Impact of Arterial Blood Pressure on Ultrasound Hemodynamic Assessment of Aortic Valve Stenosis Severity

A. Hayek, F. Derimay, L. Green, M. Rosset, H. Thibault, G. Rioufol, G. Finet

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Ahmad Hayek[1] MD, François Derimay[1] MD, PhD, Lisa Green[1] MD, Marion Rosset[2] MD, Hélène Thibault[2] MD, PhD, Gilles Rioufol[1] MD, PhD, Gerard Finet[1] MD, PhD,

[1]Department of Cardiology and Interventional Cardiology, Hôpital Cardiologique Louis Pradel, Université Claude-Bernard, Inserm UMR 1060, Lyon, France
[2]Echocardiography Lab, Hôpital Cardiologique Louis Pradel, Lyon Université Claude-Bernard, Inserm UMR 1060, Lyon, France

Corresponding author:
Pr Gérard FINET
Hôpital Cardiologique Louis Pradel
Service de Cardiologie, Filière Coronaires-Valves
28 Avenue Doyen Lépine
69677 Bron
France
Tel. : +33472118880
Email: gerard.finet@univ-lyon1.fr

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Abstract

Background

Aortic stenosis (AS) severity assessment is based on several indices. Aortic valve area (AVA) is subject to inaccuracies inherent to the measurement method, while velocities and gradients depend on hemodynamic status. There is controversy as to whether blood pressure directly affects common indices of AS severity.

Objectives

The study objective was to assess the effect of systolic blood pressure (SBP) variation on AS indices, in a clinical setting.

Methods

A prospective, single-center study included 100 patients with at least moderately severe AS with preserved left-ventricle ejection fraction. Patients underwent ultrasound examination during which AS severity indices were collected, with 3 hemodynamic conditions: 1) low SBP: <120mmHg; 2) intermediate SBP: between 120 and 150mmHg; 3) high SBP: ≥150mmHg. SBP profiles were obtained, for each patient, by injection of isosorbide dinitrate or phenylephrine.

Results

At baseline state, 59% presented a mean gradient (G_{mean}) ≥40mmHg, 44% a peak aortic jet velocity (V_{peak}) ≥4m/s, 66% a dimensionless index (DI) ≤0.25 and 87% an indexed aortic valve area (AVAi) ≤0.6cm^2/m^2. Compared with intermediate and low SBP, high SBP induced a significant decrease in G_{mean} (39±12 vs. 43±12 and 47±12mmHg respectively), ($p<0.05$) and in V_{peak} (3.8±0.6 vs. 4.0±0.6 and 4.2±0.6mmHg), ($p<0.05$). Compared with the baseline measures, in 16% of patients with an initial G_{mean}<40mmHg, gradient rose above 40mmHg after optimization of the afterload (low SBP) ($p<0.05$). Conversely, DI and AVAi did not vary with changes in hemodynamic conditions. Flow rate, not Stroke volume was found to impact G_{mean} and V_{peak} but not AVA and DI ($p<0.05$).

Conclusion

Hemodynamic conditions may affect the AS ultrasound assessment. High SBP, or afterload, leads to an underestimation of AS severity when based on gradients and velocities. SBP monitoring and control is crucial during AS ultrasound assessment.

Key-words: Aortic stenosis, afterload, Aortic valve area, Mean transaortic gradient, Dimensionless index, Echocardiography; Flow rate;

Abbreviations

AS = aortic stenosis

AVA = aortic valve area

CI = Cardiac index

DI = Dimensionless index

FR = Flow rate

$\mathbf{G_{mean}}$ = Mean gradient

LF-LG SAS = Low flow low gradient severe aortic stenosis

LVEF = left ventricle ejection fraction

LVOT = Left ventricle outflow tract

NF-LG SAS = Normal flow log gradient severe aortic stenosis

SBP = Systolic blood pressure

SPAP = systolic pulmonary arterial pressure

SVi = Indexed stroke volume

$\mathbf{V_{peak}}$ = Peak aortic jet velocity

$\mathbf{VTI_A}$ = Aortic velocity time integral

$\mathbf{VTI_{LVOT}}$ = LVOT velocity time integral

Zva = Valvuloarterial impedance

INTRODUCTION

Calcific aortic stenosis (AS) is the third most common cardiovascular disease in Western countries[1]. Doppler-echocardiography is the primary method to confirm diagnosis and severity[2]. The European Society of Cardiology guidelines[3] define a number of echocardiographic parameters to evaluate the severity of aortic stenosis, in patients with preserved left ventricle ejection fraction (LVEF). However, there may often be discrepancies between the various parameters: peak aortic jet velocity (V_{peak}), mean gradient (G_{mean}), dimensionless index (DI) and aortic valve area (AVA), generally leading to misestimating the aortic valve pathology[4]. Indeed, highly contributive studies suggested that classifying AS severity by AVA leads to a higher proportion of severe AS[5]. This is due to underestimation of left ventricle outflow tract (LVOT), due to its ellipticity[6,7], which is not taken into account in the ultrasound estimation of AVA[8].

At the same time, systemic hypertension is a high-prevalence disease[9], especially in patients with AS (32% are hypertensive)[10]. It is a global determinant of left ventricle afterload[1]. High systolic blood pressure (SBP) impact on AS severity parameters is difficult to estimate, since it includes complex changes in vascular resistance, transvalvular flow[11–13] and arterial compliance[14,15]. The natural consequence is that high SBP during examination may lead to misclassification of AS severity. As clearly mentioned by *Minners et al* in a recent editorial, trials with patients with AS of all levels of hemodynamic severity are needed to improve classification and patient care[16].

The objective of this study was to evaluate the impact of SBP variations during the ultrasound measurement of each AS severity parameter and the potential impact on severity assessment.

METHODS

Patient population

A prospective single-center study was conducted in the Louis Pradel Heart Hospital (Hospices Civils de Lyon, Bron, France). Patients were included consecutively from 2017 to 2019, after they provided a written informed consent, and the study protocol was approved by the hospital review board. The inclusion-objective was 100 patients. The included patients presented with a moderate to severe native aortic stenosis confirmed

with Doppler-echocardiography defined with at least one of the following criteria: i) peak aortic jet velocity between 350 and 500 $cm.s^{-1}$; ii) mean aortic gradient between 25 and 65 mmHg; iii) Dimensionless index between 0.20 and 0.35; and/or iv) aortic valve area between 0.6 and 1.3 cm^2. Exclusion criteria comprised concomitant valvulopathy liable to interfere with hemodynamic assessment of the aortic stenosis: significant aortic and/or mitral regurgitation grade >2/4, LVEF < 40%, hemodynamic instability and poor echogenicity making impossible all required measurements. The patients were enrolled in the study after a first ultrasound exam confirming the patient eligibility for the study.

Ultrasound measurements and hemodynamic profiles

The study used a Vivid S60 ultrasound machine equipped with a cardiologic probe (GE Healthcare Systems, Chicago, Illinois, United States). After patient inclusion and collection of clinical data, a dedicated ultrasound evaluation (baseline) was performed to collect the following baseline parameters independently of hemodynamic state and confirm patient eligibility: LVEF, visual or by the Simpson biplane method (%); Diameter of the aorta (mm) and the LVOT diameter (cm); tri- or bi-cuspid nature of the aortic valve; systolic pulmonary arterial pressure (SPAP); right atrial pressure; aortic or mitral insufficiency grade.

