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# Non-invasive Assessment of the Severity of Aortic Stenosis by Doppler Derived Aortic Valve Coefficient: A Retrospective Feasibility Study in Humans

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors AKP, MAE and RKB designed the study and wrote the protocol. Authors AKP and JJP conducted the data acquisition. Author KP performed the data analysis and wrote the first draft of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Accurate assessment of the severity of stenosis is critical in patients with aortic stenosis. The ambiguities and imprecisions of the current diagnostic parameters can result in sub-optimal clinical decisions. In this feasibility study, we investigate the functional diagnostic parameter AVC (Aortic Valve coefficient: ratio of the total transvalvular pressure drop to the proximal dynamic pressure) in the non-invasive assessment of the severity of aortic stenosis by correlating with the current diagnostic parameters.

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**Methods and Results:** AVC was calculated using Doppler measured diagnostic parameters obtained from retrospective chart reviews. A theoretical pressure recovery correction was applied to the pressure drop calculated from Doppler measurements to obtain AVC. A statistically significant and strong combined linear correlation ($r = 0.93$, $p<0.001$) of AVC with the transvalvular pressure drop and the left ventricular outflow tract velocity was observed. The mean values of AVC were shown to better delineate moderate and severe stenosis (54% difference) than the mean values of Doppler measured pressure drop and aortic valve area (22% and 25% difference, respectively), when the patients were categorized based on the catheterization measured pressure drop.

**Conclusion:** The feasibility of using pressure and flow measurements obtained from Doppler measurements in a single combined diagnostic index for the assessment of aortic stenosis severity has been evaluated. The nondimensional clinical parameter, AVC, is expected to account for the variation in flow and pressure drop and thus improve the delineation of different grades of aortic stenosis. AVC must be further evaluated in a controlled prospective study.

*Keywords: Aortic stenosis; Aortic stenosis severity; Doppler echocardiography; Aortic valve replacement.*

## NOMENCLATURE

*AS : Aortic Stenosis*
*LVOT : Left ventricular outflow tract*
$\rho$ : *Blood density (1060 kg/m$^3$)*
$Q$ : *Time-averaged flow rate (cm$^3$/s)*
$V_{jet}$ : *Doppler measured time-averaged jet velocity at the vena contracta*
$V_{LVOT}$ : *Doppler measured time-averaged LVOT velocity*
$CSA_{LVOT}$ : *Doppler measured LVOT cross-sectional area*
$CSA_{aorta}$ : *Doppler measured aortic root cross-sectional area*
$\Delta p$ : *Doppler derived time-averaged transvalvular pressure drop calculated by averaging the instantaneous pressure drops over the ejection period; $P_1$-$P_2$ in Fig. 1*
$\Delta p_{total}$ : *Time-averaged total transvalvular pressure drop with pressure recovery correction; $P_1$-$P_3$ in Fig. 1.*
$\Delta \bar{p}$ : *Pressure drop calculated from the time-averaged jet velocity ($\Delta \bar{p} = 4 \times V_{jet}^2$ )*
$\Delta p_{total,\ cath}$ : *Time-averaged pressure drop measured by invasive catheterization; $P_1$-$P_3$ in Fig. 1.*
*AVA : Doppler derived time-averaged aortic valve area calculated from the velocity time integrals and $CSA_{LVOT}$*
*VR : Velocity ratio calculated as the ratio of $V_{LVOT}$ to $V_{jet}$*
*AVC : Aortic valve coefficient calculated as the ratio of $\Delta p_{total}$ to the proximal dynamic pressure.*
$AVC_{VR}$ : *Aortic valve coefficient calculated as a function of VR, $CSA_{LVOT}$ and $CSA_{aorta}$.*

## 1. INTRODUCTION

While cardiovascular disease is the leading cause of death in United States (source: American Heart Association, 2013) and in the world (source: World Health Organization, 2013), it remains one of the primary causes of preventable death globally [1]. Aortic stenosis (AS) is a type of valvular heart disease that results from abnormal narrowing of the aortic valve opening.AS is typically caused by progressive degeneration and calcification of the aortic valve, hence the prevalence of calcific aortic valve disease increases with age [2].

