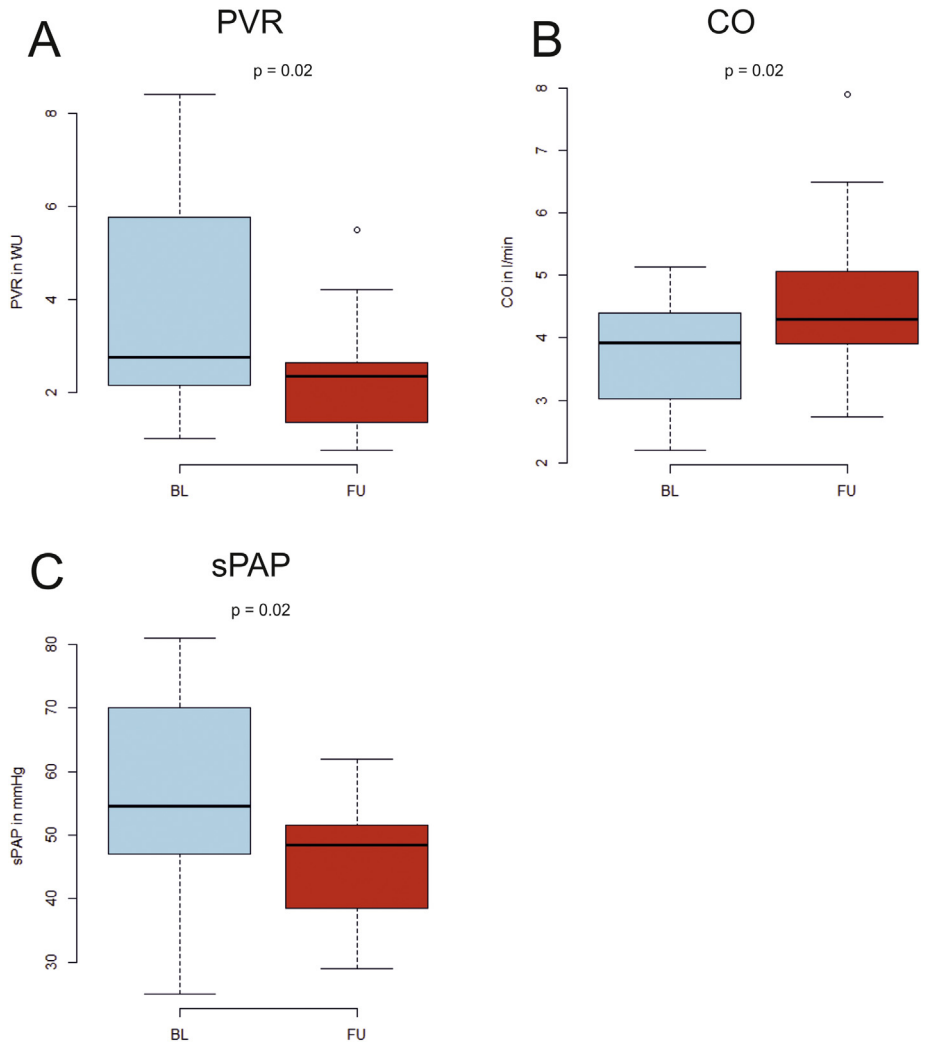

Fig. 1. Hemodynamic outcome of all patients after TMVr. A PVR in wood units before and after TMVr. B cardiac output before and after TMVr. C systolic PAP before and after TMVr.

Table 3
Hemodynamic data of patients exceeding listing criteria (PVR ≥ 3.5 WU).

Outcome	n	Baseline	Follow-up	Mean difference (95% CI)	*P* value
PVR, WU	5	6.1 (±1.4)	3.2 (±1.6)	−2.9 (0.3 to 2.1)	**0.01**
Cardiac output (CO), l/min	5	3.3 (±1.0)	4.4 (±0.9)	1.1 (−1.8 to −0.5)	**0.01**
Cardiac index (CI), l/min/m^2	5	1.6 (±0.5)	2.3 (±0.5)	0.7 (−1.6 to 0.2)	0.1
mPCWP, mmHg	5	26.8 (±8.2)	21.0 (±6.2)	−5.8 (−10.2 to 21.8)	0.37
mPAP, mmHg	5	47.0 (±7.8)	34.6 (±6.7)	−12.4 (−1.3 to 26.1)	0.07
sPAP, mmHg	5	67.4 (±12.5)	48.4 (±4.3)	−19.0 (−0.2 to 38.2)	**0.05**
TPG, mmHg	5	20.2 (±7.7)	13.4 (±6.8)	−6.8 (1.4 to 12.2)	**0.03**
SVO2, %	2	53.8 (±9.4)	59.3 (±1.8)	5.5 (−130.5 to 116.0)	0.59

Bold values signifies p ≤ 0.05.

walking distance increased from 175.9 ± 165 m at baseline to 331.5 ± 153 m at follow-up ($p = 0.06$).