We defined three different hemodynamic profiles: 1) low SBP (<120 mmHg), 2) intermediate SBP (between 120 and 150mmHg) and 3) high SBP (≥150mmHg). The different SBP targets were reached by intravenous administration of either isosorbide dinitrate (Risordan®) 1mg/ml (systemic vasodilator), in 2 mg bolus every 2 minutes to decrease blood pressure, or phenylephrine (Néo-synéphrine®) (α1 vasoconstrictor), in 250 µg (5 ml) bolus every 2 minutes, up to a maximum dose of 2mg, to increase blood pressure.

During the ultrasound exam, hemodynamic condition was systematically collected with: systolic, mean and diastolic blood pressure and heart rate, at each SBP profile. Blood pressure was collected automatically every 2 minutes, using a non-invasive blood pressure monitor, to control its stability at each profile.

As described in figure 1, the initial ultrasound exam performed was considered to be the baseline profile T_0 and then was repeated to reach all hemodynamic profiles (T_1 and T_2) according to SBP targets. Briefly, if the patient presented with a baseline

SBP<120mmHg, he would benefit from two successive injection of phenylephrine to reach the intermediate then the high SBP target. If the patient presented with a baseline SBP≥150 mmHg, he would benefit from two successive injections of isosorbide dinitrate to reach the other profile targets. If the patient presented with an intermediate baseline SBP, he would benefit from phenylephrine to reach the high SBP profile and then isosorbide dinitrate until low SBP is reached.

The ultrasound examination collected the following data at each profile: V_{peak}; G_{mean}; aortic velocity time integral (VTI_A); LVOT velocity time integral (VTI_{LVOT}); DI ($DI=VTI_{LVOT}/VTI_A$); AVA (calculated by the continuity equation); indexed AVA (AVAi); cardiac index (CI); indexed stroke volume (SVi); systolic ejection time; flow rate (FR) systemic vascular resistance (SVR) measured as: (mean blood pressure - central venous pressure)*80/CI; valvuloarterial impedance (Z_{va}). Mean blood pressure was measured using the manual tension hand cuff. Central venous pressure was estimated echographically using the maximal inferior vena cava diameter and its inspiratory collapse. For patients with non-sinus rhythm, values of AS indices were means of five recorded cycles.

All data collected were interpreted offline, blindly to the hemodynamic condition and the acquisition, by a second operator.

Study endpoint

The diagnosis of severe aortic stenosis was established according to the ASE guidelines[2] ($G_{mean} \geq 40$ mmHg, $V_{peak} \geq 4$ m/s, DI ≤ 0.25, AVA ≤ 1 cm^2, AVAi ≤ 0.6 cm^2/m^2). The primary outcome was the variation of aortic stenosis severity parameters according to changes in SBP. The secondary outcome was the correlation between the parameters.

Statistical analysis

Continuous variables were presented as mean±SD and dichotomous variables as percentages only. For continuous variables, one-way ANOVA was used to assess significant differences ($p<0.05$) between the 3 groups. For dichotomous variables, chi-squared test was used ($p<0.05$) between the groups. A logistic regression model was used to assess mean gradient effect on coherence percentage ($p<0.05$). The coherence percentage corresponds to the number of patients with an expected pattern. All analyses were performed on R software (R Core-Team, 2018) using the default functions.

RESULTS

The main baseline clinical and hemodynamic characteristics and ultrasound data of the 100 patients included are presented in *Table 1*. Briefly, mean age was 80±10 years and 53% were men. Sixty-four percent of patients had a history of hypertension and 85% were symptomatic (with dyspnea, angina or previous syncope). Their symptoms were not only related to the AS since 43% had coronary artery disease and 29% atrial fibrillation). At baseline, the average of SBP and HR were respectively 130±22mmHg and 71±14bpm. Mean LVEF was 59±9%. Regarding AS severity indices, average G_{mean}, V_{peak}, AVA, AVAi and DI were respectively 43±13mmHg, 4±0.6m/s, 0.83±0.24cm^2, 0.48±0.15cm^2/m^2 and 0.23±0.06. At baseline, 37% of the patients had low SBP (<120mmHg), 20% high SBP (≥150mmHg) and 43% intermediate pressure (120-150mmHg).

Hemodynamic profiles and aortic valve stenosis severity assessment.

The three SBP profiles were systematically reached in all patients *(Table 2)*. Mean dose to reach the high SBP profile was 400 mcg for phenylephrine while mean dose of isosorbide dinitrate in order to reach low SBP profile was 3 mg.

Induction of high SBP resulted in a significant increase in SVR (<0.05) but did not significantly influence CI or SVi (45±12 vs. 45±12 vs. 44±11 $ml.m^{-2}$ for respectively low, intermediate and high SBP; *Table 2)*. Ejection time increased (218.5±42.2 vs. 303.7±39.6 vs. 320.4±38.0 ms) when SBP rose resulting in a significant decrease in flow rate (162.2±38.0 vs. 151.0±32.0 vs. 137.2±28.3 $ml.ms^{-1}.m^{-2}$; $p<0.05$). Zva increased when SBP was brought up (3.7±1.1 vs. 4.2±1.2 vs. 4.8±1.2; $p<0.05$). Between high and low SBP state, the percentage of severe AS increased from 42% to 75% ($p<0.05$), based on $G_{mean,}$ and from 36% to 61% ($p<0.05$), based on $V_{peak.}$ Conversely, the rate of severe AS based on DI, AVA and AVAi was not significantly impacted by the hemodynamic condition changes *(Table 2)*. G_{mean} and V_{peak} values were lower at high SBP profile than when SBP was brought under 120 mmHg (respectively 47±12 vs. 39±12 and 4.2±0.6 vs. 3.8±0.6, $p<0.05$). However, DI was not impacted by SBP changes. Hemodynamic state did not affect AVAi with the latter showing a higher percentage of severe AS independently of the arterial pressure *(Figure 2)*. Based on G_{mean} and V_{peak}, the percentages of severe AS

were significantly higher when SBP was brought under 120 mmHg compared to the basal state, respectively 75% compared with 59% for G_{mean} ($p<0.001$), and 61% compared with 44% for V_{peak} ($p<0.05$) *(Figure 3)*. On the other hand, no significant changes were noted when the severity of AS was assessed by DI or AVAi *(Figure 3)*.

Correlation between Mean gradient and dimensionless index

At high SBP (≥150mmHg), the distribution of G_{mean} values with DI showed a discrepancy rate of 34% between the two indices (29%: G_{mean}<40mmHg and DI≤0.25, 5%: G_{mean}≥40mmHg and DI>0.25). At low SBP (<120mmHg), the discrepancy rate dropped significantly to 22% (6%: G_{mean}<40mmHg and DI≤0.25, 16%: G_{mean}≥40mmHg and DI>0.25, $p<0.05$) *(Figure 4)*.

