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Paradoxical Low Flow Aortic Stenosis: A Clinical Dilemma

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Key Notes

- The definition of severe Aortic stenosis includes mean transvalular gradient of 40 mmHg or higher, Aortic valve area of 1 cm^2 or less, o aortic valve index (aortic valve area adjusted for body surface area) of 0.6 cm/m^2 or less.
- It is expected that patients with reduced ejection fraction present with low trans valvular gradients despite severe aortic stenosis given that gradients depend directly on the transvalvular flow. However, is not infrequent to encounter patients with low gradients, despite normal ejection fraction.
- Up to one-third of patients with severe aortic valve stenosis present as “paradoxical low-flow aortic valve stenosis”, defined as aortic valve area ≤ 1 cm^2, mean transvalvular pressure gradient <40 mm Hg, normal EF and low transvalvular flow, defined as stroke volume index <35 mL/m^2.
- Discordant echocardiographic data create doubts about the severity of the disease
- Additional diagnostic methods such as measurement of aortic valve calcium score, dobutamine stress echocardiogram to see if stroke volume increases under stress, heart catheterization to check accuracy of low cardiac output, and longitudinal mechanics of the left ventricle can help define disease severity.
- Valve replacement may be indicated for symptomatic patients with severe paradoxical low-flow aortic stenosis.

Abstract

Paradoxical low-flow aortic valve stenosis is defined as the presence of small valve area (c/w severe Aortic stenosis), low transvalvular gradients (non -severe range) in the presence of low transvalvular flow, but with normal ejection fraction (>50%). This discordant echocardiographic data creates doubts about the severity of the disease. Depending on various reports from the literature, the prevalence rate of this condition may range anywhere from 3% to 35% of all cases of severe aortic valve stenosis. Among this population of low flow, low gradient, normal EF and severe aortic valve stenosis, there is an unknown percentage of cases that are not ‘truly severe’ and approach to this clinical population is challenging. The diagnosis of this condition is evolving as the therapeutic approaches. Many retrospective, non-randomized publications have shown that there is a possible clinical benefit from aortic valve replacement. Due to the high prevalence of aortic stenosis in any cardiology practice, and the implications of the diagnosis and management of severe aortic stenosis, we outline current trends in the diagnosis and treatment of this entity.

Problem

Internists as well as cardiologists often receive echocardiogram reports which failed to offer a clear definition of the aortic stenosis (AS) severity due to discordant data regarding the aortic valve gradients and the valve area. Sometimes AS appears severe according to the valve area criteria, in spite of the fact that gradients across the valve are not in the severe range. This implies a clinical dilemma and potential under or over diagnoses

of severe AS. AS is the most common valvular disease in Europe and North America [1]. Aortic valve replacement is the only treatment for severe aortic stenosis. The definition of severe AS according to AHA/ACC guidelines is peak aortic velocity of >4 m/sec, mean gradient of ≥ 40 mmHg, Aortic valve area (AVA) ≤ 1 cm^2 or Aortic valve area index (AVAI) ≤ 0.6 cm/m^2 [2].

However, a significant proportion of patients (3-35%) with severe AS in the base of AVA <1 cm^2 or AVAI <0.6 cm/m^2, presents with a mean gradient <40 mmHg, a low output (defined as stroke volume index less than 35 cc/m^2) despite a preserved ejection fraction (EF). This entity was defined as paradoxical low flow aortic stenosis (PLFAS) [3,4]. In these cases, discordant echocardiographic data regarding AS severity, creates confusion and uncertainty about the true severity of the disease and thus, unclear therapeutic decisions. According to Poiseuille's law, gradients across a stenotic valve are flow dependent, so, in the presence of low transvalvular flow (low cardiac output), the gradients across a severely stenotic valve will be lower than expected [5].

In patients with reduced EF and thus, low stroke volume, it seems logical to see low gradients despite severe AS given the relation between gradients and transvalvular flow. However, in the presence of normal EF, the presence of low gradient AS is more intriguing. American Heart Association/ American College of Cardiology and European Society of Cardiology guidelines, recommend aortic valve replacement in patients with low flow, low gradient AS with EF >50%, who are normotensive at the time of evaluation and have hemodynamic, and, anatomic data to support valve obstruction as the most probable explanation of the symptoms [1,2]. This recommendation shows to what extent both the diagnosis and the treatment of this entity are a challenge.

