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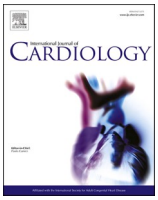

The prognostic value of changes in pulmonary vein flow patterns after surgical repair for primary mitral regurgitation

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ABSTRACT

Background: The pulmonary vein (PV) flow pattern is influenced by the presence of mitral regurgitation (MR). After a successful reduction in MR severity, the pattern is expected to be changed. We aimed to evaluate the prognostic value of a change in the PV flow pattern in patients with primary MR undergoing mitral valve repair (MVR). **Methods**: The PV flow pattern was assessed with transthoracic echocardiography in 216 patients (age 65 [IQR 56–72] years, 70% male) with primary MR before and after surgical MVR. The population was divided according to a change in the PV flow pattern following MVR into 'improvers' and 'non-improvers'. **Results**: Non-improvers (15%) had a higher prevalence of paroxysmal AF at baseline (46% vs. 22%, $p = 0.004$), left ventricular dysfunction (LVEF ≤60%) (39% vs. 21%, $p = 0.020$), and had lower systolic pulmonary artery pressure (28[IQR 25–38] vs. 35[IQR 26–48] mmHg, $p = 0.018$) compared to improvers (85%). After a median follow-up of 83[IQR 43–140] months, 26(12%) patients died. Non-improvers had higher mortality rates than improvers ($p = 0.009$). On multivariable Cox regression analysis, a lack of improvement in the PV flow pattern remained independently associated with all-cause mortality (HR 2.322, 95% CI 1.140 to 4.729, $P = 0.020$). **Conclusion:** A lack of improvement in the PV flow pattern is independently associated with worse long-term survival in patients with primary MR undergoing MVR.

1. Introduction

In a normal situation, the pulmonary vein (PV) flow consists of a three-phasic, pulsatile flow, including a systolic component (S), a diastolic component (D) and a small negative backflow during atrial contraction (Ar). The normal pattern for adults is characterized by an S ≥ D pattern [1,2]. In patients with mitral regurgitation (MR) however, the PV flow pattern is often disrupted according to the severity of the MR. Patients with mild MR generally maintain a normal PV flow pattern, whereas patients with moderate or severe MR may show a blunted or even reversed PV flow pattern, respectively [3,4]. Previous studies have shown that the PV flow pattern is associated with prognosis in patients with ischemic heart disease [5]. Similarly, in patients with significant MR, a change in the PV flow pattern after MitraClip implantation has also shown to be associated with outcomes [6]. In the current study, we evaluated the relationship between a change in the PV flow pattern and the prognosis in patients with primary MR undergoing mitral valve repair (MVR).

2. Methods

2.1. Design

Patients with significant (moderate to severe and severe) primary

Abbreviations: AF, atrial fibrillation; D, diastolic; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVR, mitral valve repair; PV, pulmonary vein; S, systolic; Dvti, diastolic velocity time integral; Svti, systolic velocity time integral; TEER, transcatheter edge-to-edge repair.

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MR who underwent MVR at the Leiden University Medical Center (The Netherlands) between 2002 and 2021 were selected based on the availability of pre-and post-operative recordings of the PV flow with Doppler echocardiography. Only patients with posterior leaflet prolapse/flail were included to avoid bias associated with the jet direction of the MR. Patients with permanent atrial fibrillation (AF) or with previous mitral valve intervention were excluded. In addition, patients with unavailable or uninterpretable echocardiographic data of the PV flow pattern or with a large beat-to-beat variability were also excluded. Demographic and clinical data were collected from the electronic patient files (EPD-vision, Leiden University Medical Center, Leiden, The Netherlands) and included heart failure symptoms, comorbidities, and medical therapy. Ischemic heart failure was defined by the presence of significant coronary artery disease on invasive coronary angiography. All data used for this study were obtained for clinical purposes and handled anonymously. For retrospective analysis of clinically acquired data, the institutional review board waived the need for written patient informed consent.