Further analysis of clinical parameters after successful TMVr revealed a significant reduction of mean NTproBNP levels (6255 pg/ml ±4508 at baseline vs. 2423 pg/ml ± 1457 at follow-up, $p < 0.001$, Table 4). Additionally, there was a post-procedural decrease of bilirubin (1.4 mg/dl at baseline vs. 0.7 mg/dl at follow-up, $p = 0.01$) and GGT (120 U/l at baseline vs. 102 U/l at follow-up, $p = 0.03$). A significant change of median levels of transaminases was not observed.

We further assessed long-term clinical outcome by telephone calls after a mean of 35.7 ± 24.6 months. Three patients underwent heart transplantation and four patients received an assist-device (LVAD). Ten patients were managed with guideline-directed medical therapy and one of these is still on the waiting list for cardiac transplantation (Fig. 3 for detailed description of the destination therapy of all patients).

During long-term follow-up, four patients died resulting in a survival rate of about 86% within one year and 71% within three years according to Kaplan-Meier-analysis. Moreover, the prevalence of patients with durable NYHA <II° was 27.3% (3/10 patients) at last follow-up.

4. Discussion

This retrospective analysis demonstrates that TMVr for severe SMR can significantly reduce PVR in selective end-stage HFrEF patients which were evaluated for heart transplantation.

Despite the progress in medical and device-based heart failure therapy, heart transplantation remains the gold standard for the treatment

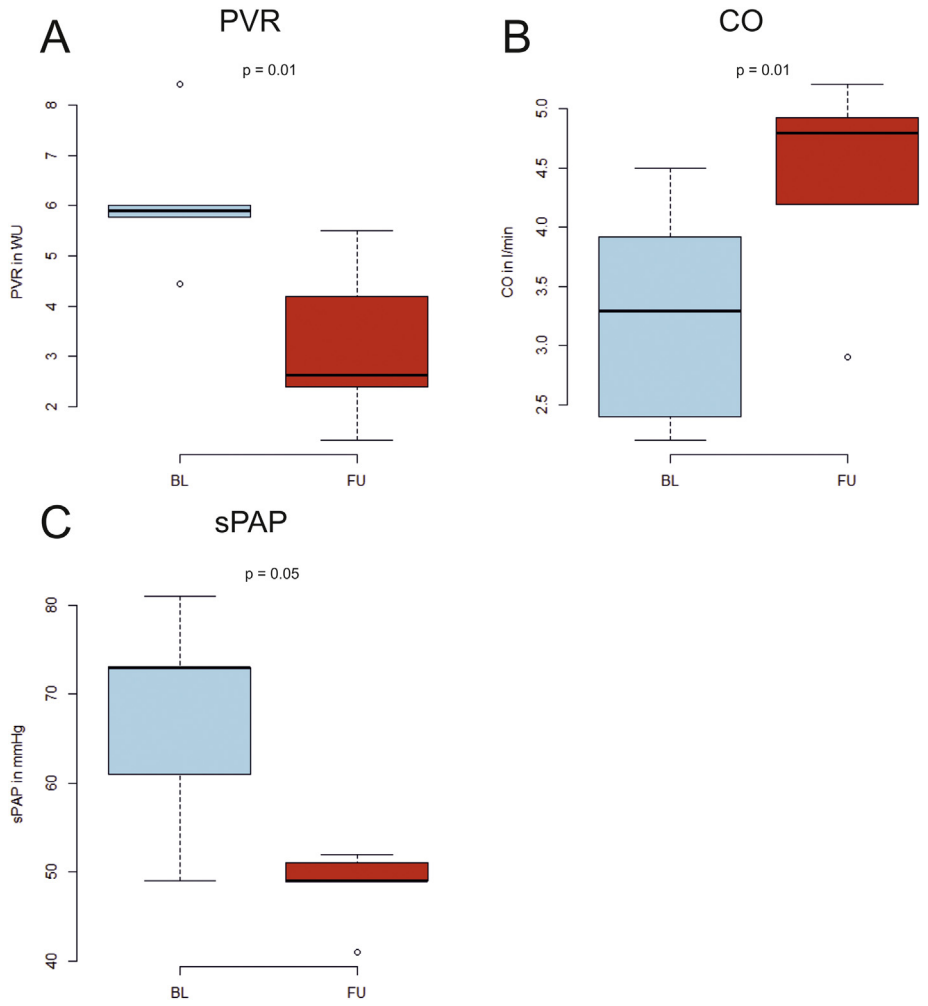

Fig. 2. Hemodynamic outcome after TMVr of a subgroup of patients with PVR > 3.5 WU. A PVR in wood units before and after TMVr. B cardiac output before and after TMVR. C sPAP before and after TMVr.