Correlation between Mean gradient and indexed aortic valve area

The discrepancy rate between G_{mean} and AVAi, dropped as well at low SBP profile compared to high SBP profile (20% compared with 43% $p<0.05$) *(Figure 4)*. Taking all blood pressure profiles together (three hundred data), there was a moderate correlation between G_{mean} and AVAi ($R^2=0.23$). An indexed AVA of 0.6 cm^2/m^2 corresponded to a G_{mean} of 36 mmHg in our cohort *(Figure 5)*.

Safety

As previously stated, only stable patients were included in our study. No significant complication, hemodynamic instability, angina, ECG ischemic changes or neurological symptom were recorded. There were no reported side effects as well.

DISCUSSION

To the best of our knowledge, this is the second study to present and directly assess the effect of blood pressure on AS severity indices in humans, using Doppler echocardiography. *Little et al.*[12], in 22 patients, found that hypertension interfered with the assessment of AS severity and was mainly related to changes in mean flow rate than to an independent effect of change in vascular resistance.

Variation of G_{mean} and V_{peak} according to the changes in SBP

High blood pressure significantly reduced G_{mean} and V_{peak}, independently of stroke volume.

In the present study, 16% of the baseline cohort, with low G_{mean} and 17% with low V_{peak} showed a rise above 40mmHg and 4m.s^{-1} respectively when SBP was brought under 120 mmHg ($p<0.05$). Several mechanisms may explain these variations in G_{mean} and V_{peak}. As shown in previous studies[12,13], aortic severity parameters are mainly determined by transvalvular flow. *Laskey et al.*[14] suggested that the gradient may decrease irrespective of flow as a direct consequence of increased systemic arterial resistance, whereas *Razzolini et al.*[15] found that, for each flow level, gradient increased linearly with systemic arterial resistance, thus overestimating AS severity. In the present study, neither SVi nor CI varied between groups. The change in blood pressure was the result of a change in systemic arterial resistance but also in flow rate *(Table 2). Kadem et al.,* in an animal model of supravalvular AS, found a significant reduction in peak-to-peak gradient measured by catheter, which was significantly related to arterial compliance and mean flow rate. In our study, we also showed an increase in Zva with the increase of SBP. Zva is an indicator of global LV load but does not discriminate valvular and arterial contribution to LV load[17]. It has been shown, to be a predictor of mortality in asymptomatic AS patients with preserved LVEF[18] and is correlated to poor clinical outcome[19]. In our work, induction of systemic hypertension contributed to an increase in the afterload and therefore in Zva with a concomitant decrease in the FR. This is related to the fact that systolic ejection time is prolonged when afterload is increased[20]. It is also worth discussing how FR impacted AS severity indices. The flow state in severe AS has been a hot topic in the last decade. *Pibarot et al*[21,22] described its importance even in patients with preserved LVEF. Transvalvular flow determination became a challenge since it influences the hemodynamic indices of AS. SV remains the most commonly transvalvular determinant used parameter in a routine setting with a cut-off value of 35 ml.m^{-2}. FR is measured as a ratio of SV to ejection time. Unlike SV which is defined by the blood volume, FR represents the volume per ejection time and may allow a better estimation of flow state[23]. In a recent retrospective study, the authors showed that FR at exercise, and not SV, could play a crucial role in the risk stratification of patients with asymptomatic AS[24], highlighting its prognostic value and that it may be the best indicator of the output state. *Namasivayam et al*[25] recently, also shed light on why flow rate assessment should be incorporated into clinical diagnosis and prognosis of AS. In

our study, the gradients and velocities decreased when afterload rose and were associated with a decrease in the FR but unchanged SV. This is related to the fact that LV ejection time depends upon LV afterload. When mean aortic pressure elevates, the duration of ejection is lengthened[20]. This shows the diagnostic value of FR in AS setting and why its measurement is necessary in any ultrasound report. On these basis, AVA and DI appear to provide a more accurate assessment when BP is high since the impact on FR (even with unchanged SV) will impact transvalvular velocities and gradients.

This result provides some explanation for the intriguing pattern associating severe aortic stenosis and low mean gradient and may partially explain why some patients with normal flow have low DI and AVA. In agreement with *Sakthi et al.*,[26] besides discrepancies between parameters, high blood pressure may interfere significantly with the assessment of aortic stenosis severity parameters on Doppler-echocardiography or catheterization.

Dimensionless index is less dependent on hemodynamic profiles

The dimensionless index, an index with relatively scarce evidence in the literature, did not vary between groups (table 2). One approach to reducing error related to LVOT ultrasound measurements is to remove cross-sectional area from the simplified continuity equation. Since this is a ratio of two hemodynamic values (VTI_{LVOT} and VTI_A), it appears that DI is less dependent than other aortic severity indices on hemodynamic conditions. In fact, in our cohort, SBP changes did not impact DI and the percentage of severe AS based on this parameter was the same at baseline and when SBP was brought under 120 mmHg. Moreover, the discrepancy rate between G_{mean} and DI was significantly lower when afterload was optimized, low SPB vs. high SPB: 22% vs. 34% respectively.

DI, as well as AVA did not vary despite an increase in gradients and unchanged SV. Since AVA= SV/VTI_A, a variation in gradients without stroke volume modification can only be explained by changes in systolic ejection time resulting in flow rate variations. This explains VTI stability (LVOT and aortic) despite gradient changes. Thus, in patients with aortic stenosis, FR appears to be a more reliable indicator of transvalvular flow (which is a basic determinant of pressure gradients[27]) than SV.

This supports the notion not only that hemodynamics interferes with the evaluation of AS severity indices, but also that DI is a robust parameter emphasizing its value, since it

was the index subject to the least variation under changing blood pressure. *Jander et al,* confirmed the prognostic value of this parameter. Four hundred thirty five patients with AVA<1cm^2 and G_{mean}≤40 mmHg and LVEF>55% were stratified according to DI with a cutoff value of 0.25. Patients with DI<0.25 had significantly more aortic valve related events[28]. As suggested by *Minners et al.* in 2019, DI may be a parameter deserving increased attention, and our result does support DI to be a flow independent parameter of stenosis severity[16].

Furthermore, LVOT diameter may be altered by volume and pressure changes. Even more in patients with severe AS, LVOT is less distensible and undergoes remodeling as shown by *Mehrotra et al.*[29]*,* another issue highlighting the importance of the DI. However, in our study, LVOT diameter did not vary.

AS severity assessment with AVA parameter

AVA is a major determinant of G_{mean}. Because fluid is incompressible, Poiseuille's law imposes that blood flow in any conduit is inversely proportional to its cross-sectional area. In our study, AVAi was not impacted by the changes in SBP and there were fewer discrepancies between G_{mean} and AVAi when blood pressure was brought under control even more highlighting the importance of SBP monitoring.

In our study, there was a higher percentage of severe AS regardless of blood pressure profile, in line with data from *Minners et al.* study[5]. This is, of course, partly the result of underestimation of LVOT because of its elliptical form and of the fact that severity cut points for AVA have been derived and extensively validated using the continuity equation methodology.

The data presented in our study suggest that cut points defining severe AS are different with severity thresholds for both DI and AVAi not well aligned. That said, since no outcome data was provided, this study cannot truly determine if the echocardiographic defined cut points are sufficient or not Clinical outcome would be of interest to assess the diagnostic and prognostic values of these indices.

