Original research

Proof of concept study on coronary microvascular function in low flow low gradient aortic stenosis

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ABSTRACT

Objectives We hypothesised that low flow low gradient aortic stenosis (LFLGAS) is associated with more severe coronary microvascular dysfunction (CMD) compared with normal-flow high-gradient aortic stenosis (NFHGAS) and that CMD is related to reduced cardiac performance.

Methods Invasive CMD assessment was performed in 41 consecutive patients with isolated severe aortic stenosis with unobstructed coronary arteries undergoing transcatheter aortic valve implantation (TAVI). The index of microcirculatory resistance (IMR), resistive reserve ratio (RRR) and coronary flow reserve (CFR) were measured in the left anterior descending artery before and after TAVI. Speckle tracking echocardiography was performed to assess cardiac function at baseline and repeated at 6 months.

Results IMR was significantly higher in patients with LFLGAS compared with patients with NFHGAS (24.1 (14.6 to 39.1) vs 12.8 (8.6 to 19.2), p=0.002), while RRR was significantly lower (1.4 (1.1 to 2.1) vs 2.6 (1.5 to 3.3), p=0.020). No significant differences were observed in CFR between the two groups. High IMR was associated with low stroke volume index, low cardiac output and reduced peak atrial longitudinal strain (PALS). TAVI determined no significant variation in microvascular function (IMR: 16.0 (10.4 to 26.1) vs 16.6 (10.2 to 25.6), p=0.403) and in PALS (15.9 (9.9 to 26.5) vs 20.1 (12.3 to 26.7), p=0.222). Conversely, left ventricular (LV) global longitudinal strain increased after TAVI (−13.2 (8.4 to 16.6) vs −15.1 (9.4 to 17.8), p=0.047). In LFLGAS, LV systolic function recovered after TAVI in patients with preserved microvascular function but not in patients with CMD.

Conclusions CMD is more severe in patients with LFLGAS compared with NFHGAS and is associated with low-flow state, left atrial dysfunction and reduced cardiac performance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Coronary microvascular dysfunction was observed in aortic stenosis using both invasive and non-invasive coronary physiology assessment. However, little is known about coronary microvascular function of patients with low flow low gradient aortic stenosis.

WHAT THIS STUDY ADDS

⇒ Patients with low flow low gradient aortic stenosis showed higher index of microcirculatory resistance and lower resistive reserve ratio and impaired measures of cardiac performance at the advanced echocardiographic imaging compared with normal flow high gradient aortic stenosis. The ventricular unloading by transcatheter aortic valve implantation acutely affected the aortic haemodynamic and the left ventricular longitudinal systolic function but had little impact on coronary microvascular function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The assessment of microvascular function may potentially refine the evaluation of disease severity by identifying patients with initial coronary microvascular dysfunction that may benefit from early intervention.

INTRODUCTION

The pathophysiology of low flow low gradient aortic stenosis (LFLGAS) and, especially, the mechanisms of left ventricular dysfunction are not clearly explained yet[1] . Compared with normal-flow high-gradient aortic stenosis (NFHGAS), patients with LFLGAS show higher grades and more extensive myocardial fibrosis at the cardiac magnetic resonance.[2 3] Myocardial fibrosis, among others (ie, valve stenosis and left ventricular hypertrophy), represents a key determinant of impaired myocardial perfusion reserve in AS[4]

Based on these data, we hypothesised that coronary microvascular dysfunction (CMD) might be more prominent in patients with LFLGAS compared with NFHGAS. If confirmed, CMD may represent a key determinant of left ventricular dysfunction in the pathophysiology of LFLGAS. In this proof-of-concept study, we sought to perform a prospective invasive assessment of coronary microcirculation in a consecutive cohort of patients with LFLGAS undergoing transcatheter aortic valve implantation (TAVI) and to compare it with patients with NFHGAS. Moreover, we aimed to assess the possible acute impact of TAVI on coronary microvascular function in the two groups and

Table 1 Clinical, echocardiographic and coronary physiology data in patients with NFHGAS and LFLGAS

	All patients	NFHGAS	LFLGAS	P value
Clinical data				
No. (%)	41 (100)	20 (48.8)	21 (51.2)	
Female	18 (43.9)	12 (60.0)	6 (28.6)	0.062
Age (years)	82.0 (79.0–86.0)	81.0 (79.0–85.5)	84.0 (79.0–87.5)	0.255
BMI	24.7 (23.3–29.9)	24.3 (23.1–31.9)	24.8 (23.4–28.2)	0.735
Hypertension	34 (82.9)	16 (80)	18 (85.7)	0.697
Dyslipidaemia	26 (63.4)	14 (70.0)	12 (57.1)	0.520
Smoker (current or former)	10 (24.4))	7 (35.0)	3 (14.3)	0.226
Diabetes	15 (36.6)	8 (40.0)	7 (33.3)	0.340
eGFR (Cockcroft Gault, mL/min)	55.0 (41.3–72.5)	63.5 (48.7–98.0)	45.0 (39.5–62.0)	**0.029**
History of atrial fibrillation	16 (39.1)	4 (20.0)	12 (57.1)	**0.026**
Peripheral vascular disease	18 (43.9)	9 (45)	9 (42.9)	1.000
Echocardiographic data				
Peak transvalvular velocity (m/s)	3.9 (3.2–4.3)	4.3 (4.0–4.5)	3.2 (2.9–3.8)	**<0.001**
Mean gradient	37.0 (25.0–43.8)	43.0 (40.2–49.5)	27.0 (19.5–33.5)	**<0.001**
AVA (cm^2)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.8 (0.6–0.9)	0.276
Ejection fraction (%)	60 (37.1–65.7)	65.2 (60.5–67.5)	38.0 (29.8–55.5)	**<0.001**
Stroke volume index (mL/m^2)	34.4 (29.6–40.2)	40.2 (36.9–47.6)	29.9 (25.0–33.3)	**<0.001**
LV end-diastolic volume index (mL/m^2)	66.7 (50.8–79.8)	63.0 (50.7–68.7)	75.0 (50.3–97.1)	0.078
GLS (%)	13.2 (8.4–16.6)	16.5 (14.0–20.3)	8.5 (7.0–12.5)	**<0.001**
PALS (%)	15.9 (9.9–26.5)	26.7 (21.0–28.8)	11.2 (5.9–15.4)	**<0.001**
Left ventricular mass index (g/m^2)	116.1	113.7 (90.4–117.2)	118.0 (104.0–160.5)	0.053
E/E'	12.5 (9.4–15.5)	13.6 (10.6–15.0)	12.0 (6.1–17.0)	0.405
LAV index (mL/m^2)	43.0 (36.5–56.0)	38.5 (33.0–49.2)	55.0 (41.0–62.5)	**0.008**
PAPs	38.0 (34.0–44.5)	38.0 (31.0–40.7)	42.0 (35.0–52.0)	0.266
Procedural data				
Balloon expandable valve	26 (63.4)	12 (60.0)	14 (66.7)	0.751
Valve size (mm)	26 (23.5–29.0)	26.0 (23.0–29.0)	29.0 (26.0–29.0	0.135
Contrast medium dose (mL)	140.0	155.0 (122.50–170.0)	130.0	0.394
Total procedural time (min)	85.0 (68.0–103.0)	87.0 (69.7–102.0)	84.0 (67.0–109.5)	0.725
Haemodynamic assessment pre-TAVI				
IMR (units)	16.0 (10.4–26.1)	12.8 (8.6–19.2)	24.1 (14.6–39.1)	**0.002**
RRR	2.0 (1.2–2.9)	2.6 (1.5–3.3)	1.4 (1.1–2.1)	**0.020**
CFR	1.6 (1.1–2-2)	2.0 (1.1–2.4)	1.5 (1.0–2.0)	0.347
FFR	0.92 (0.88–0.96)	0.91 (0.88–0.96)	0.93 (0.89–0.96)	0.927
PD/PA	0.96 (0.92–0.97)	0.96 (0.93–0.98)	0.96 (0.89–0.97)	0.695
Rest mean transit time (s)	0.335 (0.241–0.579)	0.305 (0.221–0.452)	0.433 (0.263–0.718)	0.091
Hyperaemic mean transit time (s)	0.221 (0.147–0.361)	0.207 (0.104–0.238)	0.314 (0.183–0.389)	**0.009**
LVEDP	10.0 (5.0–19.0)	7.5 (5.0–10.5)	15.0 (6.5–20.0)	0.072

Significant diffences between groups (p-value <0.05) are highlighted in bold.
AVA, aortic valve area; BMI, body mass index; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; GLS, global longitudinal strain; IMR, index of microcirculatory resistance; LAV, left atrial volume; LFLGAS, low flow low gradient aortic stenosis; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; NFHGAS, normal flow high gradient aortic stenosis; No, number of patients; PALS, peak atrial longitudinal strain; PAPs, systolic pulmonary artery pressure; PD/PA, resting distal-to-aortic pressure ratio; RRR, resistive reserve ratio; TAVI, transcatheter aortic valve implantation.

the interactions between abnormalities in microvascular function and measures of cardiac performance at advanced echocardiographic imaging.