Transthoracic echocardiography images were recorded using Vivid 7, E9 or E95 ultrasound systems (General Electric Vingmed Ultrasound, Horten, Norway) with patients at rest, in the left lateral decubitus position. Electrocardiogram-triggered echocardiographic data were acquired with 3.5 MHz or M5S transducers and digitally stored in cine-loop format for offline analysis with EchoPac (EchoPac 203, General Electric Vingmed Ultrasound, Horten, Norway). LV end-diastolic and end-systolic volumes were measured from the apical two- and four-chamber views, and the LV ejection fraction (LVEF) was calculated using the biplane Simpson's method [7]. MR quantification was performed according to contemporary guidelines and was based on an integrative approach that includes qualitative, semiquantitative and quantitative measures [8]. The tricuspid annular plane systolic excursion was used for evaluation of right ventricular systolic function and was measured on an apical 4-chamber view using M-mode imaging. Systolic pulmonary artery pressure was calculated by the peak systolic gradient across the tricuspid valve adding the estimated right atrial pressure according to the inferior vena cava diameter and collapsibility. The right superior PV was identified on the apical four-chamber or five-chamber view, using low-velocity scale color Doppler assessment. The depth was adjusted to enable visualization of the PV entering the left atrium (LA). Next, the sample volume was placed approximately 10 mm proximal to the PV junction with the LA, and the PV flow velocity was recorded with pulsed-wave Doppler imaging [9]. In each patient, the PV flow was measured at baseline (pre-operatively, 2[IQR 0–5] months before surgery) and at follow-up (postoperatively, 11[IQR 6–18] months after MVR). During each echocardiographic examination, the PV flow was classified as: "normal" (S ≥ D), "blunted" (S < D), or "reversed" (retrograde S wave) (Fig. 1). The study population was subsequently categorized according to an improvement or lack of improvement in PV flow post-MVR. A PV flow pattern was considered to be improved if the pattern changed from reversal to blunted or if the pattern changed to normal or remained as normal. The PV flow pattern was considered to be unimproved if the PV pattern changed from normal to blunted, or if the pattern changed to or remained reversed).

2.2. Endpoints

The primary outcome of the study was all-cause mortality. Mortality data were collected from the electronic patient files (the departmental cardiology information system (EPD-Vision 11.8.4.0, Leiden University Medical Center, Leiden, The Netherlands), which is linked to the governmental registry of mortality in the Netherlands.

2.3. Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous variables are reported as mean ± standard deviation if normally distributed and as median and interquartile range (IQR) if not normally distributed. Categorical data were compared using the χ^2 test, followed by post-hoc analyses of subgroups. Continuous data were compared using the student's *t*-test if normally distributed or the Mann-Whitney *U* test and the Kruskal-Wallis test if not normally distributed. The survival analysis was performed using the Kaplan-Meier test, while the log-rank test was used to compare groups. Uni- and multivariable Cox regression analyses were used to evaluate the association between clinical and echocardiographic parameters versus all-cause mortality. Clinical and echocardiographic variables that have shown prognostic importance in the univariable Cox regression analysis were used for the first multivariable Cox regression model and variables mentioned in the current guidelines to consider surgical intervention [10], were selected as covariables for the second multivariable Cox regression model. Univariable logistic regression analysis was performed to identify the variables that were associated with absence of improvement of the PV flow pattern. A p-value <0.05 was considered statistically significant and all tests were 2-sided. Statistical analyses were performed using SPSS version 25.0 (SPSS, Armonk, NY).

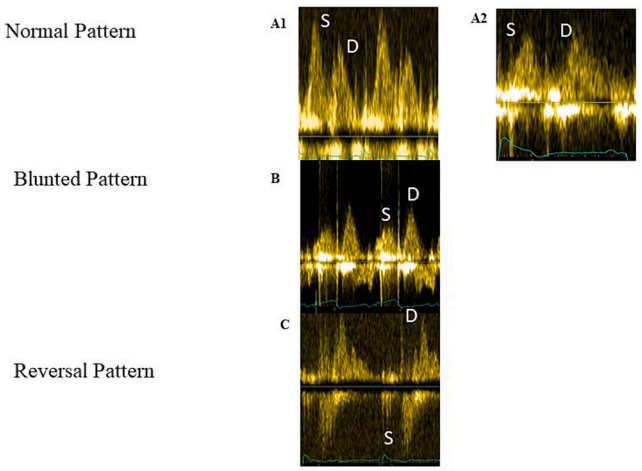

Fig. 1-. Different patterns of pulmonary vein flow.
Normal pattern: S ≥ D (panel A1, A2); Blunted pattern: S < D (panel B); and reversed pattern: retrograde S (panel C).
D: diastole; S: systole.