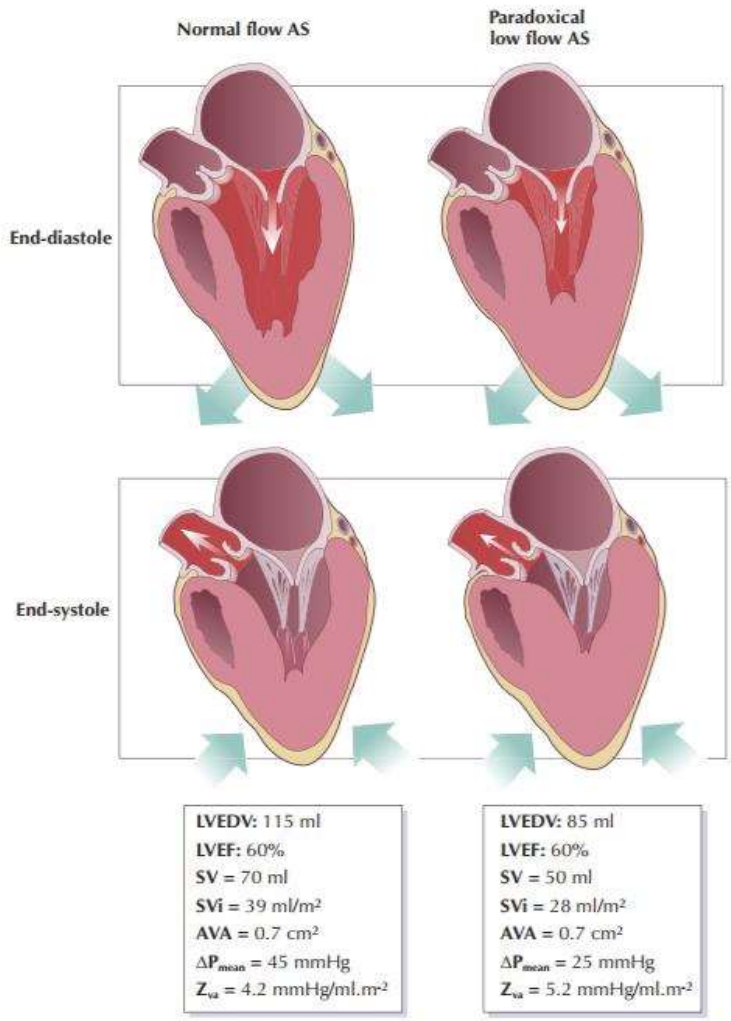

Figure 1: Exaggerated concentric remodeling in patients with paradoxical low flow Aortic stenosis. Copy with permission from JACC [15].

Definition

Paradoxical low flow refers to the presence of aortic valve area in the severe range (≤ 1 cm^2 or AVAI ≤ 0.6 cm/m^2 of BSA) but a mean gradient lower than 40 mmHg (non-severe range) despite an EF >50%, associated with the presence of low stroke volume index (<35 cc/m^2) [3]. In these cases, we encounter discordant echocardiographic data, as the valve area is compatible with severe AS but the transvalvular gradients are not in the severe range. This entity can be recognized by some echocardiographic features described in the original paper from Hachicha and colleagues in 2007 [3].

- Compared to patients with low gradient AS, normal EF and normal flow, PLFAS patients showed lower systemic arterial compliance and higher systemic vascular resistance.
- The global arterial impedance, as a measure of the total load faced by the ventricle was markedly higher in the PLFAS compared with normal flow.
- PLFAS patients also showed smaller left ventricle cavity size, similar wall thickness but increase in relative wall thickness, as a consequence of a more pronounced concentric remodeling.
- This distinctive left ventricle geometry results in a restrictive physiology with small LV cavity size and volumes and thus, lower cardiac output/stroke volume compared to the group of AS and high gradients or low gradients and normal flow (Figure 1) [3].

Pathophysiology

Why the trans valvular gradients are low despite small valve area?

There are 3 main considerations:

1. Measurement errors
2. Low cardiac output
3. Small body size

Measurement errors

Calculation of the aortic valve area is done using the continuity equation. According to the equation, the volume of blood passing through the left ventricular outflow tract (LVOT) must equal the volume of blood ejected at the valve orifice; the formula includes the left ventricular outflow tract area, the left ventricular outflow tract velocity and the aortic velocity.

$$\frac{LVOT\ Area\ X\ LVOT\ VTI}{AO\ VTI}$$

LVOT VTI: velocity time integral at the left ventricle outflow tract

AO VTI: velocity time integral at the Aortic valve

The LVOT area is assumed to be a circle in the continuity equation. It is calculated using the LVOT diameter measured by echocardiography, which is then square in the formula to estimate the left ventricular outflow tract area (multiplying any measurement error), thus, small measurement errors can lead to significant changes in LVOT area. This can be a potential explanation for the discordant echocardiographic data between gradients and valve area.

Moreover, the left ventricular outflow tract cross-sectional area that appears to be circular, has been shown by widespread use of computed tomography (CT) scans to be elliptical, which could be also a potential error in estimation the aortic valve area [6].

Some of the investigations tried to demonstrate that measuring LVOT by CT instead by echocardiography, would solve the discordance between AVA and gradients:

The results of this investigations are discordant:

Echocardiography underestimate the LVOT size in most of the studies; however, calculating the AVA with the LVOT measured by CT not always helped to improve the correlation between aortic gradients and AVA [7-10].

In one study, when data was integrated by the heart team evaluation, no advantage was seen in using the CT LOVT measurement [9].