METHODS

Study design and population

This is a prospective, single-centre, observational, case-control study designed to assess differences in microvascular function in patients with LFLGAS and patients with NFHGAS. Between 1 January 2021 and 31 December 2021, 21 consecutive patients with LFLGAS and no exclusion criteria were considered for enrolment and underwent transthoracic echocardiography with left ventricular and atrial strain assessment and invasive assessment of coronary microcirculation if no exclusion criteria were met. Twenty consecutive patients with NFHGAS were enrolled and served as unmatched controls.

Exclusion criteria were: (1) unwilling or unable to provide written informed consent; (2) previous coronary artery bypass graft; (3) significant angiographic stenosis (> 50%) on the left anterior descending; (4) previous anterior myocardial infarction; (5) severe chronic kidney disease; (6) concomitant severe aortic or mitral regurgitation; (7) history of infiltrative myocardial disease. This study was approved by the Institutional Review Board of the University of Verona (1701 CESC), and it was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The

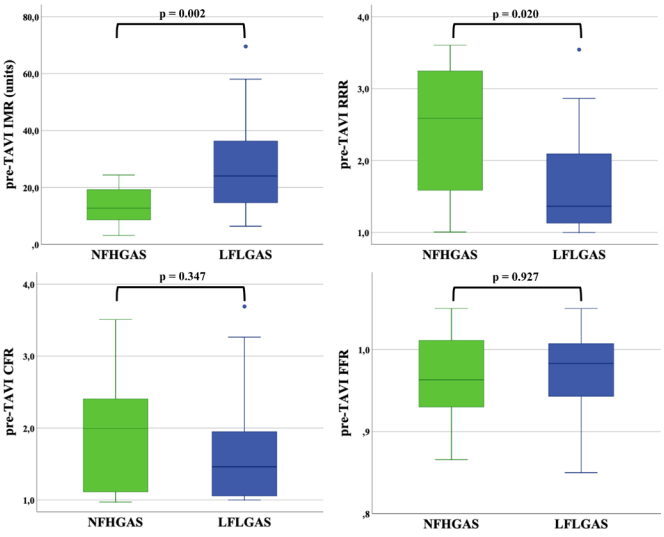


Figure 1 Coronary microvascular assessment in patients with NFHGAS and LFLGAS. Box plots represent median values with IQR of invasive indices of coronary physiology including IMR, RRR, CFR and RRR in patients with NFHGAS and in patients with LFLGAS. CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LFLGAS, low flow low gradient aortic stenosis; NFHGAS, normal flow high gradient aortic stenosis; RRR, resistive reserve ratio; TAVI, transcatheter aortic valve implantation.

primary endpoint was the difference in the index of microcirculatory resistance (IMR) between LFLGAS and NFHGAS. The secondary endpoints were: (1) correlation between measures of coronary microvascular function and non-invasive measures of cardiac performance; (2) differences in coronary microvascular assessment among different phenotypes of AS, including classical LFLGAS (cLFLGAS), paradoxical LFLGAS (pLFLGAS) and NFHGAS and (3) variations of coronary microvascular assessment and speckle tracking echocardiography measures before and after TAVI.

Aortic stenosis assessment

AS was defined according to the latest international guidelines.[5]

NFHGAS were defined as peak transvalvular velocity >4 m/s, transvalvular mean gradient >40 mm Hg and aortic valve area <1 cm^2 in normal flow state (left ventricular ejection fraction (LVEF) >50% and stroke volume indexed >35 mL/m^2). LFLGAS were defined as aortic valve area <1 cm^2 but mean gradient <40 mm Hg and peak transvalvular velocity <4 m/s in a low flow state (stroke volume index <35 mL/m^2). Patients with LFLGAS were further categorised into cLFLGAS (LVEF<50%), and pLFLGAS (LVEF>50%). In all patients with LFLGAS, severity was confirmed with low dose dobutamine stress echocardiography and/or with multidetector cardiac tomography as appropriate.[6]

Conventional and speckle tracking 2D echocardiography

Transthoracic echocardiography was performed during the hospital admission for TAVI and repeated at 6 months in all cases using commercially available ultrasound systems (Epiq 7C, Philips). Data were saved digitally and subsequently analysed offline using the TomTec software by two independent expert operators (PS, GB) blinded to the data on invasive microvascular assessment. Classic echocardiographic parameters were evaluated[7] and 2D speckle tracking analysis was performed offline with TomTec Autostrain software as reported in online supplemental methods.[8–10]

TAVI and coronary angiography

All patients underwent TAVI under conscious sedation and local anaesthesia with transfemoral access. Decisions about the technical aspects of TAVI procedures were all left to the operator's discretion. Coronary angiography was performed in all the patients to exclude the presence of significant epicardial coronary artery disease (coronary stenosis>50%), using radial or femoral arterial access with 6F guiding catheters as per standard practice.

Invasive assessment of coronary microvascular function

After careful equalisation of distal pressure and aortic pressure at the tip of the guiding catheter, standard pressure and temperature-monitoring guidewire (Abbott, Santa Clara, California, USA) was advanced in the distal segment of the left anterior descending. Coronary flow velocity was estimated using thermodilution to derive mean transit time and analysed with the Coroflow software (Coroventis, Uppsala, Sweden). Maximal hyperaemia was induced with intravenous adenosine infusion (140 mcg/kg/min). Fractional flow reserve was measured as per standard practice as the ratio between distal pressure and aortic pressure during steady-state hyperaemia.

IMR was defined as previously described[11] as:

$$\text{IMR} = \text{distal pressure (hyperaemia)} \times \text{mean transit time (hyperaemia)}$$

CFR was calculated using the equation:[12]

$$\text{CFR} = \frac{\text{mean transit time (resting)}}{\text{mean transit time (hyperaemia)}}$$

Resistive reserve ratio (RRR), a measure of coronary microvascular vasodilatory capacity, was calculated as previously described[13] using the following equation:

$$\text{RRR} = \frac{\text{distal pressure (resting)} * \text{mean transit time (resting)}}{\text{distal pressure (hyperaemia)} * \text{mean transit time (hyperaemia)}}$$

Clinically significant CMD was defined as IMR>25 Units as previously recommended[14] .

Statistical analysis

The normal distribution of the variables was tested using the Shapiro-Wilk test and histograms. Continuous variables were reported as median and IQR as appropriate. Categorical variables were reported as numbers and percentages. Continuous variables were compared with the Mann-Whitney U test or Kruskal-Wallis test as appropriate. Frequencies were compared with Fisher exact test. Wilcoxon test was used to evaluate variations of coronary physiology indices and echocardiographic parameters before and after TAVI and at follow-up. Linear regression analysis was used to assess the correlation between variables, and Spearman correlation coefficients were provided.

Logistic regression analysis was performed to identify clinical and echocardiographic determinants of CMD. Variables known to be associated with CMD in different clinical settings, including sex, diabetes and estimated glomerular filtration rate (eGFR) were included a priori in the multivariable model. Moreover, variables with p<0.10 at the univariable analysis were considered for inclusion in the final model. Area under the receiver-operating characteristic curve (AUC) were calculated and compared with the DeLong's method. The Hosmer-Lemeshow test was performed to assess the goodness of fit of the model. Multicollinearity was assessed using the variance inflation factor postestimation test. Akaike's information criterion and Bayesian information criterion were used to compare models.

Table 2 Clinical, echocardiographic data and coronary physiology assessment of patients with and without CMD

	IMR≤25 units	IMR>25 units	P value
Clinical data			
No. (%)	31 (75.6)	10 (24.4)	
Female	13 (41.9)	5 (50.0)	0.724
Age (years)	82.0 (79.0–86.0)	83.0 (77.7–88.0)	0.782
BMI	24.7 (23.3–29.7)	24.7 (21.2–30.4)	0.759
Hypertension	25 (80.6)	9 (90.0)	0.660
Dyslipidaemia	20 (64.5)	6 (60.0)	1.000
Smoker (current or former)	8 (25.9)	2 (20.0)	1.000
Diabetes	11 (35.5)	4 (40.0)	1.000
eGFR (Cockcroft Gault, mL/min)	56.0 (39.0–75.0)	47.5 (41.9–69.0)	0.554
History of atrial fibrillation	9 (29.1)	7 (70.0)	**0.007**
Peripheral vascular disease	14 (45.2)	4 (40.0)	1.000
Echocardiographic data			
Peak transvalvular velocity (m/s)	4.0 (3.8–4.3)	2.9 (2.8–3.5)	**<0.001**
Mean gradient	41.0 (32.0–45.0)	22.0 (16.5–30.7)	**<0.001**
AVA (cm^2)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	**0.024**
Ejection fraction (%)	62.0 (38.4–65.9)	53.0 (31.5–62.5)	0.364
Stroke volume index (mL/m^2)	36.7 (30.6–42.1)	31.0 (27.4–34.3)	**0.014**
LV end-diastolic volume index (mL/m^2)	68.0 (51.2–82.0)	62.0 (45.0–71.3)	0.318
GLS (%)	14.4 (8.4–19.4)	10.7 (7.2–12.9)	0.098
PALS (%)	21.0 (13.6–27.4)	9.0 (4.8–12.0)	**<0.001**
Left ventricular mass index (g/m^2)	115.8	117.0	0.706
E/E'	13.1 (7.9–15.5)	12.0 (10.6–17.0)	0.743
LAV index (mL/m^2)	40.0 (36.0–53.0)	59.0 (52.5–68.0)	**0.005**
PAPs	38.0 (33.5–45.0)	38.5 (33.5–44.5)	0.808
Haemodynamic assessment pre-TAVI			
IMR (units)	13.6 (8.9–19.2)	39.1 (31.7–60.9)	
RRR	2.1 (1.4–3.2)	1.2 (1.0–1.9)	**0.010**
CFR	1.7 (1.1–2.3)	1.4 (1.0–1.9)	0.202
FFR	0.90 (0.87–0.95)	0.95 (0.92–0.97)	**0.034**
PD/PA	0.95 (0.90–0.97)	0.96 (0.95.0.99)	**0.038**
LVEDP	10.0 (5.0–16.0)	15.0 (9.0–20.0)	0.166

