Concomitant mitral regurgitation and aortic stenosis: one step further to low-flow preserved ejection fraction aortic stenosis

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Aims
Patients with severe aortic stenosis (AS) and normal ejection fraction (EF) can paradoxically present low-transaortic flow and worse prognosis. The role of co-existing mitral regurgitation (MR) in determining this haemodynamic inconsistency has never been quantitatively explored. The hypothesis is that MR influences forward stroke volume and characterizes the low-flow AS pattern.

Methods and results
Consecutive patients with indexed aortic valve area (AVA) <0.6 cm²/m² and EF >50% formed the study population. Complete echocardiographic data were collected, and mitral effective regurgitant orifice area (ERO) and regurgitant volume were obtained with proximal isovelocity surface area method. Patients were divided into subgroups according to indexed stroke volume (SV index). Included patients were 273 [age 79 ± 10 years, 53% female, EF 65 ± 7%, indexed AVA 0.47 ± 0.09 cm²/m², mean transaortic gradient (MG) 32 ± 17 mmHg]. Mitral regurgitation was present in 89 (32%); ERO was 0.12 ± 0.08 cm² (range 0.02–0.49 cm²). A low-flow state (SV index <35 mL/m²) was diagnosed in 41 (15%) patients. The prevalence of MR was higher in with low-flow vs. normal-flow group (56 vs. 28%, P = 0.03).

Effective regurgitant orifice was associated to low-flow state univariately (OR: 1.75 [1.59–2.60]; P = 0.004) and after comprehensive adjustment (OR:1.76 [1.12–2.75]; P = 0.01). When MG was forced in the model, ERO remained significant (P < 0.009). On average, there was a 6 mL reduction in forward SV appeared per each 0.1 cm² of ERO.

Conclusion
In patients with severely reduced AVA and preserved EF, MR is a major determinant of the low-flow condition. Furthermore, MR quantification by ERO predicts the presence of reduced flow independently of chamber volumes, systolic function, and transaortic gradient.

Keywords
aortic valve stenosis • low flow • mitral regurgitation • quantification

Introduction
Patients with severe aortic stenosis (AS) with tight valve area and preserved left ventricular (LV) ejection fraction (EF) should present with high aortic jet velocity. However, different haemodynamic patterns have been described. Discordance between aortic valve area (AVA) and aortic jet velocity is frequently encountered in clinical practice, even in patients with preserved EF and severely stenotic valve. This discordance is often related to low flow, documented by stroke volume indexed to body surface area (SV index) lower than 35 mL/m². The presence of low flow is important because patients with this type of AS may encounter high mortality whether symptomatic or asymptomatic, often in the context of delayed referral to surgery. Understanding this haemodynamic pattern is particularly important because surgical benefit provided by aortic valve replacement to these patients appear similar to that of patients with normal flow AS.

However, there is little information regarding pathophysiologic processes determining the low-flow AS state. This condition is associated with increased global ventricular afterload, concentric LV...
hypertrophy and intrinsic myocardial contractility impairment.\(^9\) It is well known that moderate or severe mitral regurgitation (MR) can decrease forward stroke volume (SV) and potentially contributes to the low-flow state.\(^10\) However, the role of co-existing MR in determining these inconsistencies in AS patients has not yet been explored in a quantitative manner, covering the entire spectrum of severity, including mild MR. In particular, there are no quantitative data to assess the link between the degree of MR and the reduced aortic flow.

The aim of the present study was to analyse pathophysiological relations of quantitatively defined MR in the context of severe AS with preserved EF and to clarify whether MR is an independent determinant of forward SV and contributes to low-flow AS pattern.

**Methods**

Consecutive patients with isolated severe AS (indexed AVA \(< 0.6\, \text{cm}^2/\text{m}^2\)) and EF \(>50\%\) that had a quantitative assessment performed in the presence of MR within clinical practice, regardless of the presence of symptoms, were prospectively enrolled in two Northern Italian centres (Verona and Altavilla Vicentina) between 2008 and 2012. Exclusion criteria were: more than mild aortic regurgitation, mitral valve prosthesis, the presence of a sub-aortic obstruction (dynamic or fixed) which did not allow to assess the aortic valve disease precisely.

