Right Ventricular and Pulmonary Computed Tomography Assessments in Paradoxical Low-Flow Low-Gradient Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

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Structured Abstract:

Background: Patients with paradoxical low-flow low-gradient aortic stenosis (pLFLG-AS) have high mortality and high degree of TAVR futility. Computed tomography (CT) enables accurate simultaneous right ventricular (RV) and parenchymal lung disease evaluation which may provide useful objective markers of AS severity, concomitant pulmonary comorbidities, and transcatheter aortic valve replacement (TAVR) improvement. However, the prevalence of RV dysfunction and its association with pulmonary disease in pLFLG-AS is unknown. The study objective was to test the hypothesis that pLFLG-AS patients undergoing TAVR have decreased RV function without significant parenchymal lung disease.

Methods: Between August 2016 and March 2020, 194 consecutive AS patients completed high-resolution computed tomography (CT) imaging for TAVR evaluation. Subjects were stratified based on echocardiographic criteria as the study group, pLFLG (n=27), and two consecutive control groups: classic severe, normal-flow, high-gradient (n=27) and normal-flow, low-gradient (NFLG) (n=27) AS. Blinded biventricular function and lung parenchymal disease assessments were obtained by high-resolution CT imaging.

Results: Patient demographics were similar between groups. pLFLG-AS had lower RV ejection fraction (49±10%) compared to both classic severe (58±7%, p<0.001) and NFLG AS (55±65%, p=0.02). There were no significant differences on lung emphysema (p=0.19), air fraction (p=0.58), and pulmonary disease presence (p=0.94) and severity (p=0.67) between groups.

Conclusion: pLFLG-AS patients have lower RV ejection fraction, than classic severe and normal-flow low-gradient AS patients in the absence of significant parenchymal lung disease on

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CT imaging. These findings support the direct importance of RV function in the pathophysiology of aortic valve disease.

Keywords

Aortic stenosis; right ventricular function; cardiovascular imaging

Introduction:

Studies assessing the incidence and prognostic significance of right ventricular (RV) dysfunction by echocardiography in severe aortic stenosis (AS) have yielded contradictory results, limiting the clinical role of RV function evaluation in patients with AS[1–5]. However, volumetric evaluation is a more accurate and reproducible approach to measure RV volume and systolic function[6]. RV ejection fraction (RVEF) assessed on cardiac magnetic resonance in classic "severe" AS gradually increases and may help preserve left ventricular (LV) stroke volume[7]. Therefore, RV compensation may be important in AS pathophysiology. Further, volumetric assessment of RV dysfunction was proven prognostic in AS undergoing aortic valve replacement[8]. As a result, the volumetric assessments of RV size and systolic function may serve as a useful objective marker of AS severity and aid evaluation of pathophysiological compensation and clinical outcome.

Individuals with paradoxical low-flow, low-gradient AS (pLFLG-AS) have higher mortality compared to other forms of severe AS with preserved left ventricular ejection fraction (LVEF) and similar mortality compared to severe AS with reduced LVEF[9–11]. In addition, compared to other AS patients, pLFLG AS patients have higher incidence of comorbidities, including pulmonary hypertension and severe parenchymal lung disease[12]. pLFLG AS patients have higher rates of futile transcatheter aortic valve replacement (TAVR) treatment which may be due to RV dysfunction and lung disease[13]. However, the prevalence of volumetric RV dysfunction and whether it is associated with pulmonary disease is unknown in pLFLG-AS.

In pLFLG-AS, a lack of RV compensation may lead to an inability to maintain adequate stroke volume (SV) and gradient across the valve obstruction. This combination may partially explain the paradoxical phenotype characterized by low flow and low gradient with preserved LVEF. Therefore, we sought to test the hypothesis that RV function in pLFLG AS is reduced without significant differences in parenchymal pulmonary disease compared to other severe AS with preserved LVEF patients consisting of "classic" severe normal-flow, high-gradient (NFHG) AS and "discordant" normal-flow, low-gradient (NFLG) AS. We do so by evaluating CT-derived cardiac volumetric and pulmonary imaging in patients undergoing assessment for transcatheter aortic valve replacement (TAVR).

Methods:

A total of 194 consecutive patients with AS undergoing assessment for TAVR between August 2016 and March 2020 were reviewed with IRB-approved waiver of consent. The study selected patients with preserved LVEF and severe AS; therefore, patients were excluded if aortic valve area > 1.0 cm^2 on echocardiography. Further, given the availability

of volumetric imaging, patients were excluded if CT-derived LVEF was reduced (<45%) or if CT quality was inadequate for volumetric analysis. All patients included in the study underwent cardiac and chest CT imaging as part of the TAVR clinical evaluation[14]. Details are shown in Figure 1.