AVA, aortic valve area; BMI, body mass index; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; GLS, global longitudinal strain; IMR, index of microcirculatory resistance; LAV, left atrial volume; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; No., number of patients; PALS, peak atrial longitudinal strain; PAPs, systolic pulmonary artery pressure; PD/PA, resting distal-to-aortic pressure ratio; RRR, resistive reserve ratio; TAVI, transcatheter aortic valve implantation.

Sample size calculation was based on previous measurements of IMR in AS[15] and on the hypothesis that patients with LFLGAS presented a clinically significant impairment of coronary microvascular function compared with patients with NFHGAS (expected mean IMR in the LFLGAS group=30 units, with a common expected SD of 10 units). To achieve 80.0% power and a significance level of 0.05 in the two-sided t-test in demonstrating a significant difference in IMR between the two groups, a sample of 40 patients was found to be necessary, consisting of 20 patients with LFLGAS and 20 patients with NFHGAS.

Statistical analysis was performed with Stata V.15.1 (Stata, College Station, Texas, USA) and with SPSS V.26 (IBM, Armonk, New York, USA). P<0.05 was considered significant.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of our research.

RESULTS

Study cohort

Forty-one patients (21 LFLGAS and 20 NFHGAS) were prospectively included in the study (online supplemental figure 1). Table 1 shows clinical, echocardiographic and procedural characteristics of the study cohort. Patients with LFLGAS showed similar age, sex distribution, presence of diabetes, dyslipidaemia and peripheral vascular disease compared with patients with NFHGAS. However, LFLGAS demonstrated a lower eGFR and more frequent history of atrial fibrillation compared with NFHGAS.

Differences in coronary microvascular function between LFLGAS and NFHGAS

IMR was significantly higher in patients with LFLGAS compared with patients with NFHGAS (24.1 (14.6 to 39.1) vs 12.8 (8.6 to 19.2), p=0.002; figure 1). Similarly, the vasodilatory microcirculatory capacity measured by RRR was significantly impaired in patients with LFLGAS (1.4 (1.1 to 2.1) vs 2.6 (1.5 to 3.3), p=0.020). Conversely, no significant differences were observed in CFR (1.5 (1.0 to 2.0) vs 2.0 (1.1 to 2.4), p=0.347) between the

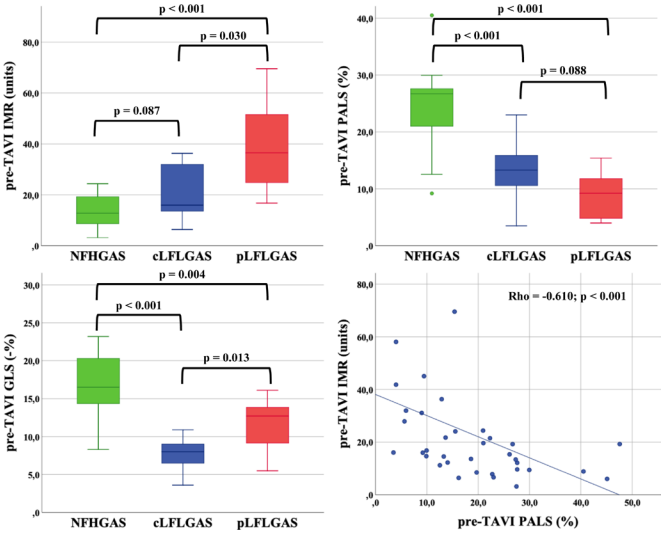
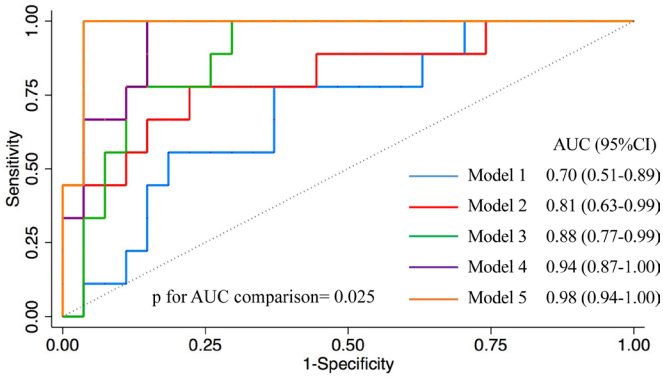


Figure 2 Index of microcirculatory resistance, PALS and GLS in patients with different AS phenotypes. Panel A shows differences in IMR between NFHGAS, cLFLGAS and pLFLGAS. Panel B shows differences in PALS between subgroups. Panel C shows differences in GLS between subgroups. Panel D shows the significant inverse correlation observed between IMR and PALS. cLFLGAS, classical low flow low gradient aortic stenosis; GLS, global longitudinal strain; IMR, index of microcirculatory resistance; NFHGAS, normal flow high gradient aortic stenosis; PALS, peak atrial longitudinal strain; pLFLGAS, paradoxical low flow low gradient aortic stenosis; TAVI, transcatheter aortic valve implantation.



Model 5*	OR (95%CI)	p-value
Sex male	0.05(0.01-8.19)	0.128
Diabetes	1.32(0.11-1.61)	0.134
eGFR	0.98(0.86-1.13)	0.861
History of AF	0.95(0.01-13.81)	0.354
PALS	0.20(0.03-1.20)	0.080
GLS	4.24(0.62-28.98)	0.141

*Hosmer-Lemeshow χ^2=6.37, p=0.606

Figure 3 Clinical and echocardiographic determinants of coronary microvascular dysfunction. The diagnostic accuracy of several logistic regression models including echocardiographic and/or clinical parameters were tested in predicting CMD. Model 1: sex, diabetes and eGFR. Model 2: sex, diabetes, eGFR and history of AF. Model 3: sex, diabetes, eGFR and history of AF and SVi. Model 4: sex, diabetes, eGFR and history of AF, SVi and PALS. Model 5: sex, diabetes, eGFR and history of AF, SVi, PALS and GLS. Model 5 demonstrated the best performance in predicting CMD, with an AUC of 0.98. AF, atrial fibrillation; AUC, area under the receiver-operating characteristic curve; CMD, coronary microvascular dysfunction; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; PALS, peak atrial longitudinal strain; SVi, stroke volume index.

groups. Other coronary physiology data are displayed in table 1. CMD was observed in 10/41 patients (24.4%) and was more frequently associated with LFLGAS compared with NFHGAS (47.6% vs 0%, p<0.001). The characteristics of patients stratified according to the presence of CMD are displayed in table 2.

Correlates of high IMR in aortic stenosis

Features of patients stratified according to the median value of IMR are presented in online supplemental table 1. High IMR values were associated with lower stroke volume index (32.3 (29.1 to 36.0) vs 38.2 (34.0 to 43.7), p=0.03). At regression analysis, an inverse correlation was observed between IMR and cardiac output (rho=−0.517, p=0.001), cardiac index (rho=−0.411, p=0.008) and stroke volume index (rho=−0.427, p=0.005) (online supplemental figure 2).

Conversely, IMR was only modestly associated with the mean pressure aortic valve gradient (rho=−0.304, p=0.054). Notably, the mean gradient was significantly associated with IMR in the NFHGAS group (rho=0.632, p=0.003) but not in the LFLGAS (rho=−0.222, p=0.333). Similarly, high IMR was associated with the aortic valve area in the NFHGAS group (rho=−0.50, p=0.025) but not in patients with LFLGAS (rho=0.157, p=0.497). Interestingly, there was only a trend towards a linear correlation between IMR and LV end-diastolic pressure (rho=0.345, p=0.057) (online supplemental figure 3).