**Doppler echocardiography**

A pre-determined echocardiographic protocol for imaging, storage, review, and measurements, performed by board certified echocardiographers with more than 10 years of experience, with commercially available ultrasound systems. LV volumes and EF were measured using biplane Simpson’s method. Left ventricular mitral inflow indices were measured by pulsed Doppler in the apical four-chamber view. Tissue Doppler velocities were measured at the septal and lateral site of the mitral anulus in systole (\(e’\)), early (\(e\)), and late (\(a’\)) diastole, and then averaged. As a non-invasive estimate of LV filling pressure, the ratios of peak early diastolic LV filling velocity to \(e’\) at septal and lateral level (\(E/e’\) ratio) were calculated and averaged.

Left ventricular outflow tract (LVOT) was measured from a parasternal long axis view. A time velocity integral at LVOT was taken from an apical view, placing the pulse wave Doppler sample volume just at the same place where the LVOT was measured taking care to avoid acceleration of the flow close to the valve. Left ventricular outflow tract stroke volume was then calculated and indexed for BSA. Transvalvular velocities were interrogated by continuous-wave Doppler (including a non-insonating Doppler from multiple windows. Maximal instantaneous gradient across the aortic valve was calculated using a modified Bernoulli equation; mean transaortic gradient (MG) was measured by tracing of the velocity the aortic valve was calculated using a modified Bernoulli equation; mean MV was then calculated and indexed for BSA. Transvalvular velocities were measured at the septal and the lateral site of the mitral annulus, where the LVOT was measured taking care to avoid acceleration of the flow close to the valve. Left ventricular outflow tract stroke volume was then calculated and indexed for BSA. Transvalvular velocities were interrogated by continuous-wave Doppler (including a non-insonating Doppler from multiple windows. Maximal instantaneous gradient across the aortic valve was calculated using a modified Bernoulli equation; mean transaortic gradient (MG) was measured by tracing of the velocity curve.\(^11\) Aortic valve area was calculated by the continuity equation and indexed for body surface area. In the presence of MR, the regurgitant volume (RV) and the effective regurgitant orifice (ERO) were measured by proximal velocity surface area method (PISA), averaging the radius of the preorifice flow taken three times. In patients in whom the regurgitant jet envelope could not be obtained correctly, RV and ERO were calculated using a simplified method.\(^12\) The semiquantitative MR grading was obtained according to European Society of Cardiology guidelines, using a multiparametric approach and different ERO threshold for organic and functional MR.\(^1\) The organic aetiology of the MR was defined as the presence of significant pathological leaflets’ abnormalities. The presence of annulus calcification was not considered sufficient to define the organic aetiology. In addition, we used ERO cut-off values to define the severity grades, and not RV amount, because the driving pressure of MR (the systolic pressure gradient between LV and left atrium) is usually higher in AS patients than in other clinical setting.

Systemic arterial compliance index and valvulo-arterial impedance were calculated.\(^7\) Patients were named as low-flow if the SV index was \(\leq 35\, \text{mL/m}^2/\text{s}\) and normal flow if the SV index was \(>35\, \text{mL/m}^2/\text{s}\), and analysed accordingly.

**Statistical analysis**

Values are expressed as means \(\pm\) standard deviation. Differences between groups were analysed using unpaired t-test, \(\chi^2\), or analysis of variance, as appropriate. Correlations between variables were evaluated with Pearson or Spearman’s coefficients as appropriate. Associations between variables were evaluated using regression analysis. Multivariate analysis was used to evaluate the independent association between variables. Clinical relevant variables, as well as variables with a \(P < 0.1\) in univariable analysis, were included in multivariable models. A \(P\)-value \(<0.05\) was considered statistically significant.