Low cardiac output

Causes

Hypertension and arterial stiffness: Hypertension (HTN) and arterial stiffness are frequent in patients with severe AS [11], leading to lower arterial compliance, high arterial impedance and higher left ventricular load. The increased afterload due to the stenotic valve in the presence of decreased systemic arterial compliance and high arterial impedance can lead to reduced transvalvular flow even in the presence of severe AS:

Briand and colleagues calculated the global arterial impedance for almost 200 patients with moderate or severe AS [12].

Compared to patients with severe AS and normal global arterial impedance, patients with severe AS and high arterial impedance, had lower systemic arterial compliance, lower stroke volume and lower gradients.

Interestingly, patients with severe AS and high arterial impedance show lower blood pressure compared with a group of moderate AS and high arterial impedance. This

suggests a "pseudo-normalization" of blood pressure in the severe AS group, possibly due to low flow across the valve [12]. Hachicha and colleagues showed that a high proportion (~ 50 %) of patients with PLFAS has a high arterial impedance (> 4.5 $mmHg/ml^{-1}/m^2$) [11]. Little et al. treated patients medically to increase blood pressure with phenylephrine infusion. After blood pressure increased and thus, reduced systemic arterial compliance, it was observed a reduction in transvalvular flow and in valve area. Twenty-three percent of the patients were re-classified based on the AVA obtained after intervention [13]. So, it seems that HTN and high global arterial impedance are associated with reduced trans valvular flow, and thus, low trans valvular gradients despite severe AS. It is also important to realize that normal blood pressure is not equal to normal arterial compliance as a pseudo-normalization of the blood pressure may occur in the presence of low transvalvular flow.

A clinical implication of this data appears to be that AS evaluation cannot be complete without taking into account blood pressure at the time of the echocardiographic examination. Calculation of arterial impedance and arterial compliance may help to identify the PLFAS phenotype [13].

Echocardiographic examination should be preferably conducted or repeated once blood pressure is under control to avoid underestimation of valvular gradients [11].

Altered LV geometry: The left ventricle remodeling in response to valvular disease, hypertension or other diseases, includes changes in LV mass and LV geometry. Relative wall thickness (RWT) is one of the parameters used to reflect LV remodeling. It can be easily calculated by echocardiography.

A normal response to hypertension is an increase in RWT in proportion to the elevation of blood pressure; however, in different pathologic states the LV response is more heterogeneous and includes: concentric remodeling (normal mass but high relative wall thickness) concentric hypertrophy (elevation in mass and relative wall thickness) and eccentric hypertrophy (elevation of mass with normal relative wall thickness) depending on different factors such as: age, sex, obesity, metabolic syndrome and diabetes [14].

Pibarot and colleagues reported that patients with PLFAS had smaller cavity size, similar wall thickness and thus, a greater relative wall thickness compared to the group with normal stroke volume index [3]. The predominant geometry was concentric remodeling showing an exaggerated or inappropriate LV hypertrophy. LV volumes and, valvular gradients, were lower [15].

Impaired longitudinal LV function: Preserved EF does not necessarily imply preserved systolic function or normal trans valvular flow rate/ stroke volume, because EF predominantly reflects transverse systolic function and mostly endocardial displacement. The myocardial fiber architecture is a complex array of longitudinal fibers (located mainly in endocardium and epicardium) and circumferentially oriented fibers (located in the mid-wall). EF mainly reflects the activity of the circumferential fibers

Long axis excursion is a measure of the function of longitudinally or spirally arranged fibers in the sub endocardium and sub epicardial layers of the myocardium. These fibers are more susceptible to ischemia in the presence of left ventricular hypertrophy and increased left ventricular mass, so, longitudinal function may be altered earlier than transverse function. In the presence of left ventricular hypertrophy, therefore, the EF may remain normal despite altered longitudinal contraction [16].

Strain and strain rate, as more advanced echocardiographic techniques are more sensitive indices of myocardial function than EF. Strain measures myocardial deformation in the longitudinal, circumferential and radial planes and identifies subtle changes in LV performance even in the presence of normal EF. When comparing a group of patients with severe AS with normal controls and with hypertensive patients, the group with severe AS has significant different values of strain, even in the presence of normal EF [17]. Ada and colleagues showed that, in a group of 340 patients with severe AS and normal EF, the group with PLFAS had significantly lower basal longitudinal strain compared to patients with low gradient AS and normal flow and high gradient aortic stenosis [18].

In summary, EF is an insensitive index of myocardial dysfunction in case of altered LV geometry; strain can help to define more properly the left ventricular function. In the presence of abnormal longitudinal function, it is possible that the stroke volume and thus, the transvalvular gradients are lower than expected. However, caution should be taken due to the limitations of the technique as strain can be significantly influenced by blood pressure at the times of echocardiographic examination [19].

Other causes of low transvalvular flow: There are other situations that need to be considered in cases of low gradient/low flow: the low stroke volume measure at the LVOT may be reflection of large regurgitating volume in the presence of severe mitral and tricuspid regurgitation [20-22]. Right ventricular failure and atrial fibrillation should also be considered to explain low gradient/ low flow situations (Figure 2) [4].