Table 4
Clinical and laboratory parameters of the study cohort.

Outcome	n	Baseline	Follow-up	Mean difference (95% CI)	*P* value
NYHA ≥ III, n (%)	17	15 (88.2)	8 (47.1)	7 (9.6 to 63.7)	**0.01**
NTproBNP, pg/ml	16	6255 (±4508)	2423 (±1457)	−3832 (1185 to 5762)	**<0.001**
GFR, ml/min	16	73.4 (±27.9)	63.9 (±29.9)	−9.5 (−8.0 to 23.5)	0.48
Bilirubin, mg/dl	14	1.7 (±0.9)	0.9 (±0.4)	−0.7 (0.2 to 1.6)	**0.01**
Gamma-GT, U/l	14	223.1 (±245.7)	146.6 (±159.8)	−76.5 (7.0 to 158)	**0.03**
AST, U/l	14	32.0 (29.0 to 47.0)	42.0 (26.0 to 83.8)	10.0 (−211.5 to 8.5)	0.29
ALT, U/l	14	34.0 (26.0 to 60.0)	25.5 (20.0 to 70.5)	−8.5 (−177.5 to 21.5)	0.9

Bold values signifies p ≤ 0.05.

of patients with end-stage HFrEF. Organ shortage with subsequent prolongation of the waiting period in some countries along with a high mortality in this group of patients require a timely listing for heart transplantation. However, end-stage HFrEF patients need to meet several hemodynamic criteria to be considered eligible for listing. On the one hand, cardiac index needs to be significantly reduced (CI < 2.0 l/min). On the other hand, this should not have led to a substantial increase in PVR as increased PVR (>3.5 WU) is associated with elevated perioperative death and worse prognosis (22,23). These partly contradictory requirements leave only a short window to list patients for heart transplantation. In particular, the subset of patients with end-stage HFrEF and SMR suffer from severe postcapillary pulmonary hypertension that ultimately leads to increased PVR and therefore patients are oftentimes not eligible for heart transplantation. Furthermore, patients have an elevated risk of becoming ineligible for transplantation while being on the waiting list (median organ waiting time in Germany in 2019: 15 months) (24). Therefore the primary objectives for physicians should not only be improving the patients' hemodynamic parameters to achieve eligibility for transplantation, but also to maintain a hemodynamically stable status as long as possible.

A previous report showed that TMVr can be successfully performed in patients on the heart transplant list awaiting transplantation (25,26). However, these patients already fulfilled the listing criteria having a PVR of <3.5 WE. Besides, Gaemperli et al. already demonstrated the hemodynamic improvement of patients with mildly reduced ejection fraction after TMVr. TMVr led to a significant decrease in mPAP and mPCWP along with an improvement of CO and CI concordant to our data (27). Other authors also demonstrated hemodynamic improvement after TMVr in patients with cardiogenic shock (28). To date, there are only case descriptions that report about the approach of TMVr to improve right heart hemodynamics in end-stage HFrEF patients with increased PVR precluding listing for heart transplantation (29,30).

Here we show for the first time that TMVr of severe SMR can significantly reduce PVR in selective patients with end-stage HFrEF evaluated for heart transplantation. The effect was particularly apparent in patients with high PVR (>3.5 WE). Furthermore, the improvement in