**Results**

**Population characteristics**

Two hundred and seventy-three patients fulfilling the inclusion criteria formed the study population. Overall, mean age of the patients was 79 \(\pm\) 10 years, and 53% were female. Mean indexed AVA was 0.47 \(\pm\) 0.09 \(\text{cm}^2/\text{m}^2\), mean MG 32 \(\pm\) 17 mmHg, and mean EF 65 \(\pm\) 7%. Mitral regurgitation was present in 89 (32%) patients. The aetiology of MR was functional in the large majority of cases (86/89 patients, 97%), and it was organic in only three patients (due to mitral valve prolapse). Mitral regurgitation was classified as mild in 50 (18%), moderate in 30 (11%), and severe in 9 (3%) patients. In patients with MR, mean ERO was 0.12 \(\pm\) 0.08 \(\text{cm}^2\) (range 0.02–0.49 \(\text{cm}^2\)) and mean RV was 19 \(\pm\) 12 mL (range 3–60 mL). Mean LVOT SV was 78 \(\pm\) 17 mL (SV index 44 \(\pm\) 8 mL/\(\text{m}^2\)), a low-flow state (i.e. SV-index \(< 35\, \text{mL/m}^2\)) was diagnosed in 41 (15%) patients. Notably, 24 (9%) patients had atrial fibrillation. They frequently presented MR (20/24), had larger indexed left atrial volumes (59 vs. 37 mL/\(\text{m}^2\)), and more frequently presented low-flow (8/24). None of the patients had significant mitral valve stenosis.

**Stroke volume correlates**

As shown in Table 1, low-flow state was more frequent in female, was associated with more frequent atrial fibrillation, smaller LV end-diastolic volumes, and increased LV impedance. Interestingly despite a preserved EF as defined in the study design, patients with low-flow state were characterized by significant impairment of LV function both in term of EF (\(P = 0.0001\)) and SV (\(P < 0.0001\)) when compared with patients with normal flow. The prevalence of MR was higher in with low-flow compared with normal flow group (56 vs. 28%, \(P = 0.03\)). Furthermore, the average value of ERO was significantly higher in patients with low-flow (\(P = 0.0002\)) vs. normal flow, as displayed in Figure 1. Same result was obtained for RV (\(P < 0.0001\)).

The SV index, computed as continuous variable, was independently associated to ERO (\(P = 0.002\)), RV (\(P < 0.0001\)), end-diastolic volume (\(P < 0.0001\)), AVA (\(P < 0.0001\)), EF (\(P < 0.0001\)), atrial fibrillation (\(P = 0.0001\)), but not with age, gender, and systolic blood pressure (\(P > 0.1\) for all).
Mitral regurgitation quantification and low-flow state

The presence of MR itself contributes to univariately characterize low-flow state [odds ratio (OR) 3.21 [95% confidence interval (CI) 1.62–6.41], P = 0.0008]. Also, logistic regression models in Table 2 show how MR quantitative parameters are associated with the presence of SV index <35 mL/m². In univariate analysis, ERO and RV significantly contributed to identify low-flow patients, with OR 1.75 ([95% CI 1.59–2.60]; P = 0.004) per ERO 0.1 cm² increase, and OR 2.19 ([95% CI 1.53–3.22]; P < 0.0001) per 10 mL RV increase. After adjusting for age and sex both parameters maintained significance, with OR 1.55 ([95% CI 1.03–2.34]; P = 0.03) for ERO, and OR 1.98 ([95% CI 1.37–2.95]; P = 0.0003) for RV. The model was then adjusted for end-diastolic volume, atrial fibrillation, and EF, resulting in OR 1.73 (95% CI 1.07–2.74; P = 0.03) for ERO, and OR 2.16 (95% CI 1.40–3.37; P = 0.0008) for RV.