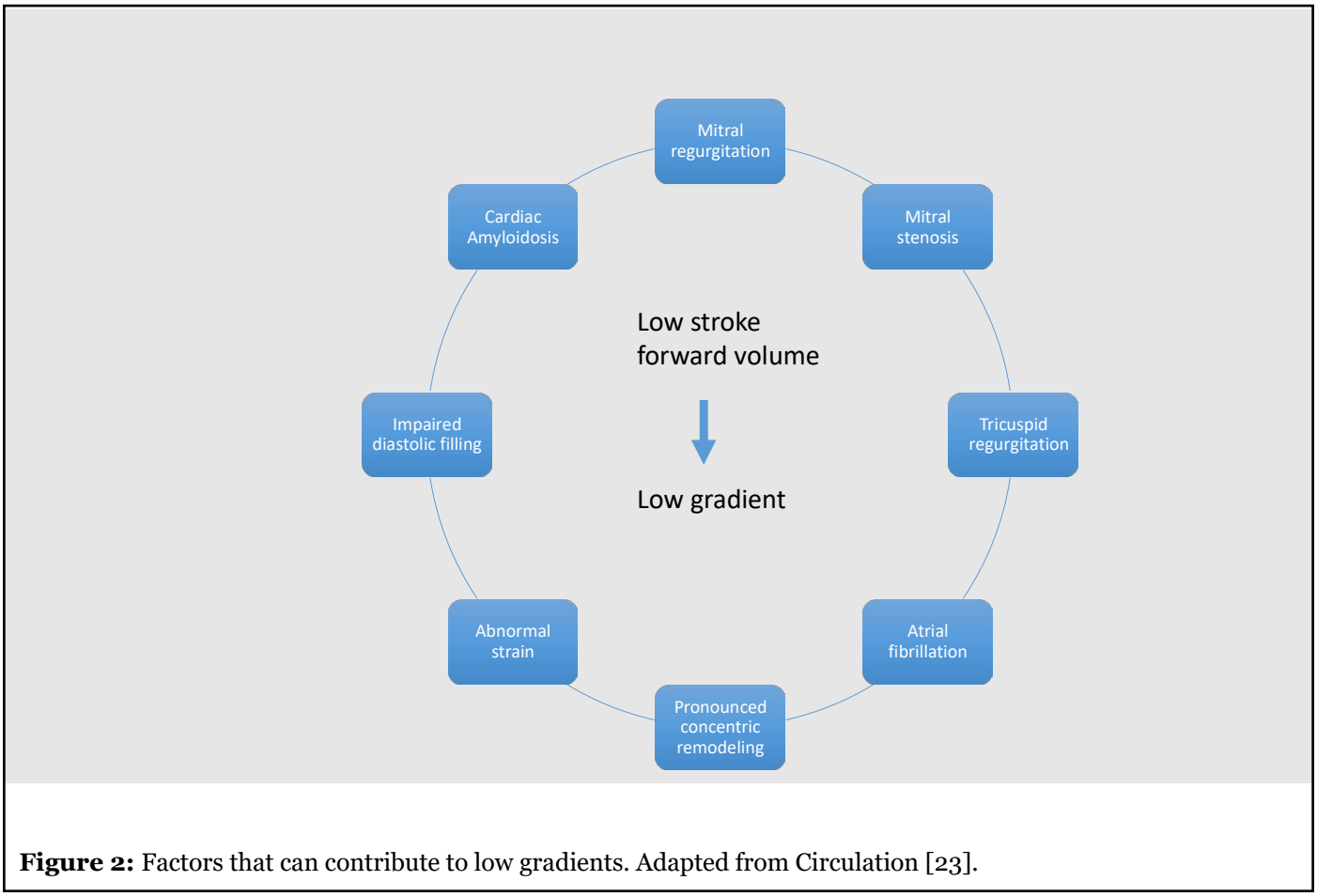

Figure 2: Factors that can contribute to low gradients. Adapted from Circulation [23].

Small body size

A small AVA may in fact correspond to a moderate AS and thus a low gradient in a patient with a small body size. Hence, in patients with paradoxical LF-LG AS and small body size, it is important to calculate the indexed AVA: a value >0.6 cm2/m2 would indicate a moderate AS [2]. On the other hand, the indexed AVA may overestimate the stenosis severity in obese patients [21]. American society of echocardiography guidelines [23] for assessment of valve stenosis recommend calculated indexed valve area when:

- Height <165 cm (5'5")
- BSA <1.5 m2
- BMI <22

How to Define the Severity of AS When Discordant Echocardiographic Data is Encountered?

Role of additional imaging

Role of cardiac computed tomography: Although Doppler echocardiography is the first line for the hemodynamic evaluation of AS severity, CT may provide important complementary information in the evaluation and management of patients with AS. There is some data regarding the correlation between degree of aortic valve calcification and AS severity:

Calcification of the aortic valve has been proposed years ago as a process that can initiate and also mediate progression of the aortic stenosis [24].

Back in 1995, Otto and colleagues demonstrated in aortic valves with different degree of stenosis severity, the presence of inflammatory cells, as well as the presence of osteopontin, a protein that is involved in normal or dystrophic calcification in different tissues. They demonstrated that there is a correlation between osteopontin levels and degree of calcification in patients with different degrees of aortic stenosis [25,26].