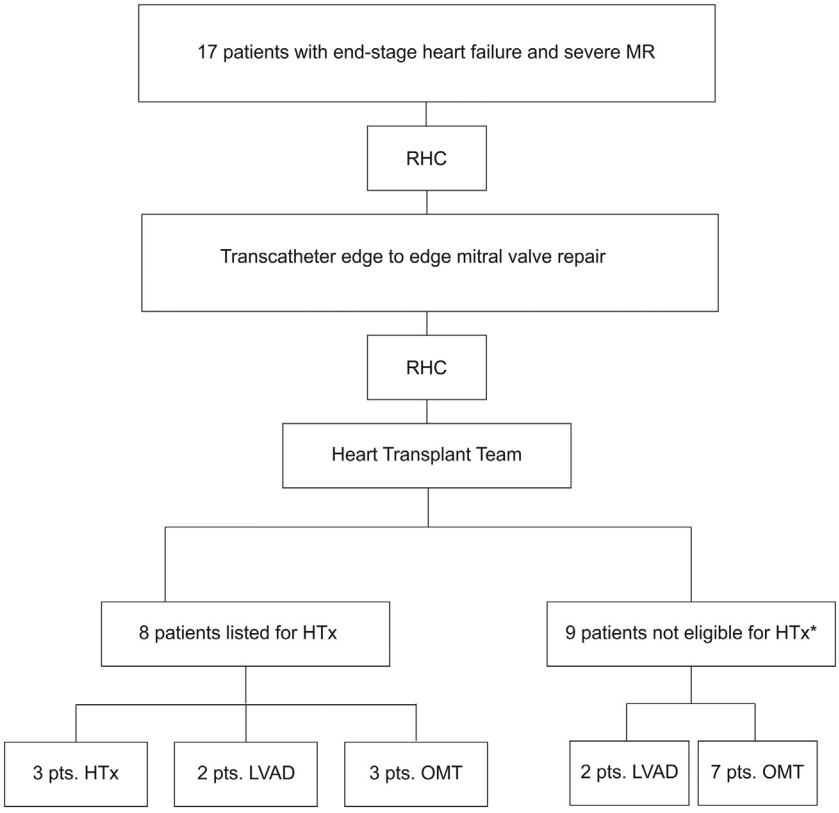

Fig. 3. Flow chart of the study cohort from baseline right heart catheterisation to destination therapy. Individual reasons for non-eligibility for HTx were lack of compliance, postinterventional improvement of LVEF, age and increased BMI.
OMT: Optimal medical therapy; LVAD: Left Ventricular Assist Device, HTx: heart transplantation, BMI: body mass index.

SMR and subsequent hemodynamic improvement correlated well with clinical improvement. Therefore, TMVr improves symptoms and may increase the number of patients with end-stage HFrEF and initially severe SMR that are eligible for heart transplantation. Thus, the window of patients waiting for heart transplantation might be extended applying this approach. However, it is unclear whether TMVr at an earlier time point in the disease process can prevent the development of severe pulmonary hypertension and subsequently increased PVR.

The results of this retrospective study are particularly remarkable given the fact that the patients treated here suffered from more advanced heart failure than the patients included in the randomised COAPT- and MITRA-FR-trials (mean LVEF 22% compared to 31% in COAPT and 33% in MITRA-FR). Moreover, regarding left ventricular end-diastolic diameter and severity of SMR the patients investigated here resemble more the patients analysed in the MITRA-FR trial, which did not show a benefit of TMVr compared to optimal medical therapy (31,32).

The limited number of patients and the retrospective nature of this study are major limitations of this analysis. Additionally, the lack of a control group and the single center design of this study lead to possible lack of generalizability and referral bias. However, this is the largest study so far evaluating the effect of TMVr in this specific cohort.

Based on the results reported here, we suggest performing right heart catheterizations at an early point of time in patients with end-stage HFrEF and severe MR. In case of pulmonary hypertension and in particular increased PVR, TMVr might be considered in order to improve symptoms and eligibility for heart transplantation. Furthermore, these patients certainly need surveillance from an experienced interdisciplinary heart failure team while being on the waiting list. In this context, modern devices for intrapulmonary pressure measurements like the CardioMEMS™ System (Abbott laboratories, Chicago, Illinois, United States) could be evaluated for an early detection of disease progression in this particular cohort (33,34).

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the International Journal of Cardiology.

Please indicate the specific contributions made by each author. The name of each author must appear at least once in each of the three categories below.

Category 1.

Conception and design of study: P.M. Doldi, D. Braun, J. Hausleiter;

acquisition of data: P.M. Doldi, D. Braun, M. Orban, M. Nabauer, P. von Samson-Himmelstjerna, U. Wilbert-Lampen, J. Hausleiter, S. Massberg;

analysis and/or interpretation of data: P.M. Doldi, D. Braun, J. Buech, J. Hausleiter;

Category 2.

Drafting the manuscript: P.M. Doldi, D. Braun, J. Buech;

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Category 3.

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Declaration of Competing Interest

D. Braun, M. Orban and M. Nabauer received speaker honoraria from Abbott Vascular. J. Hausleiter received speaker honoraria from and serves as consultant for Abbott Vascular and Edwards Lifesciences. The other authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.06.031.

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