Despite MG is a consequence of flow, when it was forced in the model, no change in the role of ERO and RV was detected (P < 0.001 for both). In a linear regression analysis, after this comprehensive adjustment (for age, sex, LV end-diastolic volume, EF, atrial fibrillation, and MG), there was an average 6 mL reduction in forward SV per each 0.1 cm² of ERO or 10 mL of RV; Figure 1 (right) summarizes the predicted probability to present low-flow state at different ERO levels. The relationship between ERO or RV and low flow was not significant in the subgroup of patients with AF (OR for ERO was 0.83 [95% CI 0.85–3.93], P = 0.8).

Overall, the combination of both low flow and low gradient, known as paradoxical low-flow low-gradient pattern, was found in

Table 1 Differences between patients with low flow (stroke volume index ≤35 mL/m²) and normal flow (stroke volume index >35 mL/m²). Univariate associations between clinical and echocardiographic variables and stroke volume

<table>
<thead>
<tr>
<th></th>
<th>SV index ≤35</th>
<th>SV index &gt;35</th>
<th>P-value</th>
<th>Association with LVOT-stroke volume (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82 ± 8</td>
<td>79 ± 10</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Female (%)</td>
<td>68</td>
<td>50</td>
<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142 ± 25</td>
<td>144 ± 19</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 12</td>
<td>78 ± 10</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Atrial fibrillation (n,%)</td>
<td>8 (20%)</td>
<td>16 (7%)</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>76 ± 15</td>
<td>69 ± 12</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic function</td>
<td></td>
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<tr>
<td>LV end-diastolic volume (mL)</td>
<td>93 ± 26</td>
<td>107 ± 27</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVOT-stroke volume (mL)</td>
<td>52 ± 7</td>
<td>83 ± 14</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Left atrial volume index (mL/m²)</td>
<td>46 ± 16</td>
<td>44 ± 15</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Aortic valve haemodynamic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Peak aortic gradient (mmHg)</td>
<td>56 ± 24</td>
<td>67 ± 23</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>33 ± 15</td>
<td>41 ± 15</td>
<td>&lt;0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.7 ± 0.2</td>
<td>0.86 ± 0.17</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mitral regurgitation</td>
<td></td>
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<tr>
<td>ERO (cm²)</td>
<td>0.07 ± 0.08</td>
<td>0.03 ± 0.06</td>
<td>0.002</td>
<td>0.0002</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>11 ± 16</td>
<td>2 ± 6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No MR (n,%)</td>
<td>18 (44%)</td>
<td>166 (70%)</td>
<td>0.001</td>
<td>0.0009</td>
</tr>
<tr>
<td>Mild MR (n,%)</td>
<td>10 (24%)</td>
<td>40 (17%)</td>
<td></td>
<td></td>
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<tr>
<td>Moderate MR (n,%)</td>
<td>9 (22%)</td>
<td>21 (9%)</td>
<td></td>
<td></td>
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<tr>
<td>Severe MR (n,%)</td>
<td>4 (10%)</td>
<td>5 (2%)</td>
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<tr>
<td>Afterload parameters</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Global impedance (Zva)</td>
<td>5.6 ± 1.0</td>
<td>4.1 ± 0.7</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure/stroke volume</td>
<td>1.18 ± 0.4</td>
<td>0.80 ± 0.25</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV, left ventricular; LVOT stroke volume, stroke volume measured at left ventricular outflow tract level; E, mitral E wave velocity; DTE, mitral E wave deceleration time; S', velocity of systolic longitudinal shortening; E/E', ratio between mitral E wave velocity and velocity of early longitudinal lengthening; ERO, mitral effective regurgitant orifice; RV, mitral regurgitant volume; RF, mitral regurgitant fraction; MR, mitral regurgitation; PAPs, systolic pulmonary artery pressure; Zva, global impedance; PP/SV, systemic pulse pressure divided by stroke volume.
24/273 (9%) patients. Mitral regurgitation was present in 54% (13/24) of these patients. Despite the modest size of the sample, ERO and RV were able to significantly characterize this subgroup of patients (OR 1.76 [95% CI 1.12–2.70], P = 0.01, and OR 1.85 [1.27–2.73], P = 0.002, respectively) vs. the rest of the cohort.