One group showed that there is strong correlation between electron beam computed tomography (EBCT) calcium score of the aortic valve specimens taken form aortic valve surgery, and calcium weight analyzed by tissue digestion. They also demonstrate a strong correlation, between the calcium score by EBCT and the aortic valve stenosis severity by echocardiography [27].

Other group analyzed the calcium score of the aortic valve (AVC) by CT, the calcium score indexed by body surface area (AVCI) and the calcium density (AVCD) as ratio of calcium/ LVOT area. They identified the best cut off point of calcium score, calcium score index and calcium density for patients with severe AS and high gradients. The cut -point values for men is >2,065 arbitrary units (AU) or >476 AU/cm^2 and for women is >1274 AU or >292 AU/cm^2. These cut-points provide a specificity to detect hemodynamically severe AS higher than 80% and a sensitivity higher than 80% for non-indexed AVC and higher than 90% for AVC indexed to aortic annulus area.

Interestingly, ~50 % of the patients with discordant gradient/AVA and severe AS, shared the same calcium density as the group with severe AS and high gradients, so the evaluation of the calcium load helped to identify a group of patients with low gradients but truly severe AS [28].

Calculation the AVA with CT by planimetry does not help to solve the discordance data given that planimetry measures the anatomical orifice that is always larger than the effective orifice area measured by echocardiography [8].

Heart catheterization: Calculation of AVA by echocardiography using the continuity equation is the preferred method to evaluate aortic stenosis. Valvular disease guidelines recommend using heart catheterization in case of conflicting data [2]. Heart catheterization can be useful to corroborate a low output state in cases when there is discrepancy between the cardiac output measured by LVOT and other echocardiographic methods (Simpson's rule or 3D). In a group of 58 patients with PLFAS by echocardiography, heart catheterization showed a good correlation between SVI measured by echocardiography and by heart catheterization when oximetry method was used. Small percentage of the PLFAS cases (1.7 %) was re-classified as moderate AS [30].

The calculation of the AVA by Gorlin hydraulic orifice principle vary with changes in transvalvular flow rate, similar to the continuity equation by echocardiography, thus heart catherization does not help to calculate the AVA in the group of patients with discordance between a low gradient and tight AVA [29].

Stress test: In low flow states, AS may appear severe due to an incomplete opening of a moderately stenotic valve, so it is imperative to distinguish this situation from the truly severe AS. With Dobutamine stress echo, the stroke volume can increase (demonstrating a contractile reserve). If the AS is truly severe, it is possible that the gradients increase with the increased stroke volume. In that case, AS can be re-classified as truly severe. It is possible that with the increased stroke volume, the aortic valve opens more. In that case, the AVA calculated under stress conditions may be bigger (in the moderate or mild range). In that case, the stress unmasked a "pseudo severe AS" due to low transvalvular flow [17].

Clavel and colleagues reported that in up to 33% of patients with PLFAS, the stenosis was "pseudo severe" as the AVA increased to >1 cm^2 with stress echo [31]. So, stress echo can help to identify a subgroup of patients in whom the aortic valve opening improved with improvement in transvalvular flow. Stress tests however, can be inconclusive in patients unable to increase stroke volume with dobutamine or in patients with restrictive physiology as dobutamine may even worsen the forward flow [32].

Role of Nitroprusside infusion: Infusion of nitroprusside (NPS) can help to unmask low gradients and re classify the degree of AS. In one elegant experiment of 18 patients with PLFAS and hypertension, progressive infusion of NPS was given under hemodynamic monitoring with right, left catheterization and echocardiography performed at baseline and at peak infusion. NPS infusion produced significant reduction in blood pressure, left ventricular end diastolic pressure, pulmonary pressures and significant increment in aortic valve area [33]. Reduced blood pressure and filling pressures may not only help to re-classify severity on the AS, but also, improved symptoms associated with HTN. Further studies are warranted.

Does PLFAS Represent a More Advanced Stage of the Disease?

One hypothesis of the etiology of PLFAS is that the high gradients have been missed in the past, and low gradients represent more advanced myocardial damage. There is some data against this hypothesis:

Dahl and colleagues [33] looked at a group of 78 patients with PLFAS who had at least a prior echocardiogram in the last five years prior to the index echocardiogram. They observed the rate of progression of the disease between serial echocardiograms and compared it to 2 other groups of patients with aortic stenosis: 1: normal EF, normal flow and high gradients severe aortic stenosis (NFHG) and 2: normal EF, normal flow, low gradient aortic stenosis (NFLG).

They analyzed longitudinal changes in AVA, mean gradient, diastolic function, left ventricle cavity size, systemic arterial compliance, global arterial load and they classified the type of LV geometry according to guidelines:

Compared to NFHG and NFLG AS, the group of PLFAS showed:

more rapid decrease in AVA per year, slower rate of increase in mean gradient, higher incidence of concentric remodeling, progressive reduction in LV size, greater increase in pulmonary pressure, and rapid progression of diastolic dysfunction.