A total of 27 pLFLG AS subjects with preserved LVEF with cardiac and chest CT imaging available for analysis were identified. The presence of pLFLG was defined according to echocardiographic criteria[15]: aortic valve area (AVA) <1 cm^2, mean gradient <40 mmHg, LVEF 50%, and SVi 35 mL/m^2. Two control groups were identified: normal-flow, high-gradient (NFHG) with normal LVEF ("classic" severe AS; AVA <1 cm^2, mean gradient >40 mmHg, LVEF 50%)[15] and "discordant" normal-flow, low-gradient (NFLG) with preserved LVEF (AVA <1 cm^2, mean gradient <40 mmHg, LVEF 50%, and SVi >35 mL/m^2)[15].

Patients underwent prospective, blinded assessment of LV and RV function via cardiac CT performed by a cardiologist expert certified in multi-modality imaging, review of chest CT radiological findings by two pulmonologists with adjudication by a third pulmonologist, and quantitative lung assessment for emphysema scoring.

All patients were imaged on wide-detector CT scanners with 16 cms of axial coverage. 74 patients were imaged on a Revolution scanner (GE Healthcare, Chicago IL) and 7 were imaged on a Aquilion One (Canon Medical, Tustin, CA). Cardiac assessment was performed on contrast-enhanced, ECG-gated axial images obtained for aortic valve evaluation while lung assessment was performed on contrast-enhanced helical acquisitions used to assess vascular access.

As described above, all patients had CT imaging that included both end-diastolic and end-systolic phases of the cardiac cycle as part of assessment for TAVR. A cardiovascular imaging certified expert (author M.R.) utilized CMR42 (Circle Inc, Calgary, Canada) to generate short-axis stacks of images at end-diastolic and end-systolic upon which contours of the RV and LV endocardial and epicardial boundaries were drawn. This enabled biventricular end-diastolic and end-systolic volumetry, measurement of stroke volume and ejection fraction, and assessment of RV and LV mass. An example of the short-axis reformatting and drawn contours is shown in Figure 2. Video 1 and Video 2 illustrate examples of patients with normal and decreased RV function.

Assessment of lung disease was obtained via use of the open-source Pulmonary Toolkit (https://github.com/tomdoel/pulmonarytoolkit) which is used to perform automated lung segmentation[16] and quantifies metrics of hyperinflation and COPD[17] which agree with histology[18]. In addition, radiological reports of the CT studies, blinded to AS group, were reviewed by two pulmonologists (with adjudication by a third pulmonologist) for tabulation of the presence of parenchymal, airway, vascular, or mixed pulmonary disease as well as grading of severity (mild, moderate, or severe).

Parameters were tested for normality via the Shapiro-Wilks test. Normal continuous variables are reported as mean ± standard deviation while non-normal variables are reported as median with first and third quartiles (Q1 and Q3, respectively). Categorical variables are reported as number (percentage). Differences between groups were evaluated via ANOVA,

Kruskal-Wallis, or chi-squared testing as appropriate using Matlab (Mathworks, Natick, MA). Study data are available upon reasonable request. The patients or public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results:

Table 1 indicates the baseline demographic and echocardiographic characteristics of the three groups. No significant differences exist in patient demographics. Differences in echocardiography characteristics were concordant with the pathophysiology of the different AS groups. Namely, patients with "classic" severe AS had higher mean aortic gradient, LV ejection fraction, and LV stroke volume index than the two control groups. In addition, "discordant" AS patients had a higher LV stroke volume index (42 ± 6 mL/m^2) than "paradoxical" LFLG (30 ± 6 mL/m^2, p<0.001). No patient had >moderate mitral or aortic valve regurgitation. 1 patient (3.7%) in the "discordant" NFLG cohort and 2 (7.4%) in the "paradoxical" pLFLG cohort had >moderate regurgitation of the tricuspid valve. PASP in "paradoxical" LFLG (mean: 39, IQR 31 – 48 mmHg) trended (p=0.25) towards being higher than "classic" NFHG AS (mean: 33, IQR 26 – 43 mmHg) and "discordant" NFLG AS (mean: 33, IQR 22 – 42 mmHg).

As shown in Table 2 and Figure 3, RVEF on cardiac CT was significantly (p<0.001) reduced in pLFLG AS ($49 \pm 10\%$) relative to both "classical" severe NFHG AS ($58 \pm 7\%$, $p < 0.001$) and "discordant" NFLG AS ($55 \pm 6\%$, p =0.02). This finding appears driven primarily by a trend towards decreased RV stroke volume ("classic": 83 ± 20 mL, "discordant": 84 ± 23 mL, "paradoxical": 72 ± 20 mL, p=0.07).