**Discussion**

The present study shows that, in patients with severely reduced AVA and preserved EF, the presence and severity of MR is a major determinant of low-flow condition. In addition, ERO and RV values can predict the presence of reduced flow independently of chamber volumes, systolic function, and trans-aortic gradient.

Generally, the expected pathophysiological consequence of volume overload, generated by MR, should be the LV enlargement. Therefore, the LV remodelling allows the heart to preserve a normal forward SV (i.e. as in the absence of the mitral regurgitation). However, it has been observed that AS patients with low-flow typically present small LV cavity size.2 Accordingly, in the present population, low-flow patients, despite the higher presence of MR and the larger ERO, are characterized by a nearly 10% lower end-diastolic volume compared with normal flow patients. This situation could be interpreted as an unforeseen LV reaction in the context of volume overload. The ventricle seems to pursue a different remodeling pattern, led by the AS, and consequently it showed a lower SV than expected.

Of note, these patients have been characterized as having a higher relative wall thickness and increased deposition of fibrotic tissue at the sub-endocardial level.13 The result is an increased LV stiffness and a reduced preload reserve.14 The superimposition of an even relatively mild volume overload due to MR leads to further reduction of LVOT SV because of the unavailable preload reserve of the left ventricle. Consequently, the presence of mitral valve incompetency might have a noticeable haemodynamic impact in these patients.

The mutual relationship between AS and MR, the context of low SV, can be even more complex. Indeed, another consequence of sub-endocardial fibrosis is the impairment of sub-endocardial LV function that determined a reduced longitudinal contraction.15 We have recently shown that a reduced longitudinal velocity of contraction due to fibrosis is associated with a less efficient mitral valve closure.
because of reduced valve closing force. In fact, we demonstrated an inverse association between LV longitudinal velocity and RV independence of LV volume and EF. An element of additional complexity is the presence of atrial fibrillation, which may both reduce cardiac stroke volume, and promote MR through left atrial enlargement. Moreover, while the mitral valve overload leads the ventricle to operate at the extremity of the Starling curve with consequently high diastolic LV filling pressure, the systolic effective SV is reduced because of the communication with the low-impedance left atrial chamber. This lead to the disadvantage haemodynamic combination of increased filling pressure and decreased cardiac output. This might explain why the coexistence of MR in patients with AS is a marker of worse haemodynamic profile and poorer clinical outcome. The low-flow AS subgroup has many similarities with patients with heart failure and preserved EF (HFpEF). A similar phenotype and LV remodeling have been highlighted between these two conditions.

Furthermore, increased ventricular and aortic stiffness are also common to both disease entities. A certain degree of MR is frequently observed in HFpEF. As is the case for AS, it has been shown that MR is an important and independent haemodynamic determinant of pulmonary artery pressure in HFpEF. It might be hypothesized that similarly to low-flow AS patients, the superimposition of a relatively mild volume overload might represent a mechanistic link associated with the progression of the disease.

The main limitation of the study is the low prevalence of patients with low-flow state. This last aspect did not allow us to stratify patients further and detect the independent predictors of the so-called ‘paradoxical low-flow low-gradient’ subgroup of patients (characterized by the presence of both low-flow and low-gradient despite the preserved EF). Also, the quantification of tricuspid valve regurgitation was not performed in all the patients, and therefore it could not be included in the model. In addition, we do not have to follow up data, to confirm the worse outcome of patients with low-flow aortic valve stenosis and to eventually identify a prognostic role for MR in this context. However, this study could be the basis for a larger longitudinal study that includes follow-up and outcome of the patients. Lastly, although we provide a pathophysiological explanation of the link between MR and low flow, based on our data and the evidences in literature, we cannot describe the entire chain of phenomena with the echocardiographic quantitative data only.

Conclusion

In this series of patients with severe AS as documented by low-indexed AVA, the presence and quantity of mitral volume overload are main determinants of low-flow pattern.

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References