Only 5% showed high gradients in the past echocardiogram, all of them were symptomatic [31].

In summary, it seems that patients with PLFAS have a different remodeling process compared to NFLG o NFHG AS. The low gradients are infrequently preceded by a high gradient stage. PLFAS unlikely represents an end stage of the high gradient AS [33].

Outcomes

There are very limited data on the outcomes in PLFAS and the potential benefit of aortic valve intervention. All, but a sub study of the PARTNER trial, are non-randomized and retrospective studies.

The difficulties to interpret outcomes can be explained by the existence of:

- Different definitions of the population studied: many groups who published data on low flow, low gradient AS, included patients with normal stroke volume index (normal flow) which do not represent a "true PLFAS".
- Different symptomatic status of the patient populations: some studies analyzed both symptomatic and asymptomatic patients together. Outcomes are significantly different in patients with asymptomatic AS, thus, the validity of the conclusion of those studies is uncertain.
- Unavoidable bias introduced in the patient selection for intervention in non-randomized studies. Valve replacement in PLFAS studies range from 17% [34] to 75% [4].

Most of the retrospective studies, reported worse outcomes in PLFAS compared to high gradient AS including worse medical outcome in medically treated group and worse surgical outcomes. Most studies report benefit of AVR (non-randomized, retrospective studies) studies [4,35-39]. PARTNER trial is the only randomized trial that analyzed in a sub study the PLFAS population.

PARTNER trial is a multicenter, randomized, clinical trial that compared trans aortic valve replacement (TAVR) with surgical aortic valve replacement (SAVR) in high risk AS patients; It included a cohort of inoperable patients in which conservative approach was randomized vs TAVR.

Three questions can be answered from the data available:

1. Is the natural history of PLFAS similar to other AS groups?

One study showed similar outcomes of PLFAS and Moderate AS if both groups are medically treated; however, all the patients were asymptomatic. The trial entry criteria was moderate AS, so it is unclear if this corresponds to the PLFAS population [40].

Two studies showed that PLFAS has worse outcomes when compared with normal flow groups and low flow/ high gradient AS [3,4]. Different rates of intervention, in a non-randomized fashion, makes difficult to interpret the results; However, data shows that symptomatic PLFAS patients share the same bad outcome as symptomatic, high gradient, severe AS, if both groups are medically treated (Figure 3) [41].

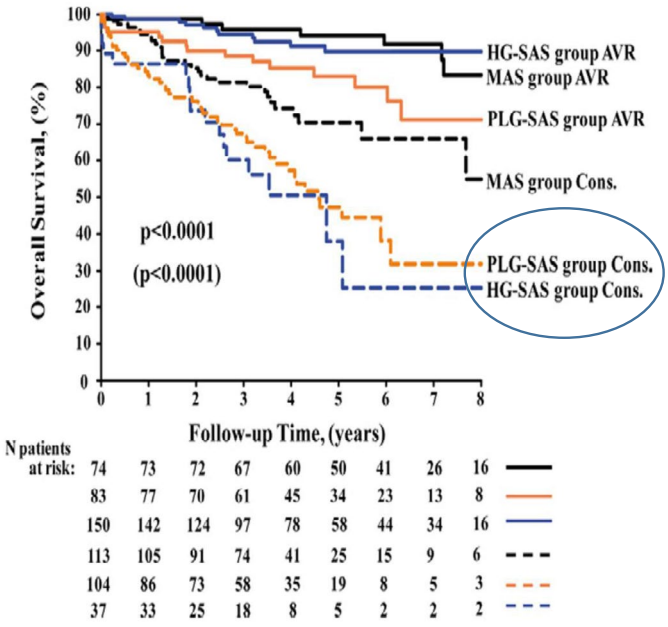

Figure 3: Similar outcomes PLFAS and NF AS when treated medically. Copy with permission from JACC [40]. HGAS: High Gradient Severe AS; MAS: Moderate AS; PLG-SAS: Paradoxical Low Gradient Severe AS.

2. What is the risk of aortic valve replacement in the PLFAS population?

Risk of intervention appears to be higher in PLFAS compared to high gradient AS, and similar to Low gradient AS with low EF (Figure 4) [35].

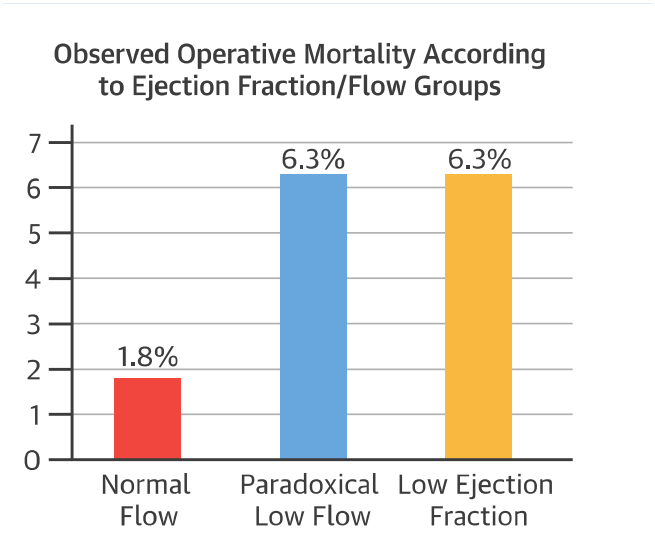

Figure 4: Observed operative mortality according to ejection fraction/flow groups. Copy with permission from JACC [34].