Invasive microcirculatory assessment and speckle tracking echocardiography measures of cardiac performance

High IMR was strongly associated with lower values of peak atrial longitudinal strain (PALS) (rho=−0.610, p=<0.001) (figure 2). Conversely, no linear association was observed between IMR and global longitudinal strain (GLS) (rho=−0.197, p=0.235). Patients with clinically significant CMD demonstrated lower values of PALS (9.0 (4.8 to 12.1) vs 21.0 (13.6 to 27.4), p<0.001) and a trend towards lower GLS compared with patients with no CMD (−10.7 (7.2 to 12.9) vs −14.4 (8.4 to 19.4), p=0.098). Cardiac performance measures and GLS were significantly reduced in LFLGAS compared with NFHGAS (table 1).

Clinical and echocardiographic determinants of CMD

Univariable logistic regression analysis of clinical and echocardiographic determinants of CMD is reported in online supplemental table 2. The multivariable model including sex, diabetes, eGFR, history of atrial fibrillation, stroke volume index, PALS and GLS showed the best diagnostic performance in predict the presence of CMD (AUC=0.98, 95% CI 0.94 to 1.00, p for AUC comparison=0.025; figure 3). PALS was the only variable with a trend towards an independent association with CMD (OR=0.20, 95% CI 0.03 to 1.20, p=0.080; figure 3).

Coronary microvascular function in paradoxical LFLGAS

Among the LFLGAS group, 8 (38.1%) patients were classified as pLFLGAS. This subgroup of patients presented significantly higher IMR values compared with patients with cLFLGAS (36.5 (23.3 to 54.8) vs 16.0 (12.9 to 32.5), p=0.03) and compared with patients with NFHGAS (36.5 (23.3 to 54.8) vs 12.8 (8.6 to 19.2), p<0.0001) (figure 2, table 3).

pLFLGAS showed lower GLS values compared with NFHGAS (−12.7 (8.8 to 14.1) vs −16.5 (14.0 to 20.3),

Table 3 Clinical, echocardiographic and coronary physiology data in patients with NFHGAS, cLFLGAS and pLFLGAS

	NFHGAS	cLFLGAS	pLFLGAS	P value
Clinical data				
No. (%)	20 (48.8)	13 (31.7)	8 (19.5)	
Female	12 (60.0)	2 (15.4)	4 (50.0)	**0.034**
Age (years)	81.0 (79.0–85.5)	82.0 (79.0–86.5)	84.5 (78.0–88.7)	0.468
BMI	24.3 (23.1–31.9)	24.8 (23.4–26.0)	25.2 (22.1–31.1)	0.881
Hypertension	16 (80)	11 (84.6)	7 (87.5)	1.000
Dyslipidaemia	14 (70.0)	8 (61.5)	4 (50.0)	0.582
Smoker (current or former)	7 (35.0)	2 (15.4)	1 (12.5)	0.765
Diabetes	8 (40.0)	5 (38.5)	2 (25.0)	0.398
eGFR (Cockcroft Gault; mL/min)	63.5 (48.7–98.0)	44.0 (39.0–52.5)	53.0 (41.2–57.0)	0.066
History of atrial fibrillation	4 (20.0)	5 (38.5)	7 (87.5)	**0.004**
Peripheral vascular disease	9 (45)	6 (46.2)	3 (37.5)	1.000
Echocardiographic data				
Peak transvalvular velocity (m/s)	4.3 (4.0–4.5)	3.2 (2.9–3.8)	3.3 (2.9–3.8)	**<0.001**
Mean gradient	43.0 (40.2–49.5)	23.0 (19.5–33.0)	27.0 (18.0–33.8)	**<0.001**
AVA (cm^2)	0.7 (0.6–0.8)	0.8 (0.6–0,.9)	0.7 (0.6–0.9)	0.542
Ejection fraction (%)	65.2 (60.5–67.5)	32.2 (25.1–37.2)	58.0 (53.5–68.4)	**<0.001**
Stroke volume index (mL/m^2)	40.2 (36.9–47.6)	29.4 (22.9–32.7)	31.3 (25.8–33.9)	**<0.001**
LV end-diastolic volume index (mL/m^2)	63.0 (50.7–68.7)	93.0 (71.8–109.6)	47.3 (45.0–63.5)	**<0.001**
GLS (%)	16.5 (14.0–20.3)	8.0 (6.0–9.5)	12.7 (8.8–14.1)	**<0.001**
PALS (%)	26.7 (21.0–28.8)	13.3 (9.9–16.2)	9.2 (4.4–12.7)	**<0.001**
Left ventricular mass index (g/m^2)	113.7 (90.4–117.2)	128.0 (115.5–187.5)	109.0 (100.1–126.5)	**0.034**
E/E'	13.6 (10.6–15.0)	12.0 (6.0–18.5)	11.5 (7.8–13.4)	0.570
LAV index (mL/m^2)	38.5 (33.0–49.2)	56.0 (41.0–62.5)	54.0 (32.2–71.7)	**0.029**
PAPs	38.0 (31.0–40.7)	45.0 (34.0–52.5)	39.5 (33.0–47.2)	0.448
Haemodynamic assessment pre-TAVI				
IMR (units)	12.8 (8.6–19.2)	16.0 (12.9–32.5)	36.5 (23.3–54.8)	**0.001**
RRR	2.6 (1.5–3.3)	1.6 (1.1–2.5)	1.3 (1.0–2.0)	**0.054**
CFR	2.0 (1.1–2.4)	1.1 (1.0–2.9)	1.6 (1.3–2.1)	0.559
FFR	0.91 (0.88–0.96)	0.90 (0.83–0.96)	0.94 (0.91–0.96)	0.492
PD/PA	0.96 (0.93–0.98)	0.94 (0.89–0.97)	0.96 (0.90–0.98)	0.664
LVEDP (mm Hg)	7.5 (5.0–10.5)	9.0 (5.0–18.5)	19 (15.0–22.0)	**0.023**

AVA, aortic valve area; BMI, body mass index; CFR, coronary flow reserve; cLFLGAS, classical low flow low gradient aortic stenosis; CMD, coronary microvascular dysfunction; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; GLS, global longitudinal strain; IMR, index of microcirculatory resistance; LAV, left atrial volume; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; NFHGAS, normal flow high gradient aortic stenosis; No., number of patients; PALS, peak atrial longitudinal strain; PAPs, systolic pulmonary artery pressure; PD/PA, resting distal-to-aortic pressure ratio; pLFLGAS, paradoxical low flow low gradient aortic stenosis; RRR, resistive reserve ratio; TAVI, transcatheter aortic valve implantation.

p=0.004) but higher GLS compared with cLFLGAS (−12.7 (8.8 to 14.1) vs −8.0 (6.0 to 9.5), p=0.013). On the other hand, pLFLGAS demonstrated a more severe impairment in PALS compared with NFHGAS (9.2 (4.4 to 12.7) vs 26.7 (21.0 to 28.8), p<0.0001) and a trend towards lower values compared with cLFLGAS (9.2 (4.4 to 12.7) vs 13.3 (9.9 to 16.2), p=0.08) (table 3).

Acute impact of TAVI on microcirculatory function and measures of cardiac performance

Overall, TAVI determined no significant variation in IMR (16.0 (10.4 to 26.1) vs 16.6 (10.2 to 25.6), p=0.403) (figure 4). Similarly, no significant variations in IMR were observed after TAVI in LFLGAS (24.1 (14.6 to 39.1) vs 20.0 (15.4 to 35.5), p=0.374) or NFHGAS (12.8 (8.6 to 19.2) vs 13.0 (6.2 to 18.2), p=0.899). Post-TAVI IMR was significantly higher in LFLGAS compared with NFHGAS (p=0.007). Similarly, no significant variations were observed in RRR (2.0 (1.2 to 2.9) vs 2.2 (1.4 to 3.1), p=0.489) and CFR (1.6 (1.1 to 2.2)] vs 1.8 (1.2 to 2.5), p=0.740) in the overall cohort and in the two subgroups (figure 4). In patients with CMD, IMR did not decrease significantly immediately after TAVI (39.1 (31.7 to 60.9) vs 35.5 (27.9 to 53.4), p=0.322).

Overall, GLS improved after TAVI (−13.2 (8.4 to 16.6) vs −15.1 (9.4 to 17.8), p=0.047). Conversely, PALS was not significantly influenced by TAVI (15.9 (9.9 to 26.5) vs 20.1 (12.3 to 26.7), p=0.222).

Variations of left ventricular and left atrial function at 6 months after TAVI

Overall, patients with LFLGAS exhibited a significant improvement in LVEF (38.0 (29.8 to 55.5) vs 54.0 (42.5 to 61.7), p=0.037), GLS (−8.5 (7.0 to 12.5) vs −13.0 (10.3 to 16.0), p<0.0001) and PALS (11.2 (5.9 to 15.4) vs 14.0 (10.5 to 21.8), p=0.018) at 6-month follow-up after TAVI. Notably, in patients with cLFLGAS, the LV systolic function recovered significantly in patients with preserved microvascular function (LVEF: 33.0 (23.0 to 37.3) vs 51.5 (39.7 to 62.5), p=0.008) but not in patients with CMD (LVEF: 30.9 (27.0 to 36.5) vs 39.5 (30.2 to 54.0), p=0.375) (online supplemental figure 4).