3. Results

A total of 216 patients (70% male, median age 65 years [IQR 56 to 72]) were included. Of these patients, 162 (75%) had heart failure symptoms (defined as New-York Heart Association functional class ≥II), 36 (17%) had a history of coronary artery disease, and 55 (26%) had previous paroxysmal AF (Table 1). The PV flow of non-improvers had a higher prevalence of paroxysmal AF compared to the PV flow improvers (46% vs.22%, $p = 0.004$). No other significant differences in baseline clinical variables were noted between patients with PV flow improvement versus patients without PV flow improvement.

A total of 51 patients (24%) had LVEF ≤60% and 40 (19%) patients had an LV end-systolic diameter ≥ 40 mm. The median LA volume index was 51[IQR 38–60] mm^2. Overall, the study population had a preserved right ventricular systolic function with a median tricuspid annular plane systolic excursion of 24 mm [IQR 22 to 27 mm].

In general, the PV flow pattern improved during follow-up in the entire study population (Fig. 2). Of note, only 3% of the patients had a reversed PV flow pattern at follow-up, as compared to 69% before MVR. The PV flow of non-improvers had a higher prevalence of reduced LVEF ≤60% (39% vs. 21%, $p = 0.002$) and a lower systolic pulmonary artery pressure (28[25–38] vs. 35[26–48], $p = 0.018$). The patients without PV flow improvement also had a significantly higher prevalence of a

Table 1-
Baseline clinical and echocardiographic characteristics.

Baseline characteristics	Overall Population (216)	Pulmonary vein Improvers (183)	Pulmonary vein Non-improvers (33)	*P* value
Age, years	65[56–72]	64[55–72]	67[59–73]	0.275
Male, n(%)	152(70)	130(71)	22(67)	0.613
Body surface area, (m^2)	1.9[1.8–2.1]	1.9[1.8–2.1]	2[1.8–2.1]	0.143
New York Heart Association class ≥II	162(75)	133(73)	29(88)	0.063
Diabetes mellitus, n (%)	5(2)	3(2)	2(6)	0.120
Hypertension, n(%)	82(38)	68(37)	14(42)	0.566
Coronary artery disease, n(%)	36(17)	29(16)	7(21)	0.455
Paroxysmal atrial fibrillation, n(%)	55(26)	40(22)	15(46)	0.004
estimated glomerular filtration rate, (ml/min/1.73m^2)	80[66–90]	79[65–90]	85[72–96]	0.283
Beta blocker, n(%)	89(41)	75(41)	14(42)	0.877
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, n (%)	104(48)	87(48)	17(52)	0.674
Calcium channel blockers, n(%)	17(8)	14(8)	3(9)	0.777
Diuretics, n(%)	75(35)	63(34)	12(36)	0.830
EuroSCORE	2.1[1.2–3.2]	2[1.2–3.3]	2.5[1.6–2.9]	0.235
Left ventricle ejection fraction; ≤60%	51(24)	38(21)	13(39)	0.020
Left ventricle ejection fraction; (%)	65[61–70]	65[61–71]	63[54–70]	0.069
Left ventricular end-diastolic diameter, (mm)	55[51–60]	55[51–60]	55[52–59]	0.798
Left ventricular end-systolic diameter, (mm)	32[28–38]	32[28–38]	32[29–40]	0.363
Left ventricular end-systolic diameter ≥ 40, (mm)	40(19)	32(18)	8(24)	0.366
Left ventricle end-diastolic volume index, (ml/m^2)	71[60–84]	71[61–84]	68[52–84]	0.211
Left ventricle end-systolic volume index, (ml/m^2)	25[19–31]	24[19–31]	25[20−31]	0.681
Left atrial volume index, (ml/m^2)	51[38–60]	50[38–61]	51[37–59]	0.922
Left atrial volume index ≥60, (ml/m^2)	56(26)	48(27)	8(24)	0.771
E/A	1.5[1.3–2.0]	1.5[1.3–2.0]	1.5[1.2–2.1]	0.986
Effective regurgitant orifice area, (mm^2)	44[34–59]	45[35–59]	39[28–56]	0.231
Vena contracta, (mm)	7[6–8]	7[6–8]	7[6–9]	0.611
Tricuspid annular plane systolic excursion, (mm)	24[22–27]	24[22–27]	24[19–28]	0.502
Systolic pulmonary artery pressure, (mmHg)	34[25–46]	35[26–48]	28[25–38]	0.018
Significant tricuspid regurgitation, n(%)	52(24)	44(24)	8(25)	0.946
Heart rate, (bpm)	73[65–82]	74[64–81]	73[68–90]	0.287
Normal pulmonary vein pattern, n(%)	22(10)	18(10)	4(12)	0.690
Blunted pulmonary vein pattern, n(%)	45(21)	21(12)	24(73)	<0.001
Reversed pulmonary vein pattern, n(%)	149(69)	144(79)	5(15)	<0.001