Currently, the severity of AS is assessed using a combination of diagnostic parameters such as transvalvular pressure drop, aortic jet velocity and stenotic aortic valve area derived from Doppler echocardiography and cardiac catheterization [3,4]. Although Doppler parameters correlate well with true severe AS [5], there are many occasions when significant discrepancies exist between patient history, clinical examination, Doppler data [6], cardiac catheterization hemodynamics [7,8] and/or operative findings. Hyperdynamic circulatory states such as in sepsis, anemia, AV fistula, hyperthyroidism, liver failure and aortic

regurgitation can exaggerate pressure drops across the aortic valve, resulting in overestimation of the degree of stenosis. Conversely, in 'paradoxical low-flow, low-gradient severe AS', pressure drop and peak velocities are low despite a normal left ventricular ejection fraction and will mask true underlying AS [6,9].

Further, Doppler derived aortic valve area represents the reduced area of the flow at the *vena contracta* and not the anatomical valve area [10]. Doppler measurements are taken at the *vena contracta* and it does not account for the pressure-recovery in the aorta. Consequently, depending on the stenosis severity and the cross-sectional area of the ascending aorta, Doppler measured pressure drop will often overestimate the AS severity [9-13]. In order to avoid unnecessary surgical procedures in low risk AS patients who would have a higher operative mortality or conversely to intervene on those patients who may be asymptomatic but would benefit from an early surgical approach, it is critical to accurately evaluate the severity of AS. With the advent of less invasive techniques for the treatment of AS, it is imperative that more accurate diagnostic end-points be pursued.

In this study we seek to establish the feasibility of using both transvalvular pressure drop and velocity measured by *non-invasive* Doppler echocardiography in a single diagnostic index for assessing the severity of AS. We *hypothesize* that the proposed hemodynamic diagnostic parameter is better characterized by the time-averaged transvalvular pressure drop and left ventricular outflow tract (LVOT) velocity simultaneously than by the respective parameters individually. Additionally, the proposed diagnostic index derived from Doppler measurements will correlate well with existing diagnostic indices and will improve the delineation of different levels of AS severity. The proposed functional diagnostic index, Aortic Valve Coefficient (AVC), is defined as the ratio of the time-averaged total transvalvular pressure drop to the time-averaged proximal dynamic pressure ($0.5 \times blood\ density \times (LVOT\ velocity)^2$). The time-averaged total transvalvular pressure drop includes the pressure-recovery correction and is represented by $P_1$-$P_3$ in Fig. 1. AVC derived from *invasive* and *non-invasive* measurements has been previously compared by our group in a recent study [14]. This study evaluates the feasibility of delineating different grades of AS severity using AVC derived only from Doppler measurements.

## 2. METHODS

### 2.1 Study Patients

Patients of all ages (above 18 years), all sexes and any ethnicity with suspected AS who underwent pre-catheterization two-dimensional transthoracic Doppler echocardiograms and left heart catheterizations were included in the study. A retrospective review of patient records from 2010 to 2012 was conducted to identify patients who met these criteria and 36 patients whose age varied from 42 to 92 years were enrolled in the study. The standard of care Doppler and catheterization reports of the enrolled patients were reviewed. Based on the initial analysis, data from three patients with inconsistent pressure-flow measurements (e.g. 1 patient with procedural error as catheterization transducer was not properly zeroed, 1 patient with time-averaged catheterization pressure drop = 4 times the Doppler derived pressure drop, 1 patient with Doppler measurement taken after cardiac arrest) and ten patients with poor quality or incomplete Doppler measurements were excluded. Three patients with bioprosthetic aortic valves were also excluded. Thus, 20 patients were included in this retrospective study.

### 2.2 Pressure-Flow Catheterization Measurements

The peak-to-peak pressure drop was obtained during cardiac catheterization using simultaneous left ventricular and aortic pressure measurements. The cardiac output was generally measured during catheterization using both the Fick's principle and thermodilution method. However, in the presence of severe tricuspid regurgitation or decreased LV systolic function only the Fick's measurement was used.