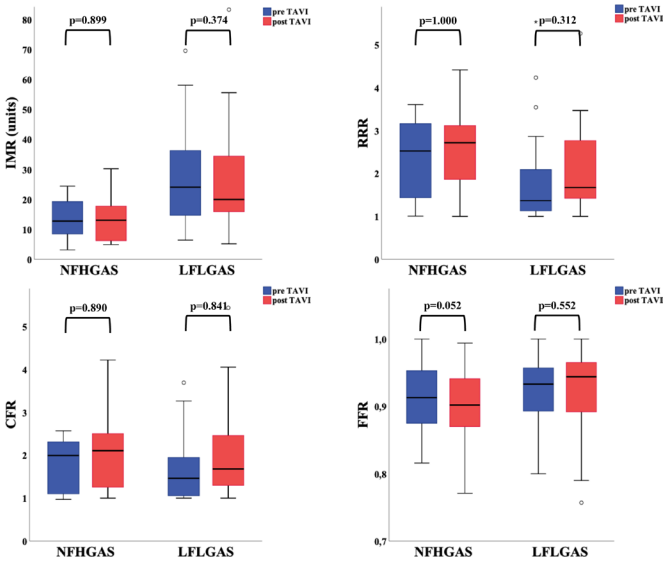


Figure 4 Variations of coronary physiology indices before and after TAVI. No significant variations were observed in IMR, RRR, CFR and FFR in the overall cohort after TAVI. Box plots represent median values with IQR. CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LFLGAS, low flow low gradient aortic stenosis; NFHGAS, normal flow high gradient aortic stenosis; RRR, resistive reserve ratio; TAVI, transcatheter aortic valve implantation.

DISCUSSION

The main findings are as follows:

1. patients with LFLGAS showed higher IMR and lower RRR compared with patients with NFHGAS, suggesting a more severe impairment of coronary microcirculatory function;
2. the most important non-invasive correlates of coronary microcirculatory impairment were cardiac output and left atrial function whereas AS severity measures were not;
3. the ventricular unloading by TAVI acutely affected the aortic haemodynamic and some measures of ventricular performance (ie, GLS) but had little impact on coronary microcirculation or atrial function.

Importantly, in this study, we excluded patients with concomitant coronary artery disease or a history of myocardial infarction that may have an impact on the assessment of coronary microcirculation.[16] Notably, CFR was reduced in all patients with AS but not statistically different between LFLGAS and NFHGAS, whereas a significant difference was detected in exclusively microcirculatory markers (ie, IMR and RRR), suggesting that the principal component of myocardial blood flow alteration in LFLGAS was primarily microcirculatory.

In this study, the combined invasive assessment of CMD and non-invasive advanced echocardiographic imaging provided a unique opportunity to link the microcirculatory function with cardiac performance in patients with AS. Our findings allowed to improve the featuring of patients with AS by identifying three main phenotypes (figure 5). Patients presenting with NFHGAS typically show preserved LVEF, normal or mildly impaired GLS and infrequent atrial dysfunction. These patients tend to display exhausted CFR but preserved microvascular function or only mildly augmented IMR. In this setting, CFR exhaustion is related to the physiological left ventricular adaptive response to the increased afterload, with left ventricular hypertrophy and augmented resting myocardial blood flow. Interestingly, IMR was associated with the left ventricular-aortic gradient only in

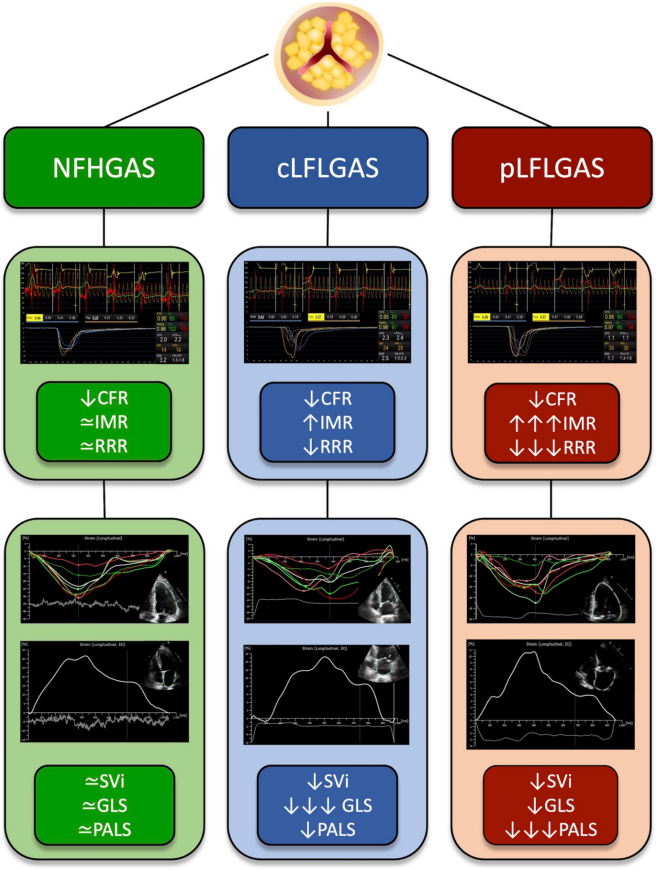


Figure 5 Microcirculatory and echocardiographic featuring of patients with aortic stenosis. Combining invasive coronary microcirculatory assessment and advanced echocardiographic measures of cardiac function three main AS phenotypes were delineated. *Presentation with NFHGAS*: with preserved LV function, normal or mildly impaired GLS, infrequent atrial dysfunction, reduced CFR but normal or only mildly augmented IMR. *Presentation with cLFLGAS:* with overt LV dysfunction, severe depression of GLS, concomitant moderate atrial dysfunction, reduced CFR and intermediate values of IMR. *Presentation with pLFLGAS*: with preserved LVEF, depressed GLS, severe atrial dysfunction and CMD with reduced CFR, high IMR and low RRR. CFR, coronary flow reserve; cLFLGAS, classical low flow low gradient aortic stenosis; GLS, global longitudinal strain; IMR, index of microcirculatory resistance; pLFLGAS, paradoxical low flow low gradient aortic stenosis; NFHGAS, normal flow high gradient aortic stenosis; PALS, peak atrial longitudinal strain; RRR, resistive reserve ratio; SVi, stroke vol index.

NFHGAS but not in LFLGAS, suggesting a different aetiology of CMD in the latter.

Patients presenting with cLFLGAS display overt left ventricular dysfunction, severe depression of GLS and concomitant moderate atrial dysfunction. These patients show intermediate values of IMR, with severe impairment of CFR and vasodilatory capacity. The cardiac performance and microvascular abnormalities observed in isolated cLFLGAS likely represent the end-stage of the natural history of patients with NFHGAS. Therefore, in these patients, CMD can be seen as a marker of disease severity. Importantly, CMD was associated with myocardial fibrosis in previous studies in patients with cLFLGAS[2] and fibrosis is likely to contribute to left ventricular adverse remodelling exacerbating subendocardial ischaemia.[17 18]

Patients presenting with pLFLGAS show preserved LVEF but depressed left ventricular systolic longitudinal function and

severe atrial dysfunction. These patients often present CMD with high IMR and low RRR. The low flow state in pLFLGAS is generally related to pronounced left ventricular concentric remodelling with restrictive physiology and impaired left ventricular diastolic filling.[6] Consistently, the LV end-diastolic pressure was remarkably augmented in this subgroup (table 3). In this AS phenotype, CMD may be an important determinant of left ventricular maladaptive response to the increased afterload and disease progression. Interestingly, extended subendocardial fibrosis was associated with pLFLGAS phenotype.[17 18]

PALS was previously associated with CMD in heart failure with preserved LVEF[19] and with left ventricular fibrosis evaluated at endomyocardial biopsy in AS.[20] In our study, patients with CMD showed reduced values of PALS and a trend towards reduced GLS. These findings were particularly consistent in LFLGAS.

According to our findings, PALS and high IMR may be markers of chronic adverse cardiac remodelling and reduced performance, leading to a chronic low flow state. Importantly, these parameters were not influenced acutely by the TAVI procedure. Conversely, GLS increased significantly in the overall cohort after TAVI. This may represent the effect of the acute left ventricular unloading induced by TAVI. Similarly, RRR, a measure of microvascular vasodilatory capacity, showed a trend towards improvement after TAVI, especially in patients with LFLGAS, in response to the decreased extravascular compression generated by the left ventricular unloading. Interestingly, in LFLGAS, we observed an overall improvement of cardiac performance measures at 6 months after TAVI. However, a clinically relevant recovery of LV systolic function was found only in patients with preserved coronary microvascular function and not in those with CMD at baseline. This hypothesis-generating finding requires further investigation. Nevertheless, if confirmed, coronary microvascular status may represent an important determinant of LV function recovery after aortic valve intervention.