As observed in echocardiographic findings, CT-derived LVEF was different between the three groups ("classic": $61 \pm 6\%$, "discordant": $58 \pm 6\%$, "paradoxical": $58 \pm 6\%$, p=0.05, Figure 4) but post hoc testing did not identify significant differences between pairs (p > 0.07).

Quantitative assessment of lung air fraction and emphysema percentage were not significantly different (p = 0.58 and p = 0.19, respectively) amongst the study cohorts (Table 2, Figure 5). Further, the presence of pulmonary disease (p = 0.94) and severity based on expert grading (p = 0.67) was not different between study groups.

Discussion:

In patients with pLFLG-AS who have lower SV and preserved LVEF, we observed decreased RV systolic function relative to patients with other forms of AS with preserved LVEF. Importantly, RV changes were observed in the absence of any significant parenchymal lung disease.

This observation suggests that the right ventricle may be involved in the paradoxical AS phenotype. Previously, RV function has been shown to be elevated early in AS[7]. Therefore, decreased RV function or lack of RV compensation in pLFLG may represent a later stage of disease which leads to LV underfilling and inability to maintain left-sided SV and flow across the valve obstruction, resulting in a lower measured gradient. Therefore,

RV dysfunction may explain clinical decompensation and negative prognostic features of pLFLG-AS. However confirmatory studies are needed to prove this hypothesis and carefully evaluate PH.

RV dysfunction is common in severe AS, involving up to 25% of AS patients[2] and may even be more frequently in pLFLG-AS[12]. Patients with pLFLG-AS have a worse prognosis compared to patients with normal flow high gradient AS [9]. They also manifest higher degree of TAVR futility [13]. Worse prognosis and TAVR futility may both be directly associated with RV dysfunction or may result from concomitant pulmonary comorbidities.

High-resolution CT imaging is currently recommended for TAVR pre-assessment in patients with AS[19,20] and to confirm pLFLG[21] . In addition, CT can provide quantitative RV volumetric and function assessment[22,23] as well as quantitative measures of lung parenchyma findings[24–26]. Since RV dysfunction may be caused by either left-sided cardiac disease or by underlying pulmonary comorbidities, we utilized CT-based pulmonary disease assessment to identify the association with lung findings and exclude the presence and severity of parenchymal abnormalities such as emphysema or fibrosis.

In this cohort, we did not find any differences in pulmonary comorbidities between the three AS subgroups analyzed. We did not have spirometry available in all our participants as these assessments are not routinely obtained. However, spirometry results would be confounded by elderly age and heart failure in this particular AS cohort[27,28]. Nonetheless, we excluded clinically significant pulmonary parenchymal disease by both quantitative emphysema assessment and radiologic analysis. Lastly, RV impairment could also be due to pulmonary hypertension (PH) driven by left-sided dysfunction. However, we did not observe differences in RV pulmonary pressures on echocardiography amongst our groups[15,29].

Our findings motivate a prospective study to confirm our results and assess the impact of CT-based RV and pulmonary evaluation on TAVR futility and outcome in pLFLG. If confirmed in larger studies, pLFLG-AS may require early intervention to avoid RV dysfunction which seems driven by the AS disease rather than lung comorbidities.

This study was limited in the measurements available for evaluation due to its retrospective nature. As mentioned above, assessment of lung disease with spirometry was not available and would be limited in this population. In addition, while measurement of total lung capacity and diffusing capacity of the lung for carbon monoxide would help to further characterize lung function, we expect CT evaluation to have detected interstitial lung disease that would cause hemodynamic impairment. Further, RV systolic pressure was performed using echocardiography surrogates as right heart catheterization is not routinely performed in this cohort. Doppler echocardiography is routinely performed clinically and was therefore utilized to exclude detectable (significant) **PH**[30]. However, non-invasive estimation is known to be limited[31,32]. Therefore, PH may be unrecognized or underestimated. Further studies involving invasive assessment of pulmonary pressures will be required to accurately assess RV performance in AS and PH. Lastly, our limited sample size precluded multivariate evaluation to assess whether RV dysfunction is independently associated with pLFLG-AS.

Non-invasive CT-based evaluation could be readily applied clinically as TAVR patients undergo preprocedural CT imaging[14]. We evaluated biventricular function using volumetric measures which are highly accurate when obtained via CT. However, to further investigate the mechanism of RV-LV interaction (for example, ventricular interdependence or Bernheim type effect) septal wall motion abnormalities could be assessed using regional approaches[33,34].

Conclusion:

Patients with pLFLG-AS have lower RVEF than "classic" severe and "discordant" normal-flow low-gradient AS patients in the absence of significant parenchymal lung disease. These findings support the major and direct importance of the right ventricle in the pathophysiology of AS.