Clinical implications

Systolic hypertension is highly prevalent in patients with calcific AS (one third of patients)[10]. As shown in our study, Doppler echocardiographic parameters of the aortic stenosis may lead to a misjudgment of the AS severity if the hemodynamic properties of

the circulation are not taken into account. When evaluating for possible aortic stenosis, the mean gradient is only a single variable that can be misleading. This has been shown with patients with low output low gradient, concomitant mitral regurgitation and low ejection fraction[30]. High SBP may lead to underestimation of AS severity, based on G_{mean} or V_{peak}, and hence misclassification of patients, which may delay surgical valve replacement. Conversely, if DI or AVA are used, the severity doesn't change during hemodynamic manipulations (or natural variations in pressure or flow) with both parameters less dependent on the hemodynamic conditions, despite their severity cut points not well aligned. These patients present a challenge with regard to management, as they may have symptomatic AS without for severity criteria according to international guidelines. Thus, the following recommendations can be made: 1) blood pressure monitoring must be an integral part of AS assessment (as recommended by ASE[31]), and control must be optimal (< 120 mmHg); 2) DI seems to be less dependent on hemodynamic properties and should be measured in any ultrasound report; and 3) Every parameter should be taken into account keeping in mind their respective limits.

During pharmacological challenge, no side effects or AS related de novo symptom were reported. We chose to include patients with G_{mean}<65 mmHg, since hemodynamic manipulations could be riskier at higher velocities (Vmax ≥ 5 m/s) and even useless at this stage of the pathology. That said, these maneuvers remain interesting in the case of discrepancies between severity indices. Furthermore, in patients with moderately severe AS based on G_{mean} with concomitant high SBP, isosorbide dinitrate administration during ultrasound examen may be beneficial in revealing severe AS.

Study limitations

The patients in the present study had been admitted to hospital; prevalence of systemic hypertension (64%) was higher than reported by *Antonini et al.*[10], who assessed the prevalence of systemic hypertension in a cohort of symptomatic patients with AS. Also, the present study was performed in a single center with acquisition realized by only one operator. Finally, there was no invasive continuous monitoring during ultrasound measurement, but blood pressure was measured several times (/2 min) during all data acquisition.

Routine hemodynamic evaluation, particularly in cardiac catheterization, showed discrepancies between systemic blood pressure measured by non-invasive peripheral

monitoring and central arterial pressure measured by catheter in the ascending aorta. Reduced arterial compliance in the present cohort may be the principal reason for this. Finally, since patients had their blood pressure manipulated by vasoconstriction or vasodilatation, any deleterious or favorable impact of these hemodynamic alterations on myocardial blood pressure blood flow and therefore on myocardial mechanics and ejection fraction can be suspected but hardly assessed.

Lloyd et al.[32] in a recent study showed, invasively, changes in SV and AVA following nitrate. He compared the acute hemodynamic response to nitrate between low flow low gradient severe AS (LF-LGSAS) and normal flow low gradient severe AS (NF-LGSAS) with preserved LVEF. SV did vary significantly in the LF-LGSAS group but not in the NF-LGSAS. In our study, only 13% of a 100 patient cohort *(Supplementary table 1)* had a LF state (SV<35ml/m^2). This mainly explains the discordance between both studies. As for AVA determination, it was calculated using the Gorlin invasive formula while we used the Doppler continuity equation. Flow-related discrepancies between Gorlin AVA and Doppler AVA assessment can occur in the clinical setting of patients with isolated AS[33]. On the other hand, there were similarities showing a decrease in gradients and velocities when SBP is increased.

CONCLUSION

Hemodynamic profiles during AS severity assessment influence the parameters. High blood pressure might cause a significant decrease in indices, and notably in gradients and velocities, mainly due to decreased flow rate. This may lead to underestimation of AS severity. In this regard, blood pressure monitoring should be an integral part of Doppler ultrasound examination. Finally, DI and AVA appeared to be the less influenced by changes in hemodynamic profiles.

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Figure legends:

Figure 1: Protocol for obtaining blood pressure target according to baseline

Description of protocol according to baseline systolic blood pressure (T_0). The green squares refer to the three blood pressure profiles at baseline ultrasound. Néo-synéphrine (N) and/or Risordan (R) were administered to reach the other blood pressure profiles, T_1 and T_2. SBP = systolic blood pressure, TTE = transthoracic echography.

Figure 2: Evolution of the AS severity parameters when modulating blood pressure

Graphs show mean ± SD (n=100/group). A: Mean gradient, B: Peak aortic jet velocity, C: velocity ratio, D: indexed aortic valve area. Threshold red lines for severe aortic stenosis are shown ($G_{mean} \geq 40$mmHg; $V_{peak} \geq 4 m.s^{-1}$; $DI \leq 0.25$; $AVAi \leq 0.6 cm^2/m^2$).

* p<0.05* and ** p<0.001 vs. other SBP profiles. SBP=systolic blood pressure.

Figure 3: Reclassification after hemodynamic optimization for each ultrasound AS severity parameter. (n=100)

Optimal state refers to the group with SBP ≤ 120 mmHg. * p<0.05* and ** p<0.001 vs. baseline state.

Figure 4. Comparison of distribution of mean gradient with dimensionless index and with indexed aortic valve area according to the blood pressure profiles. (n=100)

Dots in green areas correspond to patients with concordant aortic stenosis parameters and dots in red areas to discordant parameter distribution. * p<0.05 vs. high SBP

Figure 5. Correlation between mean gradient and indexed aortic valve area independently of blood pressure (n=300)

Figure 6. Clinical illustration of SBP impact on AS severity estimation.

The patient was an asymptomatic 89 year-old man with history of systemic hypertension. No coronary artery disease was found and ECG was in sinus rhythm. Her echocardiogram showed a LVEF of 55% SBP, no myocardial hypertrophy. Left ventricular outflow tract was 2.1 cm. The aortic valve was tricuspid. At baseline, SBP was high 174 mmHg. TTE showed inconsistencies with G_{mean} 35mmHg, DI 0.18 and AVAi 0.29 cm^2/m^2. The top row shows continuous-wave Doppler spectrograms of the aortic valve jet.