Data is presented as mean ± SD if normally distributed or median (25th–75th percentile) if not normally distributed.

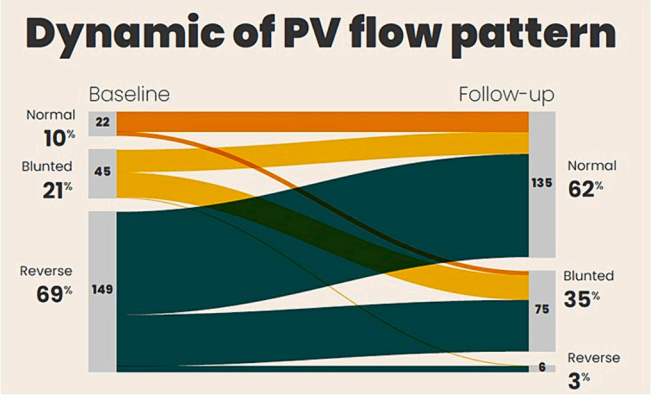

Fig. 2-. Change in PV flow pattern after mitral valve surgery.
On the left side, the percentages of the different PV flow patterns are shown at baseline, whereas on the right side, the PV flow patterns are shown at follow-up.
PV: pulmonary vein.

blunted PV flow pattern at baseline, while patients with PV flow improvement had a higher prevalence of the reversed pattern (73% vs. 12%, $p < 0.001$ and 15% vs. 79%, $p < 0.001$, respectively) (Table 1).

The patients without improvement in PV flow more frequently underwent a concomitant MAZE procedure during MVR, compared to the patients with PV flow improvement (39% vs. 19%, $p = 0.01$). Patients without improvement PV flow also had a higher prevalence of residual MR >2+ after surgery (27% vs. 5%, $p < 0.001$) (Table S4).