Funding/Disclosure:

Abbreviations:

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AS	Aortic Stenosis
LV	Left Ventricle
RV	Right Ventricle
SV	Stroke Volume
CT	Computed Tomography
EF	Ejection Fraction
AVA	Aortic valve area
pLFLG AS	paradoxical low-flow low-gradient aortic stenosis
NFHG AS	normal-flow high-gradient aortic stenosis
NFLG AS	normal-flow low-gradient aortic stenosis

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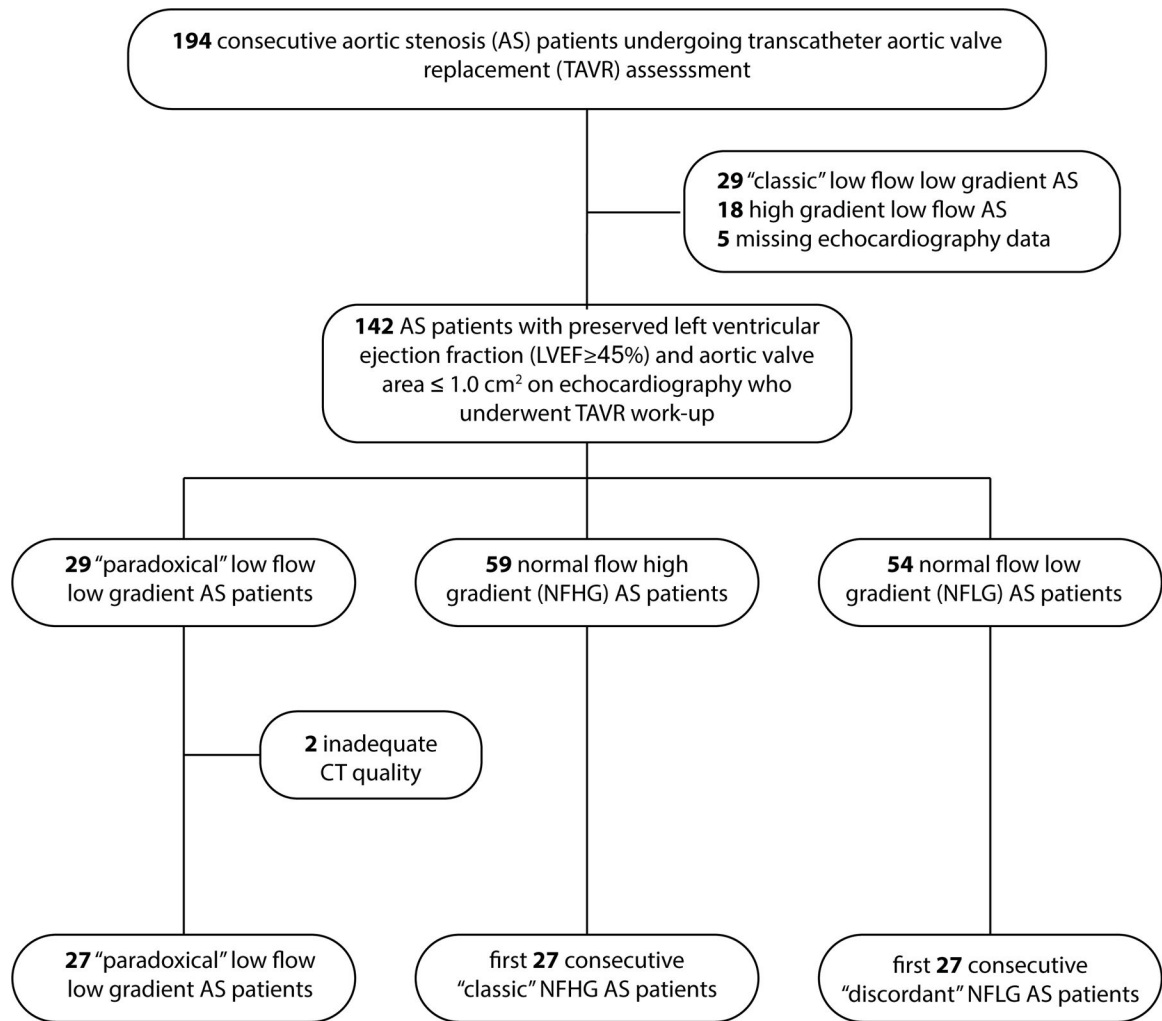
Figure 1: Flow diagram of study cohorts.