613 **Table 1: Baseline characteristics of the study population**

	population (n=100)
Clinical data	
Age	80 year±10
Male sex	53
Body surface (m^2)	1.8±0.2
Systemic hypertension	64
Diabetes mellitus	27
Dyspnea	
NYHA 1	17
NYHA 2	10
NYHA 3	45
NYHA 4	28
Angina	15
Syncope	5
Sinus cardiac rhythm	64
Anti-hypertensive therapy	62
Coronary artery disease	43
Haemodynamic data	
Systolic blood pressure, mmHg	130±22
Cardiac index ($ml/min/m^2$)	3.2±0.9
Indexed stroke volume (ml/m^2)	46± 2
SVR ($dynes.s.cm^{-5}$)	1262±525
Zva ($mmHg/ml/m^2$)	4.1±1.3
Echocardiographic data	
Peak aortic jet velocity (m/s)	4.0±0.6
Mean gradient (mmHg)	43±13
Dimensionless index	0.23±0.06
Aortic valve area (cm^2)	0.83±0.24
Indexed aortic valve area (cm^2/m^2)	0.48±0.15
LV ejection fraction (%)	59±9
SPAP (mmHg)	42±15
Tricuspid aortic valve	84
Diameter of the aorta (mm)	35±5

614

Values are mean± SD for continuous variables and percentage for dichotomous variables. LV=left ventricular, SVR=systemic vascular resistance, SPAP=systolic pulmonary artery pressure, Zva = valvuloarterial impedance

647 **Table 2: Comparison of the severity aortic stenosis parameters between the three**
648 **hemodynamic profile groups.**

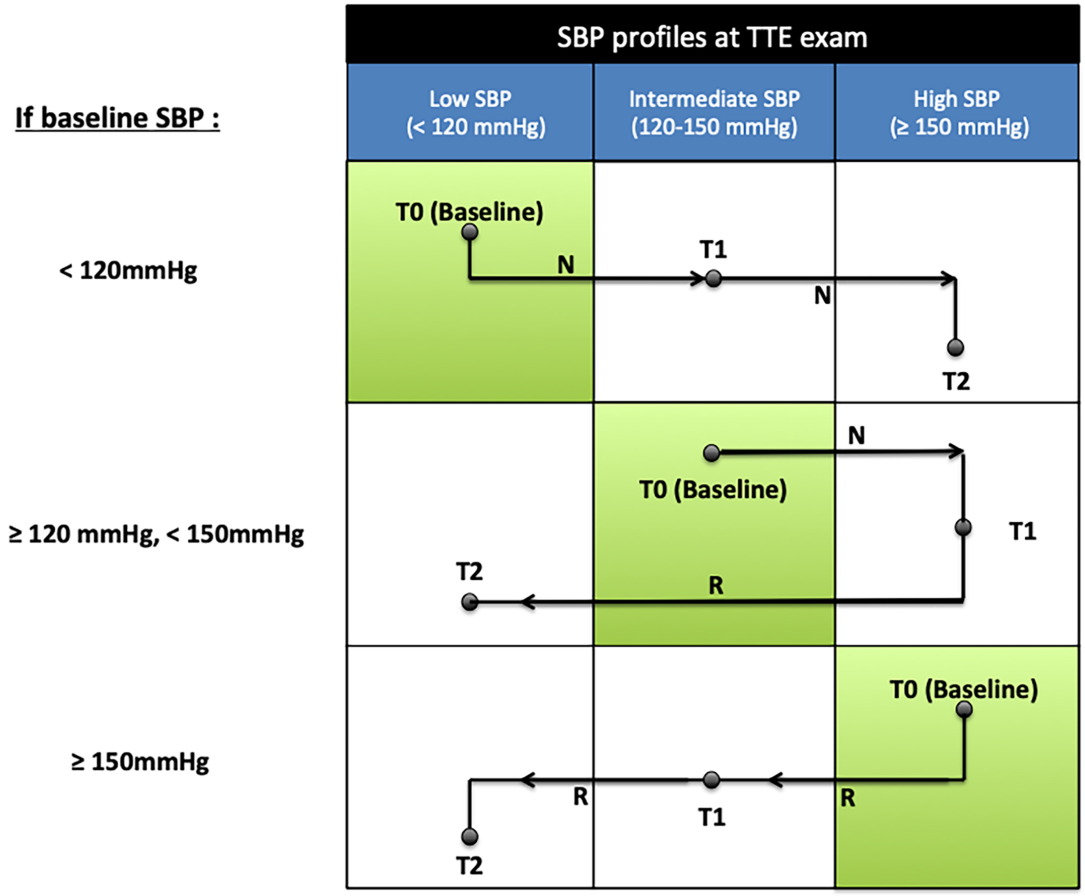
Variables	Low SBP <120 mmHg N = 100	Intermediate SBP between 120-150 mmHg N = 100	High SBP ≥150 mmHg N = 100	P value
SBP (mmHg)	110±9	132±9	158±15	p<0.05
DBP (mmHg)	62±10	71±12	77±12	p<0.05
MBP (mmHg)	78±10	91±10	104±13	p<0.05
HR (bpm)	73±13	72±14	69±15	NS
LVOT (mm)	21.2±1.6	21.2±1.6	21.2±1.6	NS
VTI_{LVOT}	22.3±4.4	22.2±4.7	21.9±4.4	NS
VTI_A	96.8±20.6	96.4±19.9	93.8±19.3	NS
CI (ml/min/m^2)	3.2±0.8	3.2±0.8	3.0±0.8	NS
Svi (ml/m^2)	45±12	45±12	44±11	NS
SVR (dynes.s.cm^{-5})	1083±346	1306±471	1575±446	p<0.05
Zva (mmHg/ml/m^2)	3.7±1.1	4.2±1.2	4.8±1.2	p<0.05
Gm (mmHg)	47±12	43±12	39±12	p<0.05
Vmax (m/s)	4.2±0.6	4.0±0.6	3.8±0.6	p<0.05
DI	0.24±0.06	0.24±0.06	0.24±0.06	NS
AVA (cm^2)	0.85±0.25	0.84±0.23	0.86±0.24	NS
AVAi (cm^2/m^2)	0.48±0.16	0.47±0.14	0.48±0.14	NS
Gm ≥ 40 mmHg	75	54	42	p<0.05
Vmax ≥ 4 m/s	61	38	36	p<0.05
DI ≤ 0.25	65	65	64	NS
AVA ≤ 1 cm^2	75	80	74	NS
AVAi ≤ 0.6 cm^2/m^2	85	83	83	NS
Variables	**Low SBP <120 mmHg N = 72**	**Intermediate SBP between 120-150 mmHg N = 72**	**High SBP ≥150 mmHg N = 72**	**P value**
Ejection time (ms)	218.5±42.2	303.7±39.6	320.4±38.0	p<0.05
Flow rate (ml.s^{-1}.m^{-2})	162.2±38.0	151.0±32.0	137.2±28.3	p<0.05