### 2.3 Data Analysis

The values of jet velocity at the *vena contracta* ($\widetilde{V}_{jet}$), LVOT velocity ($\widetilde{V}_{LVOT}$), cross-sectional area of the aortic root ($CSA_{aorta}$), cross-sectional area of the LVOT ($CSA_{LVOT}$), aortic valve area ($\widetilde{AVA}$) and transvalvular pressure drop ($\Delta\tilde{p}$; superscript '~' indicates time-averaged values) were obtained from the standard of care Doppler measurements and two-dimensional imaging data. The corresponding locations of the *vena contracta* and the LVOT are shown schematically in Fig. 1. For simplification of the nomenclature in the subsequent manuscript, the time-averaged

symbol (~) is dropped with the understanding that the time-averaged flow quantities are considered. $\Delta p$ is the time-averaged pressure drop ($P_1$-$P_2$ in Fig. 1) calculated by averaging the instantaneous pressured drops over the ejection period [4]. AVA was calculated from the Doppler measured velocity time integrals and $CSA_{LVOT}$[4]. The pressure-flow hemodynamic diagnostic parameter, AVC, was calculated from Doppler measurements, where $\Delta p_{total}$ is the time-averaged total transvalvular pressure drop following pressure recovery ($P_1$-$P_3$ in Fig. 1). The $\Delta p_{total}$ was calculated from the modified Bernoulli equation with pressure recovery correction using the Doppler measured velocities and the cross-sectional area measurements from two-dimensional imaging data [4,11-13].

$$AVC = \frac{\Delta p_{total}}{4 \times {V_{LVOT}}^2} \quad (1)$$

$$\Delta p_{total} = \Delta p \left( 1 - \left( 2 \frac{AVA}{CSA_{aorta}} \left( 1 - \frac{AVA}{CSA_{aorta}} \right) \right) \right)$$

A detailed explanation of the derivation of AVC is provided in the Appendix, section A. An example calculation of AVC for one patient is also provided in the Appendix, section B. The AVC can also be calculated directly from the Doppler calculated velocity ratio (VR) and the measured cross-sectional areas as described in the Appendix, section C.

$$AVC_{VR} = \frac{1}{VR^2} - \frac{2}{VR} \frac{CSA_{LVOT}}{CSA_{aorta}} + 2 \left( \frac{CSA_{LVOT}}{CSA_{aorta}} \right)^2 \quad (2)$$

$$VR = \frac{V_{LVOT}}{V_{jet}} \quad (3)$$

## 2.4 Statistical Analysis

A linear regression analysis was performed on data from the 20 patients to assess any significant linear correlations between AVC and measured parameters. Multiple linear regression analysis was performed to assess the simultaneous correlation between AVC and measured parameters. A variance inflation factor (VIF) value greater than 5.0 indicates multicollinearity in multiple linear regression analysis. A probability value of $p < 0.05$ was considered to be statistically significant. The statistical analysis was performed using the commercially available SAS software. All Doppler measurements and diagnostic parameters are represented as mean ±SE.

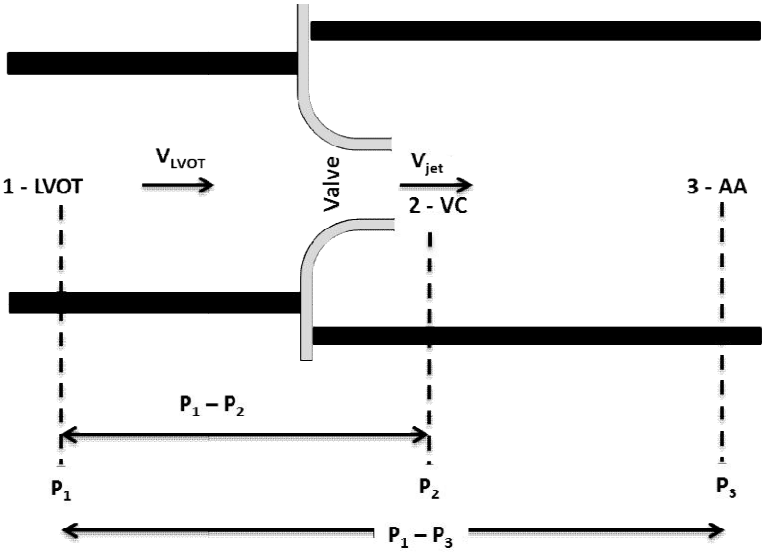


**Fig. 1. Schematic representation of the left ventricular outflow tract (LVOT), aortic valve, *vena contracta* (VC) and ascending aorta (AA), the total pressure gradient ($P_1 – P_3$) and the measurement location of the LVOT velocity ($V_{LVOT}$) and jet velocity ($V_{jet}$)**