During a median follow-up of 83 [IQR 43–140] months, 26 (12%) patients died. When dividing the patient population according to the absence or presence of PV flow pattern improvement following MVR, the cumulative survival rates at 12-, 60-, and 120-month follow-up were significantly lower for PV flow non-improvers compared to PV flow improvers (94%, 91% and 79% versus 99%, 97% and 93%, respectively; $p = 0.009$) (Fig. 3). On univariable Cox regression analysis, age (HR 1.136; 95% CI 1.078–1.198; $p < 0.001$), estimated glomerular filtration rate (HR 0.963; 95% CI 0.945–0.982; $p < 0.001$) and a PV flow without improvement (HR 2.937; 95% CI 1.254–6.878; $p = 0.013$) were independently associated with outcomes (Table 2). On multivariable analysis, adjusting for age and estimated glomerular filtration rate, a PV flow without improvement remained independently associated with outcomes (HR: 2.655, 95% CI 1.107 to 6.367, $p = 0.03$) (multivariable model 1, Table 2). In a second multivariable model, adjusting for LVEF ≤60% and LV end-systolic diameter ≥ 40 mm, a PV flow without improvement remained independently associated with outcomes (HR: 2.924, 95% CI 1.235–6.925, $p = 0.02$) (multivariable model 2, Table 2). To further evaluate the prognostic value of a change in PV flow pattern, a first sensitivity analysis (adjusting for paroxysmal AF) and a second sensitivity analysis (adjusting for MAZE procedure) and a third sensitivity analysis for residual MR >2+ were performed, showing that a PV flow without improvement pattern remained independently associated with outcomes (Supplementary data, Table S1). To identify predictors of PV flow without improvement, logistic regression was performed. On univariable analysis, paroxysmal AF, LVEF ≤60%, and residual MR >2+ were significantly associated with non-improvement in the PV flow pattern, while systolic pulmonary artery pressure had a protective effect. (Supplementary data, Table S2). On logistic regression analysis, all the above-mentioned variables, except systolic pulmonary artery pressure, which had a negative correlation, remained significantly associated with a PV flow without improvement in flow pattern following MVR (Supplementary data, Table S3).

4. Discussion

The current study shows that the PV flow pattern was improved in

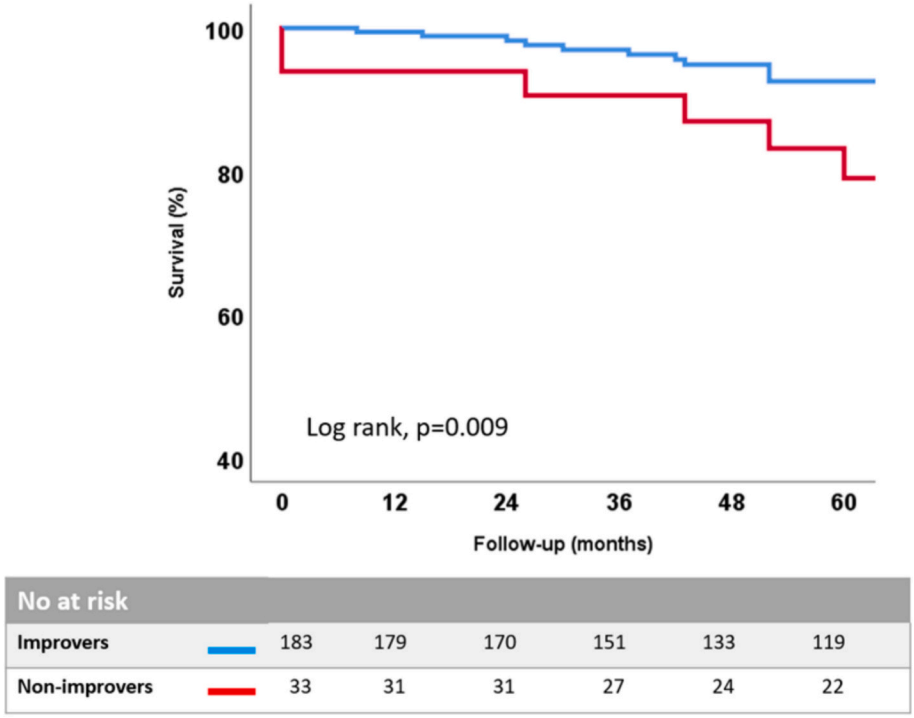

Fig. 3-. Kaplan-Meier survival curve for all-cause mortality.
The Kaplan-Meier curves demonstrate the reduced survival of PV non-improvers (red line) compared to PV improvers (blue line).

Table 2-
Uni- and multivariable Cox regression analyses to investigate the association between pulmonary vein flow pattern changes, and outcomes in patients with primary mitral regurgitation following mitral valve repair.