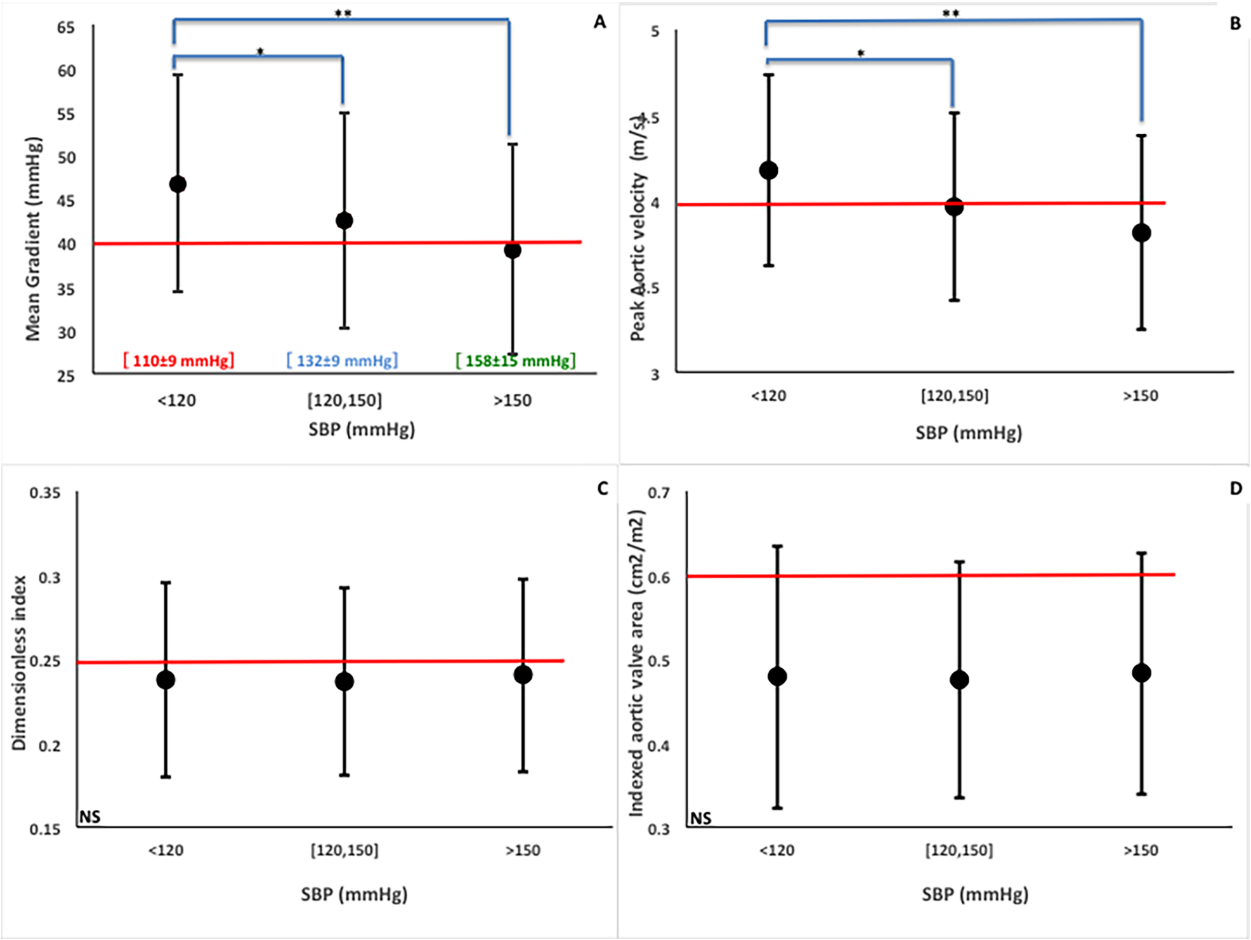
649

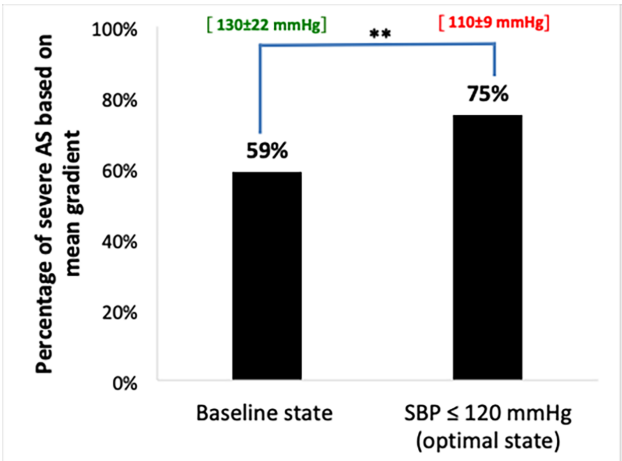
Values are mean±SD for continuous variables and percentage for dichotomous variables.

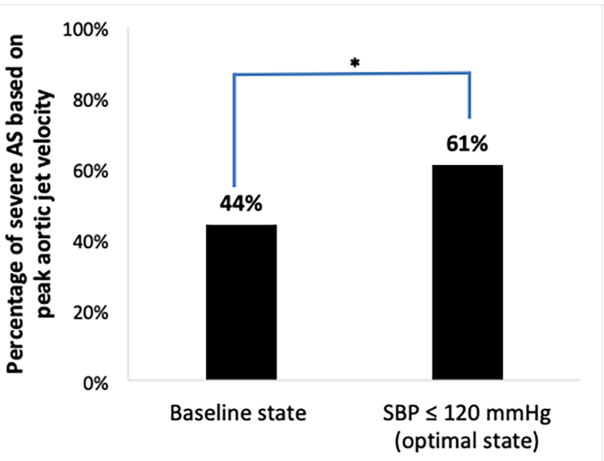
The significance threshold was p<0.05.

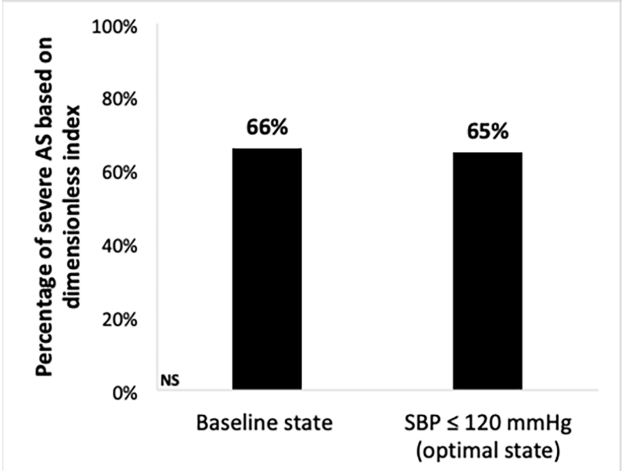
AVA=aortic valve area, AVAi=indexed aortic valve area, HF=Heart rate, DBP=diastolic blood pressure, DI=Dimensionless index, G_{mean}= mean gradient, CI=cardiac index, LVOT=Left ventricle outflow tract, MBP=mean blood pressure, SBP=systolic blood pressure, SVi=indexed stroke volume, SVR=systemic vascular resistance, V_{max}= peak aortic jet velocity, VTI_A=Aortic velocity time integral, VTI_{LVOT}=LVOT velocity time integral, Zva=valvulo-arterial impedance.