A significant proportion of patients continue to experience residual morbidity and mortality after valve replacement.[21–24] LFLGAS is a high-risk subset of patients with worse clinical outcome after aortic valve replacement compared with NFHGAS. The severity of the disease often remains undetected using conventional tools until left ventricular adverse remodelling is overt and a chronic low flow state is established. Moreover, factors used to define the timing of aortic valve replacement are insensitive to the determinants of left ventricular dysfunction and interstitial replacement fibrosis, which ultimately impact postintervention outcomes. Therefore, there is an unmet need for the identification of more sensitive markers of disease progression and refinement of risk assessment strategies in patients with AS. The assessment of microvascular function may potentially refine the diagnosis of disease severity by identifying patients with initial CMD that may benefit from early intervention. This hypothesis requires further dedicated investigations.

Limitations

This was a single-centre observational study with a relatively small sample size designed to detect differences in IMR between NFHGAS and LFLGAS. Therefore, it was not powered to assess differences between cLFLGAS and pLFLGAS. Advanced imaging modalities to assess the presence of interstitial or focal fibrosis were not available. Therefore, the correlation between fibrosis and invasively detected CMD could not be confirmed by our analysis and only be inferred based on previous reports.[20] Given these limitations, our results should be considered hypothesis-generating and require further dedicated studies to confirm the clinical significance of CMD in LFLGAS.

CONCLUSION

LFLGAS is associated with impaired coronary microvascular function compared with NFHGAS. Combined invasive assessment of microvascular function and advanced non-invasive imaging contributed to defining different AS phenotypes. CMD was associated with low-flow state, left atrial dysfunction and reduced cardiac performance in patients with aortic stenosis.

Contributors All authors have contributed to conception and design or analysis and interpretation of data, or both, to drafting of the manuscript or revising it critically for important intellectual content and to final approval of the manuscript submitted. RS acts as guarantor of the study, accepting full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institutional Review Board of the University of Verona (1701 CESC). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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SUPPLEMENTARY MATERIAL

Proof of concept study on coronary microvascular function in low flow low gradient aortic stenosis

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Supplementary Material

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Supplementary Methods

Left ventricular mass was calculated with Teichholz formula acquiring left ventricular septal, posterior wall widths, and left ventricular end-diastolic diameter in parasternal long axis view. Simpson's biplane method was used to assess LV diastolic and systolic volumes, LVEF and left atrial volume in apical 4-chamber and 2-chamber views. Diastolic function was determined by measuring E/A ratio, E/E' ratio, deceleration time, left atrial volume and maximum velocity of tricuspidalic regurgitation. Right chambers were examined with tricuspidalic annular plane systolic excursion, S' velocity at tissue doppler imaging and systolic pulmonary arterial pressure. Valve function was assessed with color doppler, continuous-wave Doppler and pulsed wave Doppler in all the appropriate projections as previously described. Particularly, the severity of AS was evaluated by measuring peak transvalvular velocity and transvalvular mean gradient and peak gradient with continuous-wave Doppler on the aortic valve in the apical 5 chamber view and in the right parasternal view when appropriate, calculating the aortic valve area applying the continuity equation and measuring left ventricular outflow tract on a zoomed parasternal long axis view. Stroke volume index was calculated to determine flow state with pulsed wave Doppler on left ventricular outflow tract in apical 5 chamber view.

2D speckle tracking advanced analysis was performed offline with TomTec Autostrain® software for obtaining left ventricular global longitudinal strain (GLS) and peak atrial longitudinal strain (PALS). GLS was measured in 3 acoustic windows (apical 4-chamber, 2-chamber and 3-chamber) and PALS was measured in 2 acoustic windows (apical 4-chamber and 2-chamber). Manual editing of the automated region of interest and of tracking cardiac cycle landmarks was applied when the quality of automatic analysis was suboptimal. Patients with poor acoustic windows were excluded. Transthoracic echocardiography with GLS and PALS assessment was repeated the day after TAVI and at 6 months follow-up in all patients.

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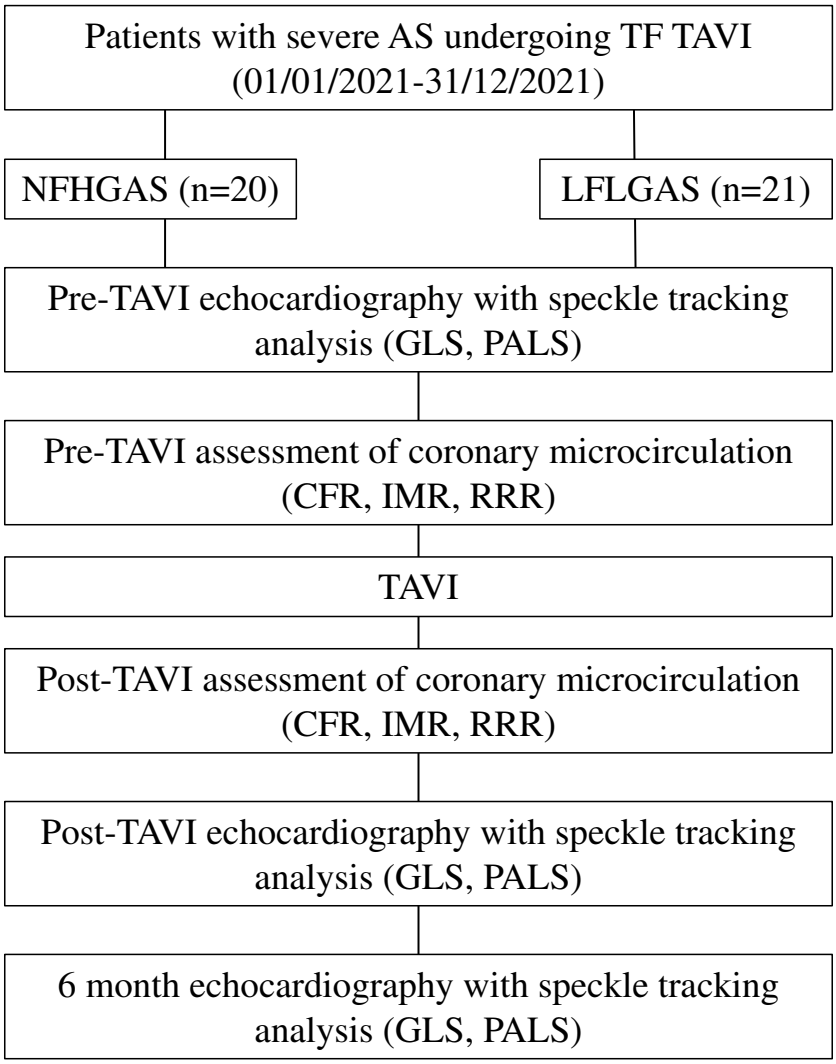
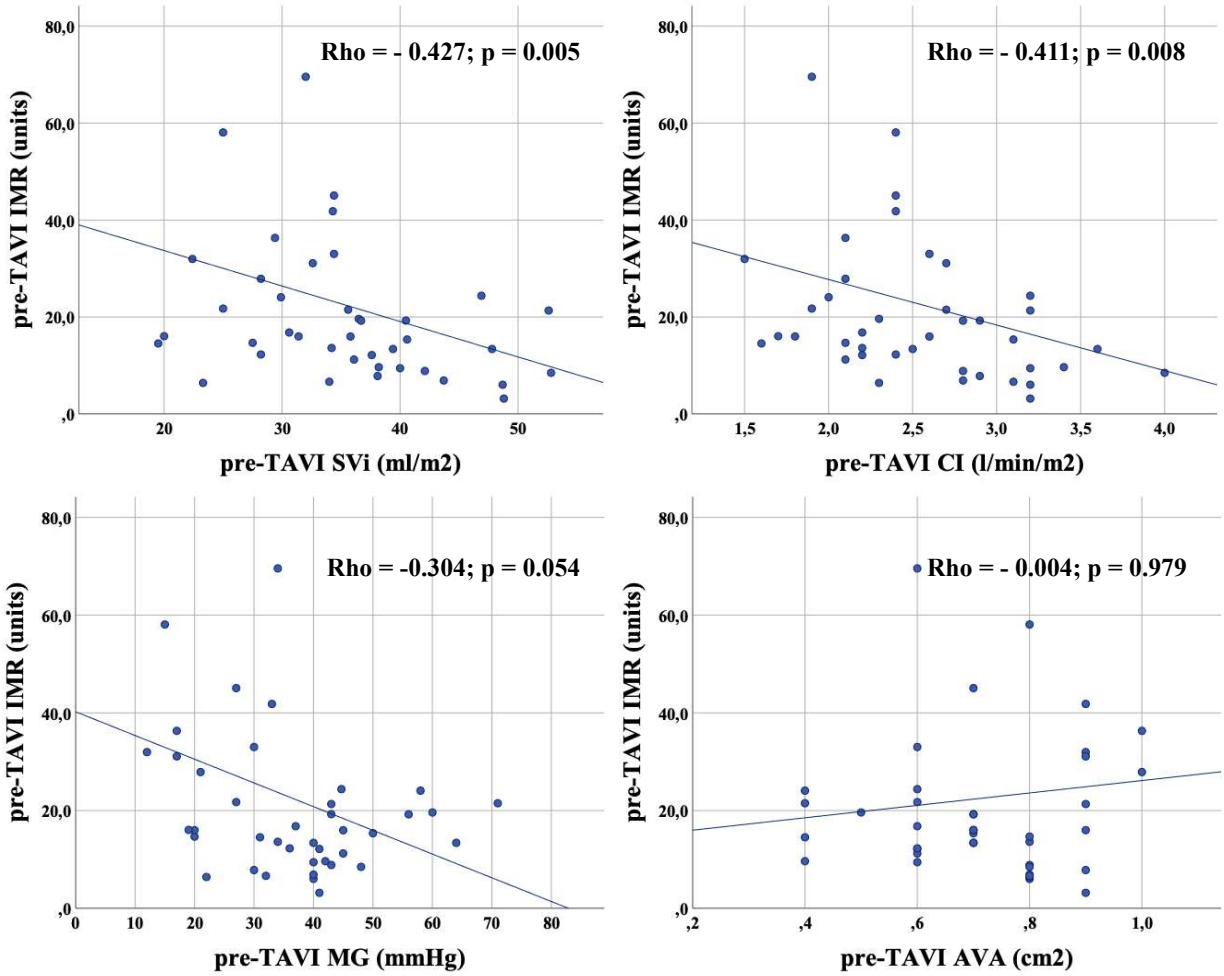