## 3. RESULTS

Table 1 summarizes the Doppler data obtained by retrospective review of the records of the 20 patients (9 females) included in this study. The average age of the patients was 65 years with a mean BSA of 2.2 $m^2$. 8 patients were hypertensive with a systolic blood pressure greater than 140 mm Hg. The stroke volume ranged from 27 ml to 137 ml with a mean of 81 ml and the mean left ventricular ejection fraction (LVEF) was 58% with a range of 26-79%. Following ASE guidelines [4] for classifying AS severity by $\Delta$p, 14 patients had moderate AS (20 to 40 mm Hg) and 6 patients had severe AS (greater than 40 mm Hg). However when the same patient group was categorized using AVA [4], 1 patient had mild AS (greater than 1.5 $cm^2$), 6 patients had moderate AS (1.0 to 1.5 $cm^2$) and 13 patients had severe AS (less than 1.0 $cm^2$).

### 3.1 AVC Correlations

The results of the linear regression analysis of AVC with $\Delta$p and $V_{LVOT}$ are presented in Fig. 2. It can be seen that AVC exhibits a moderately positive linear correlation with $\Delta$p (r = 0.56, p = .01; Fig. 2A). Similarly, AVC has a negative linear correlation with $V_{LVOT}$ (r = 0.76, p <.001; Fig. 2B). However, AVC exhibits a statistically significant and superior simultaneous correlation with $\Delta$p and $V_{LVOT}$ measurements (r = 0.93, p <.001). The explanatory variables, $\Delta$p and $V_{LVOT}$, did not exhibit multicolinearity (VIF = 1.0) in the simultaneous correlation with AVC. AVC also exhibits a moderate negative correlation with AVA (r = 0.63, p = .003) as shown in Fig. 3. It should also be noted that AVC increases with increasing severity of AS, i.e. with increasing $\Delta$p and decreasing AVA. The corresponding linear regression equations associated with Fig. 2 and Fig. 3 are summarized in Table 2.

### 3.2 Effect of AS Severity on $\Delta$p, AVA and AVC

The patients were categorized as having severe (n=5) and moderate (n=14) AS based on the functional time-averaged pressure drop measured by *invasive* catheterization ($\Delta p_{total,\ cath}$) following ASE guidelines [4]. The effect of AS severity on the mean values of $\Delta$p is presented in Fig. 4A. The mean value of $\Delta$p for patients with severe AS (40.8±5.4 mm Hg) is higher than the mean value of $\Delta$p for patients with moderate AS (33.4±2.3 mm Hg) by 22% ([40.8 – 33.4] /33.4). The mean value of AVA for patients with moderate AS (0.85±0.09 $cm^2$) was 25% larger than the mean value of AVA for patients with severe AS (0.64±0.14 $cm^2$) as shown in Fig. 4B. The effect of AS severity on the mean values of AVC is shown in Fig. 4C. The mean value of AVC for patients with severe AS (32.8±8.1) was 54% higher than the mean value of AVC for patients with moderate AS (21.3±4.2). While the difference in the mean values of $\Delta$p and AVA for patients with severe and moderate AS based

**Table 1. Mean values and range of age, BSA, stroke volume, left ventricular ejection fraction, blood pressure, doppler measured time-averaged jet velocity, left ventricular outflow tract velocity, pressure drop, aortic valve area and aortic root cross-sectional area obtained retrospectively (n=20)**

| | Mean | Range |
|---|---|---|
| Age [years] | 65 ±2.8 | 42-92 |
| BSA [$m^2$] | 2.2±0.11 | 1.52–3.32 |
| Stroke volume [ml] | 81 ±7.2 | 27-137 |
| LVEF [%] | 58 ±3.2 | 26-79 |
| Systolic blood pressure [mm Hg] | 133.6 ±5.0 | 88-173 |
| Diastolic blood pressure [mm Hg] | 69.8 ±2.4 | 45-86 |
| $V_{jet}$ [m/s] | 2.75 ±0.09 | 2.0-3.55 |
| $V_{LVOT}$ [m/s] | 0.60 ±0.036 | 0.42-0.93 |
| $\Delta$p[mm Hg] | 34.6 ±2.3 | 20-57 |
| AVA [$cm^2$] | 0.79 ±0.07 | 0.25-1.56 |
| $CSA_{aorta}$ [$cm^2$] | 7.1±0.62 | 2.6–11.9 |