Consecutive patients undergoing TAVR evaluation were evaluated for enrollment based on clinical echocardiography findings. After identification of the "paradoxical" low flow low gradient cohort, two cohorts of the first 27 consecutive "classic" NFHG and "discordant" LGNF" cases were selected for comparison.
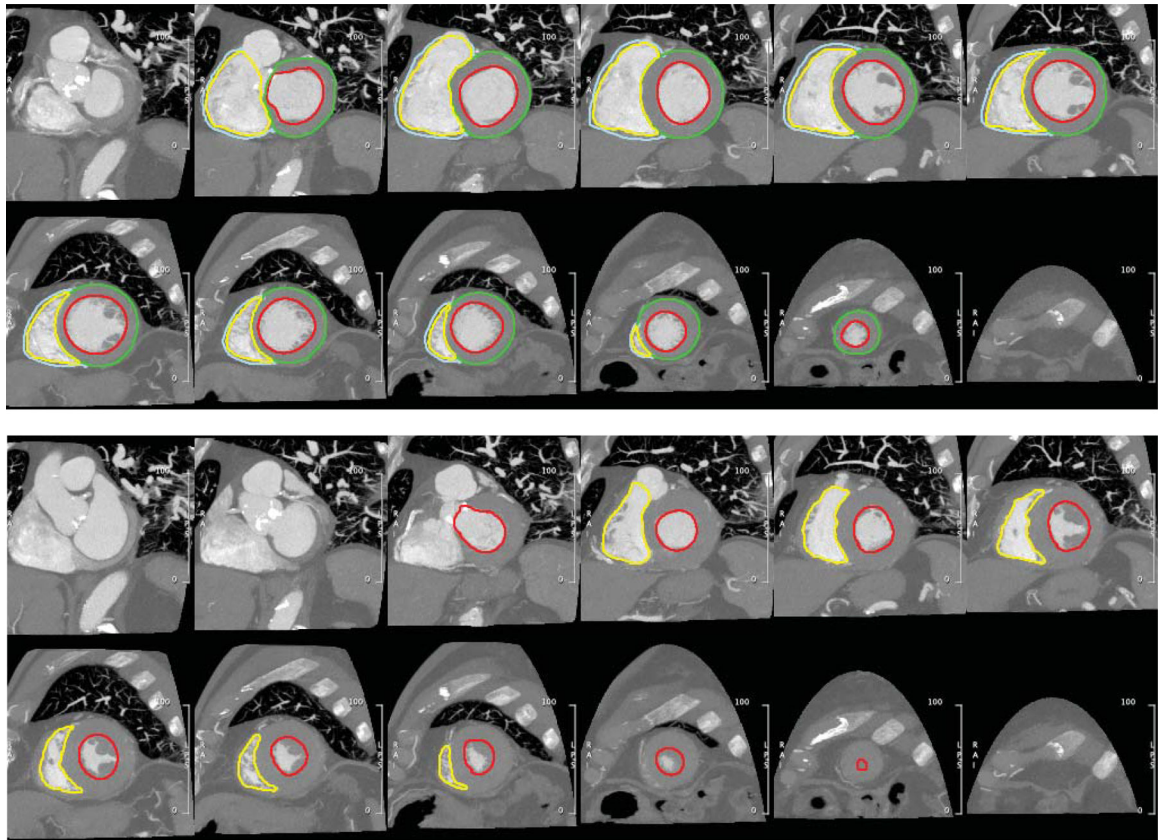
Figure 2: Example of biventricular function analysis via cine CT.
Endocardial LV (red) and RV (yellow) contours were annotated on short-axis reconstructions of the end-diastolic (top) and end-systolic (bottom) phases for volumetric evaluation of chamber size and function. Epicardial contours of the LV (green) and RV (cyan) in the end-diastolic phase enabled assessment of myocardial mass.