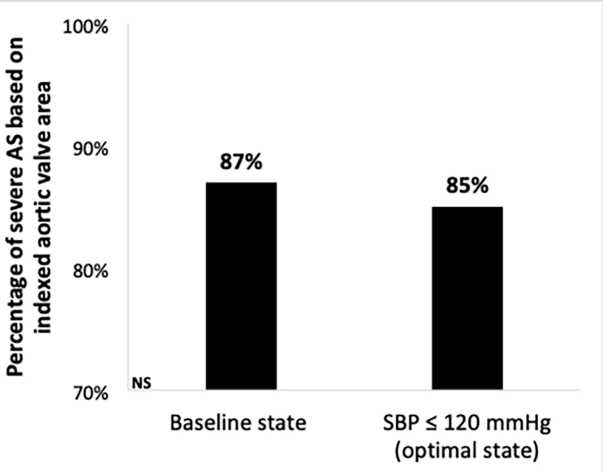

If baseline SBP :
SBP profiles at TTE exam
Low SBP (< 120 mmHg)
Intermediate SBP (120-150 mmHg)
High SBP (≥ 150 mmHg)
< 120mmHg
≥ 120 mmHg, < 150mmHg
≥ 150mmHg
T0 (Baseline)
N
T1
N
T2
N
T0 (Baseline)
T1
T2
R
T0 (Baseline)
R
T1
R
T2

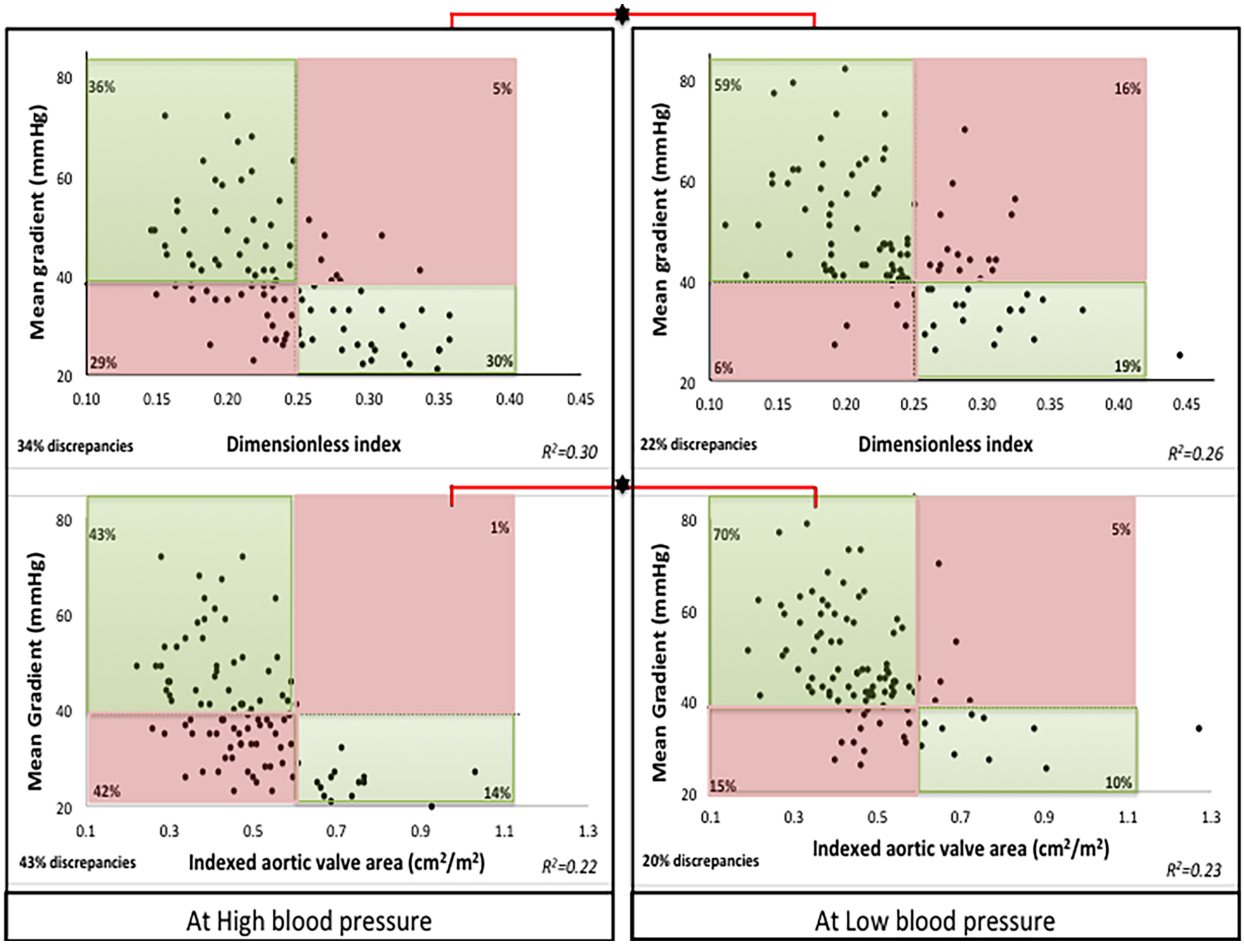

A
Mean Gradient (mmHg)
65
60
55
50
45
40
35
30
25
**
*
[110±9 mmHg]
[132±9 mmHg]
[158±15 mmHg]
<120
[120,150]
>150
SBP (mmHg)
B
Peak Aortic velocity (m/s)
5
4.5
4
3.5
3
**
*
<120
[120,150]
>150
SBP (mmHg)
C
Dimensionless index
0.35
0.3
0.25
0.2
0.15
NS
<120
[120,150]
>150
SBP (mmHg)
D
Indexed aortic valve area (cm2/m2)
0.7
0.6
0.5
0.4
0.3
NS
<120
[120,150]
>150
SBP (mmHg)