*BSA: Body surface area, LVEF: left ventricular ejection fraction; $V_{jet}$: Doppler measured time-averaged jet velocity at the vena contracta of the aortic valve; $V_{LVOT}$: Doppler measured time-averaged left ventricular outflow tract velocity; $\Delta$p: Doppler measured time-averaged pressure drop; AVA: Doppler measured time-averaged valve area, $CSA_{aorta}$: aortic root cross-sectional area*

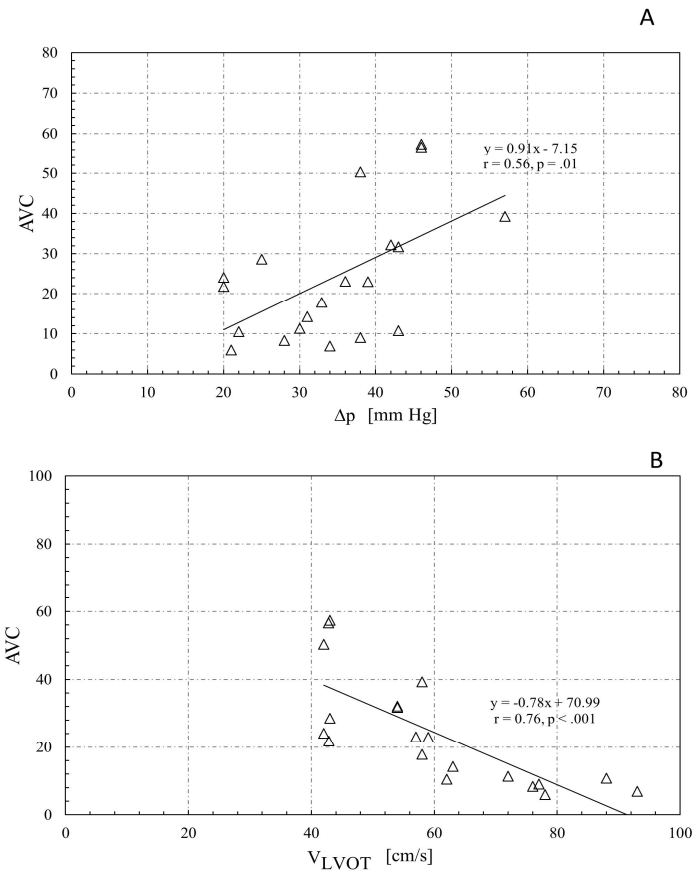


**Fig. 2. Correlation of (A) AVC and with time-averaged pressure gradient (∆p) and (B) AVC with time-averaged LVOT velocity ($V_{LVOT}$)**

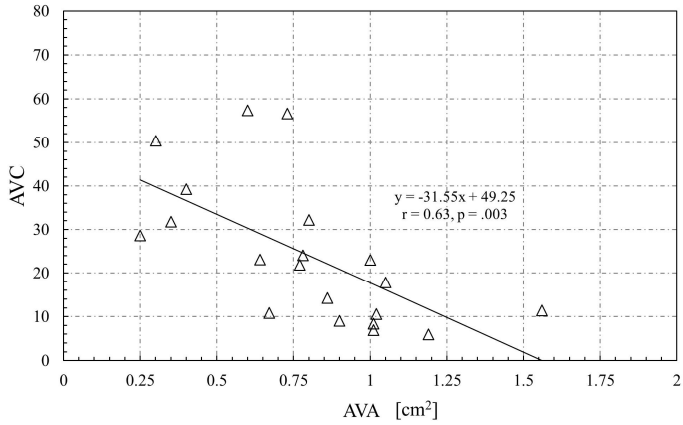


**Fig. 3. Relationship between Aortic Valve Coefficient (AVC) and time-averaged aortic valve area (AVA)**

on $\Delta p_{total, cath}$ was 22% and 25%, respectively, the corresponding difference on in mean values of AVC was higher (54%). The p-values for the comparison of the means presented in Fig. 4 are similar and are expected to improve with a larger sample size.