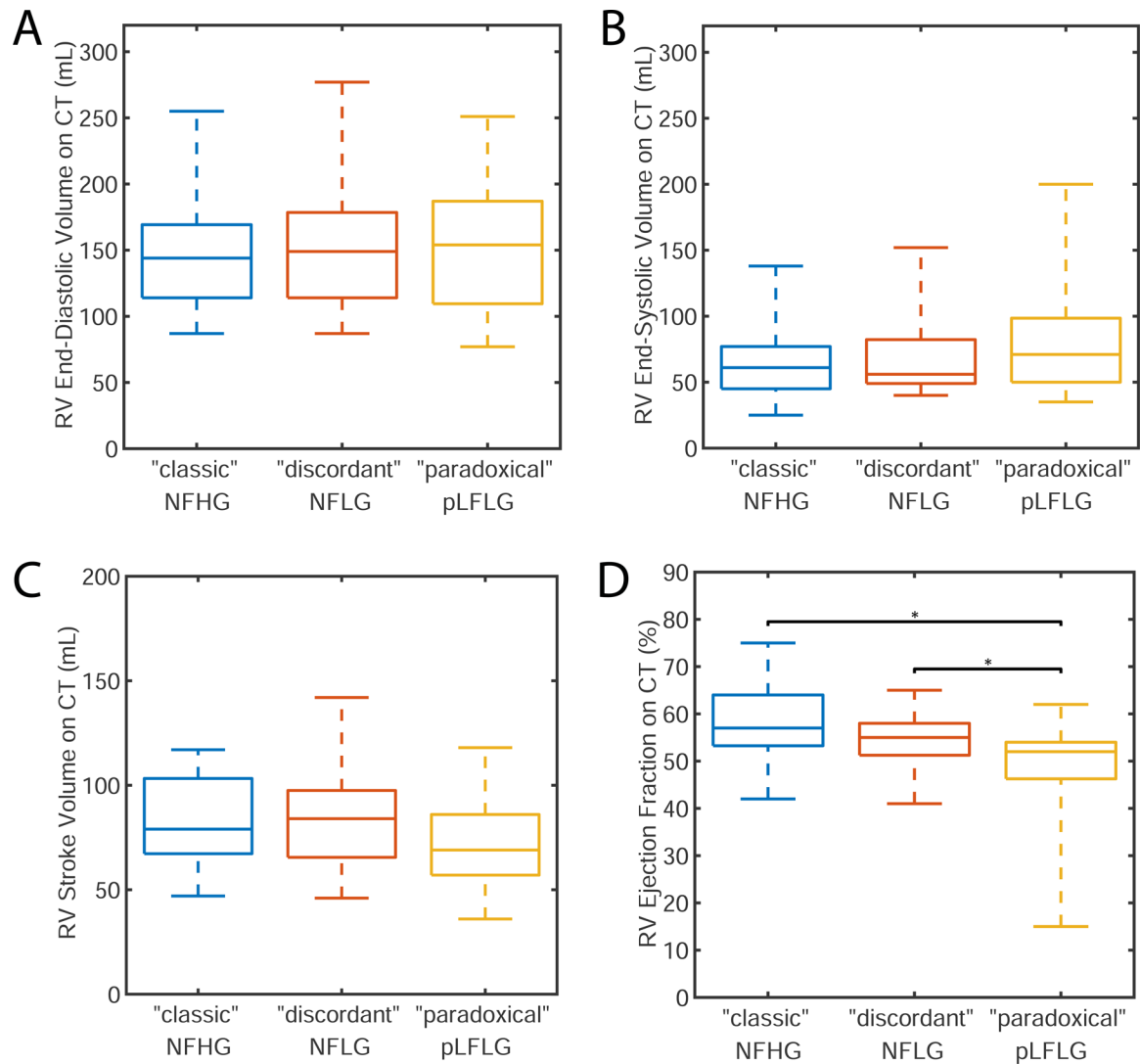
Figure 3: Evaluation of Right Ventricular Function on CT.
Differences did not exist in end-diastolic (panel A), end-systolic (panel B), or stroke volume (panel C). pLFLG AS patients had significantly lower RV ejection fraction (panel D) when compared to "classic" NFHG and "discordant" NFLG AS subjects. pLFLG AS: paradoxical low-flow low-gradient aortic stenosis, NFHG AS: normal-flow high-gradient aortic stenosis, NFLG AS: normal-flow low-gradient aortic stenosis
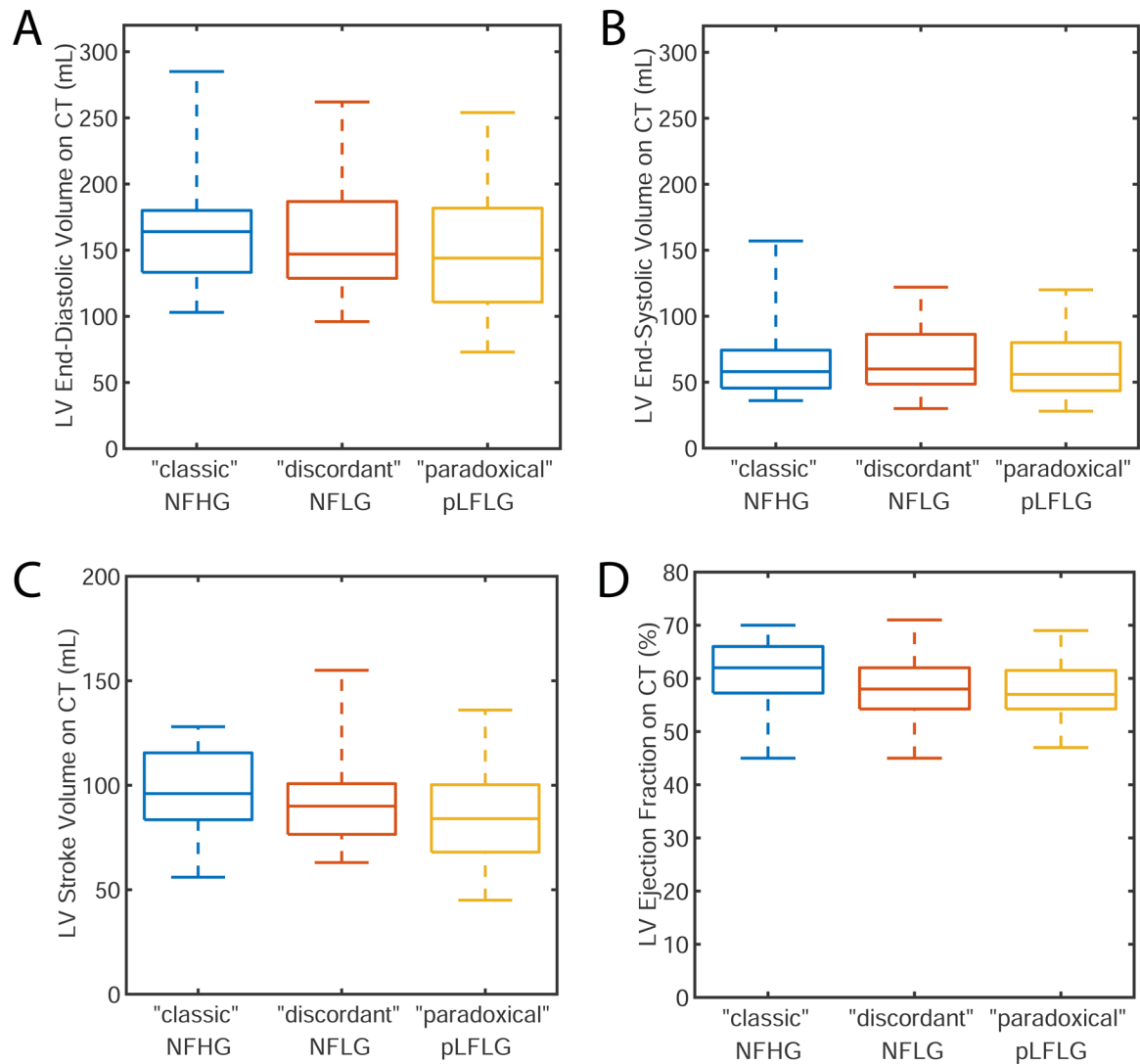
Figure 4: Evaluation of Left Ventricular Function on CT.