3. Does Aortic valve replacement improve outcomes PLFAS?

The only randomized data comes from a sub study of the PARTNER trial. In a high-risk group of inoperable patients with PLFAS, TAVR confers significant benefit compared with conservative approach [42].

In the high-risk cohort that compared TAVR vs SAVR in PLFAS, the 2-year mortality was high ~40% [41].

Conclusion

The diagnosis of AS is not as simple as it appeared to be in the past. New classification of the entity in base of EF, cardiac output o transvalvular flow, high or low gradients and symptomatic status makes the clinical approach complex. PLFAS is not an uncommon condition, encountered frequently in daily cardiology practice. It is not the result of technical errors at the time of acquisition of echocardiographic images, although, suboptimal techniques may lead to over diagnose this entity. It appears to have a similar or worse prognosis than typical, high gradient, AS. These patients are characterized by a different LV response to the valvular load imposed by the aortic stenosis, often combined with high arterial load as a result of decreased arterial compliance. It is imperative to understand echocardiographic findings given the implications of therapeutic decisions.

Once discordant echocardiographic data is encountered, it requires a detailed and careful analysis from echo-cardiographers and cardiologists. Echo-cardiographers should be educated to search for potential measurement errors. The treatment decision is complex and will likely require additional imaging test. There is still uncertainty regarding what is the best approach.

There are numerous reports on outcomes in non-randomized populations. This can create doubts about the validity of the conclusions. There are, however, data to support intervention from the sub study of the PARTNER trial that showed benefit with aortic valve replacement. The fact that some groups observed a similar outcome in patients treated medically with PLFAS and severe, typical, high gradient aortic stenosis, speaks also in favor of intervention. Team approach is essential in the decision and all the data should be integrated.

Ultimately, the gold standard to assess the severity of the AS is a direct visualization of the valve. A piece of data that might be helpful is the cardiac surgeon's observations and impressions when looking at the aortic valve in the operating room in the PLFAS population. It would be interesting to correlate its clinical assessment.

It is unlikely that a randomized clinical trial to compare medical vs surgical outcomes will take place.

We need that the cardiology community continues to report data on the topic so we can continue to learn more about this fascinating entity.

References

1. Authors/Task Force Members, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, et al. Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2012 Oct 1;33(19):2451-96.

2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2017 Jul 3;70(2):252-89.

3. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Clinical Perspective. Circulation. 2007 Jun 5;115(22):2856-64.

4. Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: clinical characteristics and predictors of survival. Circulation. 2013 Oct 15;128(16):1781-9.

5. Anderson B. Echocardiography: the normal examination and echocardiographic measurements. Blackwell Publishers; 2002 Oct 1.

6. Clavel MA, Malouf J, Messika-Zeitoun D, Araoz PA, Michelena HI, Enriquez-Sarano M. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. JACC: Cardiovascular Imaging. 2015 Mar 1;8(3):248-57.

7. O'Brien B, Schoenhagen P, Kapadia SR, Svensson LG, Rodriguez L, Griffin BP, et al. Integration of 3D imaging data in the assessment of aortic stenosis: impact on classification of disease severity. Circulation: Cardiovascular Imaging. 2011 Sep;4(5):566-73.

8. Clavel MA, Malouf J, Messika-Zeitoun D, Araoz PA, Michelena HI, Enriquez-Sarano M. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. JACC: Cardiovascular Imaging. 2015 Mar 1;8(3):248-57.

9. Arsalan M, Squiers JJ, Filardo G, Pollock B, DiMaio JM, Parva B, et al. Effect of elliptical LV outflow tract geometry on classification of aortic stenosis in a multidisciplinary heart team setting. JACC: Cardiovascular Imaging. 2017 Nov 1;10(11):1401-2.

10. Kamperidis V, van Rosendael PJ, Katsanos S, van der Kley F, Regeer M, Al Amri I, et al. Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data. European Heart Journal. 2015 Aug 14;36(31):2087-96.

11. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. Journal of the American College of Cardiology. 2009 Sep 8;54(11):1003-11.

12. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. Journal of the American College of Cardiology. 2005 Jul 19;46(2):291-8.

13. Little SH, Chan KL, Burwash IG. Impact of blood pressure on the Doppler echocardiographic assessment of severity of aortic stenosis. Heart. 2007 Jul 1;93(7):848-55.

14. Pibarot P, Dumesnil JG. Improving assessment of aortic stenosis. Journal of the American College of Cardiology. 2012 Jul 17;60(3):169-80.