Cox Regression	Univariable	P value
Age	1.136(1.078-1.198)	<0.001
Gender	0.694(0.314-1.533)	0.366
Coronary artery disease	1.875(0.815-4.316)	0.139
Hypertension	0.832(0.371-1.869)	0.656
estimated glomerular filtration rate (ml/min/ 1.73 m^2)	0.963(0.945-0.982)	<0.001
New York Heart Association class >1	1.071(0.428-2.677)	0.883
Paroxysmal atrial fibrillation	1.971(0.893-4.349)	0.093
LVESD ≥40, (mm)	1.352(0.506-3.613)	0.548
Left atrial volume index ≥60 (ml^2)	0.989(0.395-2.478)	0.981
Left ventricular ejection fraction ≤60 (%)	1.202(0.504-2.867)	0.679
E/A ratio	0.928(0.554-1.553)	0.775
Effective regurgitant orifice area, (mm^2)	0.996(0.972-1.020)	0.722
Systolic pulmonary artery pressure, (mmHg)	1.006(0.982-1.031)	0.611
Tricuspid annular plane systolic excursion, (mm)	0.924(0.832-1.027)	0.143
Pulmonary vein non-improvers	2.937(1.254-6.878)	0.013
Residual mitral regurgitation >2+	2.182(0.639-7.451)	0.213
Tricuspid regurgitation >1	1.992(0.912-4.351)	0.084
Pulmonary vein pattern, baseline: Blunted Reversal	0.395(0.131-1.193)	0.1
	0.258(0.097-0.688)	0.007
Pulmonary vein pattern, follow-up: Blunted Reversal	1.671(0.761-3.670)	0.201
	2.806(0.363-21.691)	0.323
	Multivariable -Model 1	
Pulmonary vein, non-improvers	2.655(1.107-6.367)	0.029
Age (years)	1.108(1.038-1.183)	0.002
estimated glomerular filtration rate (ml/min/ 1.73 m^2)	0.998(0.964-1.113)	0.34
	Multivariable-Model 2	
Pulmonary vein, non-improvers	2.924(1.235-6.925)	0.015
Left ventricular ejection fraction ≤60 (%)	0.962(0.368-2.516)	0.937
Left ventricular end-systolic diameter ≥40 (mm)	1.343(0.458-3.937)	0.591

most patients undergoing MVR for primary MR caused by posterior leaflet pathology (85%). Those patients who did not show an improvement in the PV flow pattern showed higher mortality rates at follow-up. In addition, PV flow non-improvement was independently associated with worse outcomes. Paroxysmal AF, LV systolic dysfunction, and residual significant MR after MVR were independently associated with a PV flow without improvement in flow pattern, while pulmonary artery pressure was negatively correlated.

A normal PV flow pattern is characterized by an S ≥ D pattern. However, different variables, such as heart rate and age, may influence the PV flow pattern and/or velocity [11]. Moreover, there is an important relationship between the PV flow and the pressure gradient between the PV and the LA, which in turn is influenced by the LA-LV pressure gradient and the LA compliance. In patients with significant MR, the pressure gradient between the PV and the LA is decreased which, together with a reduced systolic mitral annular motion, may induce a reduction in the S wave velocity and an increase in the D wave velocity [12]. Diastolic function also affects the PV flow pattern, however, assessing diastolic function poses significant challenges in the presence of severe mitral regurgitation, where the increased transmitral flow can artificially elevate peak E velocity. This phenomenon often renders conventional diastolic assessments less reliable, particularly in patients with primary severe mitral regurgitation and preserved left ventricular function. In the current study, we found no substantial disparities in the E/A ratio between the study groups at baseline, emphasizing the similarity in their diastolic function profiles.

Changes in the PV flow pattern are associated with the severity of the underlying MR. Klein et al. studied the association between MR severity and PV flow patterns and showed that 93% of patients with grade 4+ MR had a reversed PV flow pattern (93% sensitivity and 100% specificity), and 92% of patients with grade 3+ MR, as well as 50% of patients with grade 2+ MR had a blunted PV flow pattern [13]. A reversed PV flow pattern was also correlated with the size of the MR jet area [14]. In addition, Pu et al. noted that S wave reversal was highly specific for grade 3+/4+ MR, and normal pattern (S ≥ D) was highly specific for mild to moderate MR, whereas a blunted pattern could be observed in all

MR grades, especially in the presence of LV dysfunction [15]. The current study included patients with significant MR, of whom 10%, 21% and 69% had a normal, blunted, or reversed PV flow pattern, respectively.