Supplementary Figure 1

Study flow chart

*AR=aortic regurgitation; AS= aortic stenosis; CABG=coronary artery bypass graft; CAD=coronary artery disease; CFR=coronary flow reserve; CKD=chronic kidney disease; GLS=global longitudinal strain; IMR=index of microcirculatory resistance; LFLGAS=low flow low gradient aortic stenosis; MI=myocardial infarction; MR=mitral regurgitation; NFHGAS=normal flow high gradient aortic stenosis; PALS=peak atrial longitudinal strain; RRR=resistive reserve

ratio; SAVR=surgical aortic valve replacement; TAVI=transcatheter aortic valve implantation; TF=transfemoral;



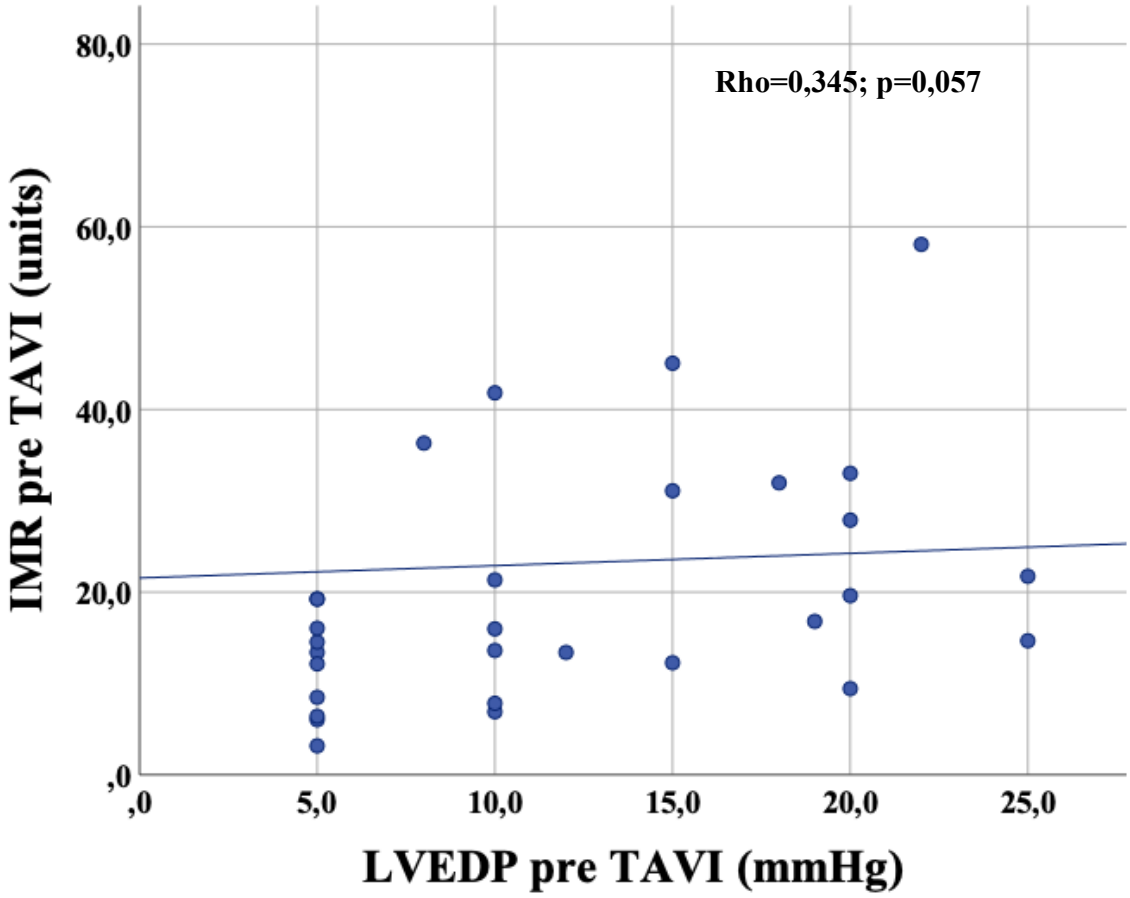
Supplementary Figure 2

Correlation between IMR and measures of cardiac function and AS severity

Panels A and B show a significant correlation between IMR and stroke volume index (SVi) and cardiac index respectively. Panels C and D show the correlation between IMR and MG and AVA.

*AVA=aortic valve area; CI=cardiac index; IMR=index of microcirculatory resistance; MG=mean gradient; SVi=stroke volume index; TAVI=transcatheter aortic valve implantation.