15. Pibarot P, Dumesnil JG. Aortic stenosis: look globally, think globally. JACC Cardiovasc Imaging. 2009;2(4):400-403.

16. Takeda S, Rimington H, Smeeton N, Chambers J. Long axis excursion in aortic stenosis. Heart. 2001 Jul 1;86(1):52-6.

17. Delgado V, Tops LF, van Bommel RJ, van der Kley F, Marsan NA, Klautz RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. European Heart Journal. 2009 Dec 1;30(24):3037-47.

18. Adda J, Mielot C, Giorgi R, Cransac F, Zirphile X, Donal E, et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circulation: Cardiovascular Imaging. 2012 Jan;5(1):27-35.

19. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. Journal of the American Society of Echocardiography. 2013 Feb 1;26(2):185-91.

20. Magne J, Mohty D. Paradoxical low-flow, low-gradient severe aortic stenosis: a distinct disease entity. Heart. 2015;101(13):993-995.

21. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. European Heart Journal. 2016;37(34):2645-2657.

22. Itabashi Y, Shibayama K, Mihara H, Utsunomiya H, Berdejo J, Arsanjani R, et al. Significant reduction in mitral regurgitation volume is the main contributor for increase in systolic forward flow in patients with functional mitral

regurgitation after transcatheter aortic valve replacement: hemodynamic analysis using echocardiography. Echocardiography. 2015 Nov;32(11):1621-7.

23. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Journal of the American Society of Echocardiography. 2009 Jan 1;22(1):1-23.

24. Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarval S, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. Journal of the American College of Cardiology. 2014 Sep 23;64(12):1202-13.

25. O'Brien KD, Kuusisto J, Reichenbach DD, Ferguson M, Giachelli C, Alpers CE, et al. Osteopontin is expressed in human aortic valvular lesions. Circulation. 1995 Oct 15;92(8):2163-8.

26. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of'degenerative'valvular aortic stenosis. Histological and immunohistochemical studies. Circulation. 1994 Aug;90(2):844-53.

27. Messika-Zeitoun D, Aubry MC, Detaint D, Bielak LF, Peyser PA, Sheedy PF, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation. 2004 Jul 20;110(3):356-62.

28. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. Journal of the American College of Cardiology. 2013 Dec 17;62(24):2329-38.

29. Tandon A, Grayburn PA. Imaging of low-gradient severe aortic stenosis. JACC: Cardiovascular Imaging. 2013 Feb 1;6(2):184-95.

30. Lauten J, Rost C, Breithardt OA, Seligmann C, Klinghammer L, Daniel WG, Flachskampf FA. Invasive hemodynamic characteristics of low gradient severe aortic stenosis despite preserved ejection fraction. Journal of the American College of Cardiology. 2013 Apr 30;61(17):1799-808.

31. Clavel MA, Ennezat PV, Maréchaux S, Dumesnil JG, Capoulade R, Hachicha Z, et al. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. JACC: Cardiovascular Imaging. 2013 Feb 1;6(2):175-83.

32. Clavel MA, Pibarot P, Dumesnil JG. Paradoxical low flow aortic valve stenosis: incidence, evaluation, and clinical significance. Current cardiology reports. 2014 Jan 1;16(1):431.

33. Dahl JS, Eleid MF, Pislaru SV, Scott CG, Connolly HM, Pellikka PA. Development of paradoxical low-flow, low-gradient severe aortic stenosis. Heart. 2015 Jul 1;101(13):1015-23.

34. Tribouilloy C, Rusinaru D, Maréchaux S, Castel AL, Debry N, Maizel J, et al. Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. Journal of the American College of Cardiology. 2015 Jan 6;65(1):55-66.

35. Clavel MA, Berthelot-Richer M, Le Ven F, Capoulade R, Dahou A, Dumesnil JG, et al. Impact of classic and paradoxical low flow on survival after aortic valve replacement for severe aortic stenosis. Journal of the American College of Cardiology. 2015 Feb 24;65(7):645-53.

36. Pai RG, Varadarajan P, Razzouk A. Survival benefit of aortic valve replacement in patients with severe aortic stenosis with low ejection fraction and low gradient with normal ejection fraction. The Annals of Thoracic Surgery. 2008 Dec 1;86(6):1781-9.

37. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Piérard LA. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. Journal of the American College of Cardiology. 2012 Jan 17;59(3):235-43.

38. Ozkan A, Hachamovitch R, Kapadia SR, Tuzcu EM, Marwick TH. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. Circulation. 2013 Aug 6;128(6):622-31.

39. Belkin RN, Khalique O, Aronow WS, Ahn C, Sharma M. Outcomes and survival with aortic valve replacement compared with medical therapy in patients with low-, moderate-, and severe-gradient severe aortic stenosis and normal left ventricular ejection fraction. Echocardiography. 2011 Apr;28(4):378-87.

40. Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, Chambers JB, Egstrup K, Kesäniemi YA, Malbecq W, Nienaber CA. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation. 2011 Mar 1;123(8):887-95.

41. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Sénéchal M, Pibarot P. Outcome of patients with aortic

stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. Journal of the American College of Cardiology. 2012 Oct 2;60(14):1259-67.

42. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. Circulation. 2013 Jun 11;127(23):2316-26.