Differences did not exist in end-diastolic (panel A), end-systolic (panel B), or stroke volume (panel C) between different study groups. While there was a significant difference in LV ejection fraction (panel D), subsequent pairwise differences were not significant. pLFLG: paradoxical low-flow low-gradient aortic stenosis, NFHG: normal-flow high-gradient aortic stenosis, NFLG: normal-flow low-gradient aortic stenosis
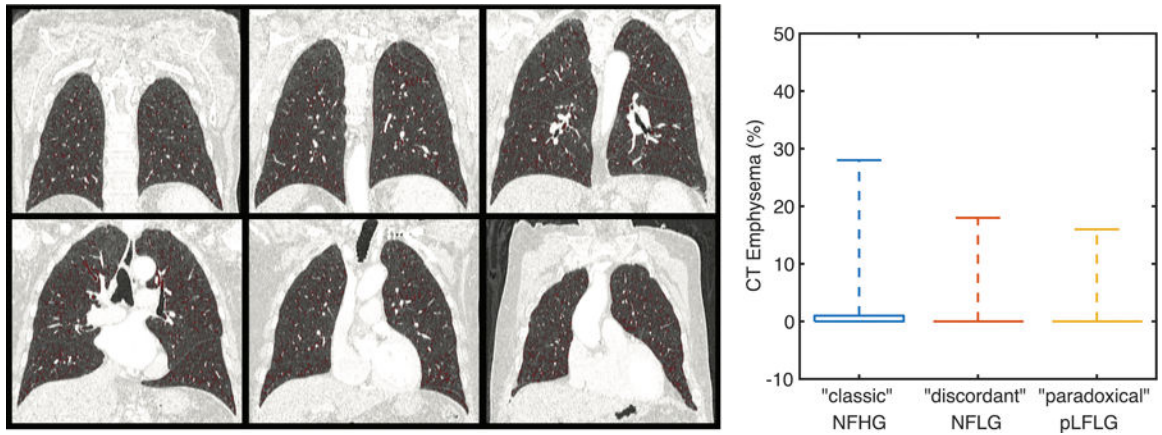
Figure 5: CT Assessment of Lung Disease.
The percentage of lung identified as emphysematous on CT was low for all subjects without significant difference between groups. The boxplot shows the median (0 for all groups) and extends upwards to the 75th percentile. Whiskers extent to the maximum reported value. pLFLG: paradoxical low-flow low-gradient aortic stenosis, NFHG: normal-flow high-gradient aortic stenosis, NFLG: normal-flow low-gradient aortic stenosis