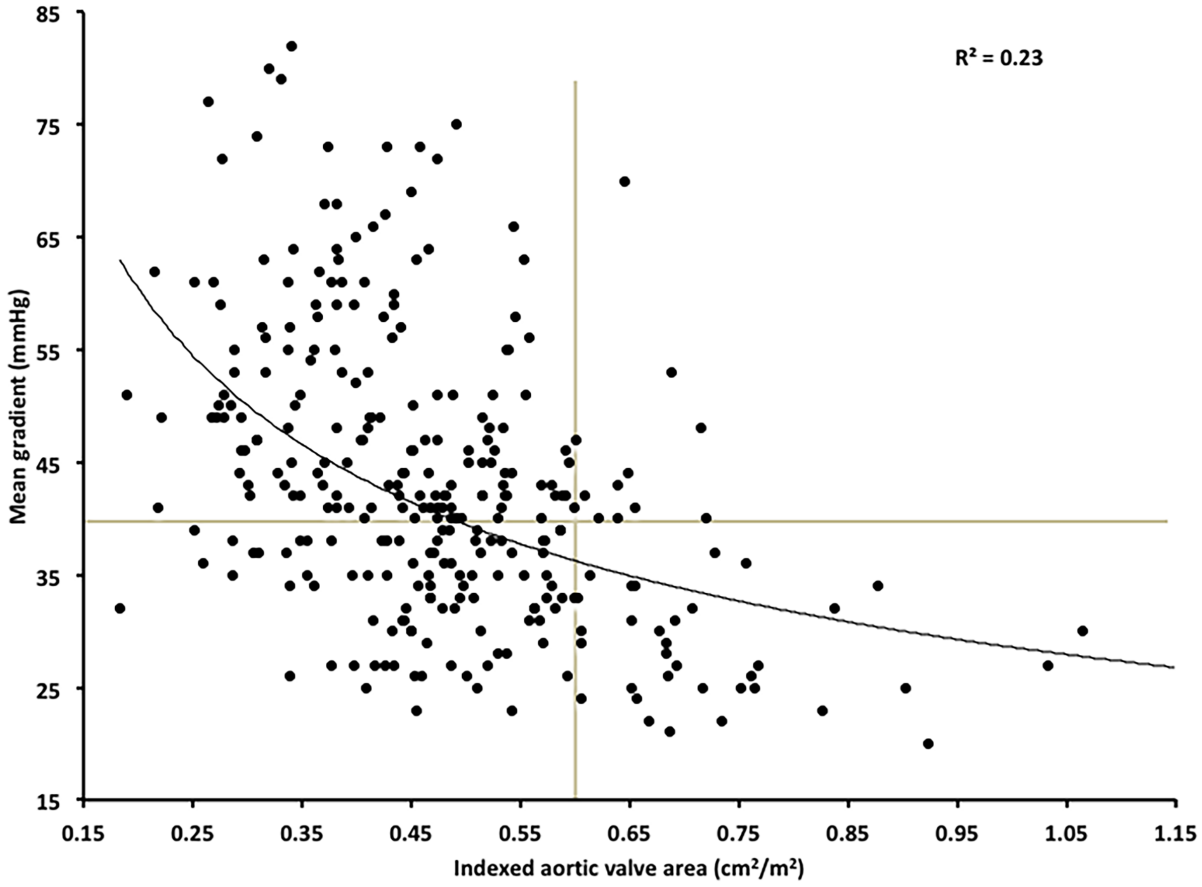

Percentage of severe AS based on mean gradient
100%
80%
60%
40%
20%
0%
[130±22 mmHg]
**
[110±9 mmHg]
59%
75%
Baseline state
SBP ≤ 120 mmHg (optimal state)

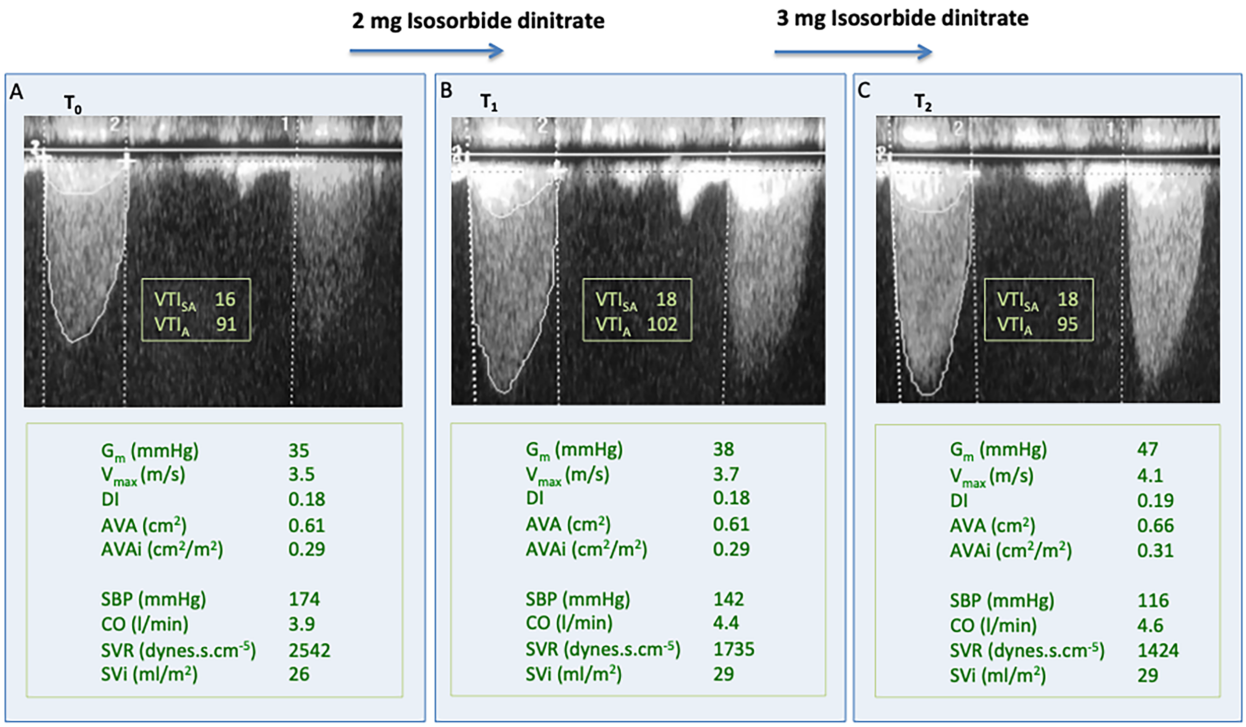

Percentage of severe AS based on peak aortic jet velocity
100%
80%
60%
40%
20%
0%
*
44%
61%
Baseline state
SBP ≤ 120 mmHg (optimal state)


Percentage of severe AS based on dimensionless index
100%
80%
60%
40%
20%
0%
66%
65%
NS
Baseline state
SBP ≤ 120 mmHg (optimal state)


Percentage of severe AS based on indexed aortic valve area
100%
90%
80%
70%
87%
85%
NS
Baseline state
SBP ≤ 120 mmHg (optimal state)


Mean gradient (mmHg)
80
60
40
20
36%
5%
29%
30%
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
34% discrepancies
Dimensionless index
R^2=0.30
59%
16%
6%
19%
22% discrepancies
Dimensionless index
R^2=0.26
Mean Gradient (mmHg)
43%
1%
42%
14%
0.1
0.3
0.5
0.7
0.9
1.1
1.3
43% discrepancies
Indexed aortic valve area (cm²/m²)
R^2=0.22
70%
5%
15%
10%
20% discrepancies
Indexed aortic valve area (cm²/m²)
R^2=0.23
At High blood pressure
At Low blood pressure


R² = 0.23
Mean gradient (mmHg)
85
75
65
55
45
35
25
15
0.15
0.25
0.35
0.45
0.55
0.65
0.75
0.85
0.95
1.05
1.15
Indexed aortic valve area (cm²/m²)


2 mg Isosorbide dinitrate
3 mg Isosorbide dinitrate
A
T0
VTISA 16
VTIA 91
Gm (mmHg) 35
Vmax (m/s) 3.5
DI 0.18
AVA (cm2) 0.61
AVAi (cm2/m2) 0.29
SBP (mmHg) 174
CO (l/min) 3.9
SVR (dynes.s.cm-5) 2542
SVi (ml/m2) 26
B
T1
VTISA 18
VTIA 102
Gm (mmHg) 38
Vmax (m/s) 3.7
DI 0.18
AVA (cm2) 0.61
AVAi (cm2/m2) 0.29
SBP (mmHg) 142
CO (l/min) 4.4
SVR (dynes.s.cm-5) 1735
SVi (ml/m2) 29
C
T2
VTISA 18
VTIA 95
Gm (mmHg) 47
Vmax (m/s) 4.1
DI 0.19
AVA (cm2) 0.66
AVAi (cm2/m2) 0.31
SBP (mmHg) 116
CO (l/min) 4.6
SVR (dynes.s.cm-5) 1424
SVi (ml/m2) 29

Highlights

- In aortic stenosis, high blood pressure is reponsible for a significant decrease in gradients and velocities.
- Blood pressure should be brought under control during any ultrasound exam dedicated to an aortic stenosis assessment.
- Dimensionless index is a flow independent parameter deserving increased attention.
- There is a higher proportion of severe aortic stenosis when its evaluation is exclusively based on aortic valve area.
- Flow rate, not stroke volume was found to impact the transvalvular velocities and gradients but not the aortic valve area or the dimensionless index.