In a previous study, Klein et al. already described the normalization of the PV flow pattern following MVR [16], which has also been described following MV replacement [17]. However, the study populations in both studies were limited (22 and 10 patients, respectively), limiting the generalizability of the results and conclusions regarding outcomes. In a study including 300 patients who underwent transcatheter edge-to-edge repair (TEER), Ikenaga and colleagues showed that the systolic-velocity time integral (Svti) increased after the procedure [18]. In another study which also included patients who underwent TEER (64% with primary MR), the pattern of the PV flow changed from 3%, 29%, 63% at baseline to 27%, 48%, 3% immediately after TEER for normal, blunted and reversed PV flow pattern, respectively [6]. In the current study, the PV flow pattern changed from 10%, 21% and 69% to 62%, 35% and 3% for the normal, blunted and reversed PV flow patterns, respectively.

In the latter study, paroxysmal AF (or history of AF) was associated with a lower likelihood of improvement in the PV flow pattern. Similarly, in our study, patients with paroxysmal AF or those who had undergone MAZE procedure were also less likely to improve the PV flow following MVR (Table 1, S1, S3) suggesting a left atrial pathology, despite both groups had a similar LA volume at baseline.

The prognostic value of PV flow indices has already been studied in different populations. In 145 patients with LV systolic dysfunction, Dini et al. showed that the duration of the PV flow and mitral flow at atrial contraction (ARD-Ad) was independently associated with prognosis [19]. Iwashima et al. showed that the S/D ratio was also an independent predictor of cardiovascular events in patients with essential hypertension [20]. In addition, Buffle and coworkers found that the S/D ratio provided incremental prognostic information over routine diastolic parameters in patients with preserved LVEF who were in sinus rhythm [21]. Finally, in patients with ischemic heart disease, it was found that a blunted PV flow pattern was associated with the combined endpoint of heart failure hospitalization and mortality [22].

The association between PV flow and outcomes was also studied in patients undergoing TEER. Ikenaga et al. measured the systolic velocity-time integral/diastolic velocity-time integral (Svti/Dvti) immediately after implantation of a MitraClip and showed that patients with an Svti/Dvti ratio < 0.72 had a higher risk of major adverse cardiovascular events within 12 months of follow-up [18]. In contrast to the study of Ikenaga et al., who used transesophageal echocardiography for their PV flow measurements, the current study used transthoracic echocardiography, which is more readily available. Corrigan et al. also included patients who were treated with TEER and showed that an improvement in the PV flow pattern immediately after TEER was associated with lower rates of rehospitalization and mortality at 24 months follow-up [6]. In the current study, 85% of the patients had an improvement in their PV flow pattern following MVR. The different treatments (TEER vs. MVR) and different study populations (primary versus secondary MR) can at least partially explain the differences in the improvement rates.

4.1. Study limitations

This is a retrospective, single-center study. Patients with permanent AF, anterior leaflet prolapse, or insufficient echocardiographic data for PV Doppler analysis were excluded, potentially introducing a selection bias. Furthermore, using transthoracic echocardiography, we only measured the PV flow in the right upper PV, and therefore changes in the PV flow in the other three veins may have been overlooked. However, by consistently using the right upper PV, each patient was a control of his/her previous measurement. All-cause mortality was chosen as the primary endpoint because the exact cause of death could not be systematically evaluated.

5. Conclusion

The current study demonstrates that the PV flow pattern improves in most patients following MVR for primary MR. Importantly, non-improvement of the PV flow pattern is associated with higher mortality rates.

Disclosures

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CRediT authorship contribution statement

Idit Yedidya: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jan Stassen:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Steele Butcher:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Aniek L. van Wijngaarden:** Investigation, Data curation. **Yoska Wu:** Investigation, Data curation. **Pieter van der Bijl:** Writing – review & editing, Investigation. **Nina Ajmone Marsan:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Victoria Delgado:** Supervision, Methodology. **Jeroen Bax:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132414.

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