Video 1:

Normal RV function in a patient with high gradient aortic stenosis on CT. Short-axis reformat of volumetric ECG-gated cineCT enables biventricular assessment and illustrates normal RV function despite high gradient aortic stenosis.

Video 2:

RV dysfunction in a patient with paradoxical low-flow low-gradient aortic stenosis. Short-axis reformat of volumetric ECG-gated cineCT enables biventricular assessment and illustrates RV dysfunction in pLFLG.

Table 1:

Patient characteristics.

Normal continuous variables are reported as mean ± standard deviation while non-normal variables are reported as median with first and third quartiles (Q1 and Q3, respectively). Categorical variables are reported as number (percentage).

	"Classic " NFHG (n=27)	"Discordant" NFLG (n=27)	"Paradoxical" pLFLG (n=27)	p-value
Clinical Characteristics				
Age, years	80 ± 9	81 ± 9	82 ± 14	0.73
Gender, male	15 (56%)	13 (48%)	16 (59%)	0.71
BSA, m^2	1.9 (1.7 to 2)	1.7 (1.6 to 1.9)	1.9 (1.6 to 2)	0.15
BMI, kg/m^2	26 ± 5	26 ± 5	28 ± 11	0.65
Echocardiographic Characteristics				
Aortic Valve area, cm^2	0.87 (0.72 to 0.91)	0.8 (0.71 to 0.92)	0.74 (0.65 to 0.86)	0.13
Aortic Mean Gradient, mmHg	45 (41 to 55) [†,‡]	34 (28 to 37) [*]	31 (23 to 35) [*]	<0.01
LV Stroke Volume Index, mL/m^2	50 ± 11 [†,‡]	42 ± 6 [*,‡]	30 ± 6 [*,†]	<0.01
LV Ejection Fraction, %	69 ± 8 [†]	64 ± 9 [*]	64 ± 8	0.03
Mitral Regurgitation, % >Moderate	0 (0%)	0 (0%)	0 (0%)	1.0
Tricuspid Regurgitation, % >Moderate	0 (0.0%)	1 (3.7%)	2 (7.4%)	0.35
Aortic Regurgitation, % >Moderate	0 (0%)	0 (0%)	0 (0%)	1.0
PASP, mmHg	33 (26 to 43)	33 (22 to 42)	39 (31 to 48)	0.25

NFHG: normal-flow high-gradient aortic stenosis, NFLG: normal-flow low-gradient aortic stenosis, pLFLG: paradoxical low-flow low-gradient aortic stenosis

[*] p<0.05 compared NFHG AS

[†] p<0.05 compared to NFLG AS

[‡] p<0.05 compared to pLFLG AS

Table 2:

Cardiac and Lung Assessment on CT.

Normal continuous variables are reported as mean ± standard deviation while non-normal variables are reported as median with first and third quartiles (Q1 and Q3, respectively). Categorical variables are reported as number (percentage).

	"Classic" NFHG (n=27)	"Discordant" NFLG (n=27)	"Paradoxical" pLFLG (n=27)	p-value
LV Assessment				
LV End-Diastolic Volume, mL	164 (133 to 180)	147 (129 to 187)	144 (111 to 182)	0.57
LV End-Systolic Volume, mL	58 (46 to 74)	60 (49 to 86)	56 (44 to 80)	0.53
LV Stroke Volume, mL	96 ± 19	92 ± 21	86 ± 23	0.17
LV Ejection Fraction, %	61 ± 6	58 ± 6	58 ± 6	0.05
LV total mass, g	159 ± 48	151 ± 45	134 ± 42	0.12
LV Septum Max, mm	14 ± 3	13 ± 3	13 ± 2	0.15
RV Assessment				
RV End-Diastolic Volume, mL	146 ± 38	155 ± 52	152 ± 49	0.77
RV End-Systolic Volume, mL	63 ± 24	72 ± 32	81 ± 41	0.14
RV Stroke Volume, mL	83 ± 20	84 ± 23	72 ± 20	0.07
RV Ejection Fraction, %	58 ± 7[‡]	55 ± 6[‡]	49 ± 10[*,†]	<0.01
RV total mass, g	30 ± 7	33 ± 9	33 ± 12	0.43
Lung Assessment				
Air Fraction (%)	75 ± 7	73 ± 8	74 ± 6	0.58
Emphysema (%)	0 (0 to 1)	0 (0 to 0)	0 (0 to 0)	0.19

NFHG: normal-flow high-gradient aortic stenosis, NFLG: normal-flow low-gradient aortic stenosis, pLFLG: paradoxical low-flow low-gradient aortic stenosis

[*] p<0.05 compared NFHG AS

[†] p<0.05 compared to NFLG AS

[‡] p<0.05 compared to pLFLG AS