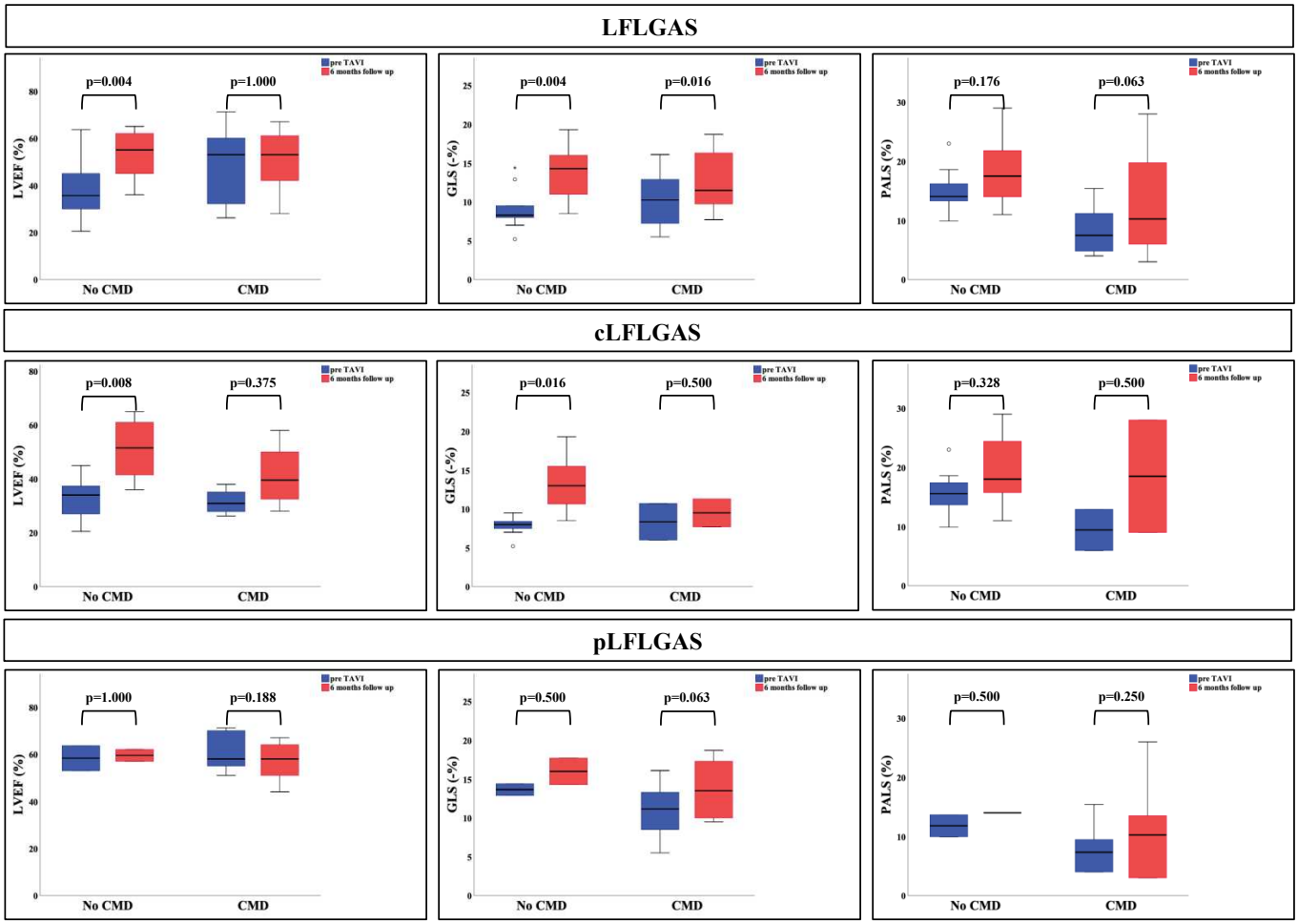
Supplementary Figure 3



Correlation between IMR and LVEDP

This figure shows only a trend towards a linear correlation between IMR and LV end-diastolic pressure.

*IMR=index of microcirculatory resistance; LVEDP=left ventricular end-diastolic pressure; TAVI=transcatheter aortic valve implantation.



Supplementary Figure 4

Variation of left ventricular and left atrial function in LFLGAS at 6 months follow-up

LVEF improved in patients with LFLGAS with preserved coronary microvascular function but not in patients with CMD. As expected, the LVEF recovery was consistent in patients with cLFLGAS and low IMR. Conversely, non-significant variations were observed in LVEF at 6 months in the subgroup of pLFLGAS.

The longitudinal systolic LV function expressed by GLS increased significantly at 6 months in LFLGAS in patients with and without CMD. However, in patients with cLFLGAS, a significant improvement in GLS was evident only in patients with low IMR.

Overall, PALS improved significantly at 6 months after TAVI. However, no significant variations were observed in the subgroups with or without CMD.

Box plots represent median values with interquartile range.

*CMD=coronary microvascular dysfunction; GLS=global longitudinal strain; IMR=index of microcirculatory resistance; cLFLGAS=classical low flow low gradient aortic stenosis; pLFLGAS= paradoxical low flow low gradient aortic stenosis; LFLGAS= low flow low gradient aortic stenosis; LVEF=left ventricular ejection fraction; PALS= peak atrial longitudinal strain; TAVI=transcatheter aortic valve implantation.

Supplementary Table 1 Clinical, echocardiographic data and coronary physiology assessment of patients stratified according to median value of IMR

	IMR <16 Units	IMR ≥ 16 Units	p value
Clinical data			
No. (%)	19 (46.3)	22 (53.7)	
Female	7 (36.8)	11 (50.0)	0.531
Age (years)	82.0 (79.0-86.0)	82.0 (77.7-86.2)	0.953
BMI (kg/m2)	24.4 (23.0-29.7)	24.8 (23.5-30.4)	0.693
Hypertension	15 (78.9)	19 (86.4)	0.685
Dyslipidemia	10 (52.6)	16 (72.7)	0.211
Smoker (current or former)	6 (31.6)	4 (18.2)	0.271
Diabetes	7 (36.8)	8 (36.4)	1.000
eGFR (Cockcroft Gault, ml/min)	62.0 (45.0-76.0)	47.5 (38.2-65.7)	0.119
History of atrial fibrillation	4 (21.1)	12 (54.6)	**0.036**
Peripheral vascular disease	11 (57.9)	7 (31.8)	0.122
Echocardiographic data			
Peak transvalvular velocity (m/s)	4.0 (3.8-4.3)	3.6 (2.9-4.2)	0.074
Mean gradient (mmHg)	40.0 (32.0-43.0)	31.5 (19.7-44.8)	0.204
AVA (cm2)	0.8 (0.6-0.8)	0.7 (0.6-0.9)	0.869
Ejection fraction (%)	62.0 (35.0-65.9)	55.5 (38.3-65.6)	0.872
Stroke volume index (ml/m2)	38.2 (34.0-43.7)	32.3 (29.1-36.0)	**0.030**
LV end-diastolic volume index (ml/m2)	68.9 (62.0-92.2)	58.9 (47.5-79.4)	0.076
GLS (-%)	14.7 (8.5-20.2)	12.5 (8.3-16.1)	0.321
PALS (%)	23.0 (15.1-27.6)	11.2 (5.9-20.9)	**< 0.001**
Left ventricular mass index (g/m2)	114.0 (102.1-146.0)	118.0 (100.9-128.5)	0.703
E/E’	14.2 (9.1-18.8)	12.0 (9.3-14.2)	0.208
LAV index (ml/m2)	41.0 (36.0-50.0)	54.0 (36.7-62.2)	0.250
PAPs (mmHg)	37.5 (28.0-45.5)	38.0 (35.0-45.0)	0.404
Hemodynamic assessment pre-TAVI			
IMR (units)	9.6 (6.9-13.4)	24.2 (19.2-37.7)	**< 0.001**
RRR	2.8 (1.7-3.4)	1.3 (1.1-2.5)	**0.006**
CFR	1.8 (1.1-2.6)	1.5 (1.0-2.0)	0.106
FFR	0.90 (0.87-0.96)	0.93 (0.89-0.96)	0.267
PD/PA	0.95 (0.90-0.97)	0.96 (0.93.0.98)	0.340
LVEDP (mmHg)	7.5 (5.0-12.75)	15.0 (6.5-20.0)	0.161

AVA=aortic valve area; BMI=body mass index; CFR=coronary flow reserve; CMD=coronary microvascular dysfunction; eGFR=estimated glomerular filtration rate; FFR=fractional flow reserve; GLS=global longitudinal strain; IMR=index of microcirculatory resistance; LAV=left atrial volume; LV=left ventricular; LVEDP=left ventricular end diastolic pressure; No.=number of patients; PALS=peak atrial longitudinal strain; PAPs=systolic pulmonary artery pressure; PD/PA= resting distal-to-aortic pressure ratio; RRR=resistive reserve ratio; TAVI=transcatheter aortic valve implantation;

Supplementary Table 2. Determinants of CMD. Univariable logistic regression analysis

Variable	OR (95% CI)	p value
Age	1.03(0.88-1.20)	0.748
Sex	1.38(0.33-5.79)	0.656
BMI	0.96(0.82-1.12)	0.590
Hypertension	2.16(0.23-20.49)	0.502
Dyslipidemia	0.82(0.19-3.56)	0.797
Smoker (current or former)	0.92(0.37-2.30)	0.859
Diabetes	1.21(0.28-5.24)	0.797
eGFR (Cockcroft Gault)	0.98(0.95-1.02)	0.365
History of AF	3.76(1.47-9.60)	**0.006**
PVD	0.81(0.19-3.45)	0.775
Previous heart failure	0.86(0.15-4.99)	0.864
Angina	0.86(0.14-4.99)	0.864
NYHA class	1.14(0.46-3.05)	0.795
AVA	96.0(2.02-419.1)	**0.029**
Vmax	0.05(0.01-0.34)	**0.002**
Mean pressure gradient	0.85(0.77-0.94)	**0.002**
Stroke volume index	0.89(0.80-0.99)	**0.040**
Cardiac index	0.24(0.05-1.13)	0.071
LVEDVi	0.99(0.96-1.02)	0.548
LVEF	0.98(0.94-1.02)	0.372
E/A	2.90(0.32-26.08)	0.341
Deceleration time	0.99(0.97-1.01)	0.169
E/E'	1.01(0.88-1.17)	0.847
LA volume index	1.07(1.01-1.13)	**0.015**
Interventricular septal thickness	0.67(0.41-1.09)	1.000
Posterior wall thickness	0.74(0.45-1.24)	0.256
LV end-diastolic diameter	1.04(0.95-1.15)	0.360
LV mass index	1.01(0.98-1.02)	0.828
Relative wall thickness	0.01(0.00-8.01)	0.185
GLS	0.86(0.73-1.02)	0.086
PALS	0.75(0.60-0.93)	**0.009**
LVEDP	1.09(0.97-1.22)	0.163

AVA=aortic valve area; AF= atrial fibrillation; BMI=body mass index; CMD=coronary microvascular dysfunction; eGFR=estimated glomerular filtration rate; GLS=global longitudinal strain; LA=left atrial; LV=left ventricular; LVEDP=left ventricular end diastolic pressure; LVEDVi=left ventricular end diastolic volume index; LVEF=left ventricular ejection fraction; NYHA= New York Heart Association; OR=odd ratio; PALS=peak atrial longitudinal strain; PVD=peripheral vascular disease.