## 4. DISCUSSION

The relationship between the time-averaged pressure drop (∆p) and the time-averaged flow rate (Q) in flows through constrictions like arterial lesions and stenosed valves is curvilinear and is described as $\Delta p = A \times \mathrm{Q} + B \times Q^2$ [15]. Here A and B are constants representing the linear pressure loss due to frictional (viscous) effects and the nonlinear pressure loss due to momentum change caused by area reduction. At the higher Reynolds numbers (~5000) that is typically observed in the human ascending aorta [16], the flow is transitional to turbulent and the nonlinear pressure loss due to area reduction is generally more than the linear pressure loss due to frictional effects. For pressure drop calculations of fluid flowing through a valve, it is engineering practice to use non-dimensional numbers derived from fluid dynamic fundamentals. The AVC is analogous to the parameters commonly used for analyzing fluid dynamics problems where the pressure drop through a valve or in a device is important [17]. Consequently, AVC (Equation 1) is a non-dimensional hemodynamic parameter that incorporates the effects of flow variation and better accounts for the largely nonlinear pressure loss in stenosed aortic valves. This is illustrated by the variation of AVC observed in Fig. 2 for similar values of ∆p and $V_{LVOT}$. It is well known that the magnitude of ∆p depends on AS severity and cardiac output. Therefore, a similar ∆p may be observed for different AS severity due to the variability in $V_{LVOT}$ (Fig. 2A). However, the combined parameter AVC can vary for the cases with similar ∆p since it simultaneously accounts for the variations in pressure drop and square of the velocity (or flow; Equation 1). Similarly, AVC can vary with changes in pressure drop or AS severity for similar values of $V_{LVOT}$ (Fig. 2B). By incorporating the flow variation, AVC is also expected to improve the evaluation of AS severity in hypertensive patients with variations in left ventricular ejection fraction or stroke volume due to the ventricular-vascular coupling [18]. This must be evaluated in a future prospective study.

Although similar in concept to the Euler number ($\Delta p/\rho V^2$; where V is the characteristic flow velocity), AVC is calculated from the corrected time-averaged pressure drop ($\Delta p_{total}$; $P_1$-$P_3$ in Fig. 1) which accounts for the pressure recovery phenomenon (Equation 1). In contrast, the hemodynamic parameter aortic valve resistance obtained by Doppler echocardiography is a dimensional flow dependent parameter with limited prognostic value [4] and it primarily represents the linear pressure loss due to viscous (frictional) effects that is commonly observed in diffused arterial lesions. A discussion of the differences between AVC and existing diagnostic parameters such as the *energy loss coefficient* (ELCo) and *velocity ratio* (VR) is provided in the Appendix, section D. A discussion of dobutamine stress echo and AVC in the diagnosis of '*low-flow, low-gradient AS*' [4] is also provided in the Appendix, section E.

Prior to conducting our data analysis, we excluded 16 patients from the study due to poor data acquisition, thereby minimizing technical limitations that may have inflated the potential for random bias and inter-observer variability. Additionally, in order to determine the reproducibility of the obtained Doppler echocardiographic parameters, we evaluated the inter-observer variability using a second reader versus the original readers of the Doppler studies and between the same reader's evaluations that were repeated (two separate evaluations conducted by the same reader 48 hours apart) for the intra-observer variability. The inter-observer and intra-observer analysis was carried out using the recorded images. The parameters studied were the component measurements included in the definition of AVC, namely $V_{jet}$, $V_{LVOT}$, LVOT diameter and aortic root diameter.

**Table 2. Summary of correlations**

| Dependent vs. independent variable | Regression equation | r | p-value |
|---|---|---|---|
| AVC vs. ∆p | $0.91 \times \Delta p - 7.15$ | r = 0.56 | p = .01 |
| AVC v s. $V_{LVOT}$ | $-0.78 \times V_{LVOT} + 70.99$ | r = 0.76 | p < .001 |
| AVC vs. ∆p,$V_{LVOT}$ | $0.87 \times \Delta p - 0.76 \times V_{LVOT} - 39.9$ | r = 0.93* | p < .001 |
| AVC vs. AVA | $-31.55 \times \mathrm{AVA} + 49.25$ | r = 0.63 | p = .003 |

*AVC: Aortic valve coefficient calculated from Doppler measurements; $V_{LVOT}$ : Doppler measured time-averaged left ventricular outflow tract velocity; ∆p: Doppler measured time-averaged pressure gradient; AVA: Doppler measured time-averaged valve area; * significant outcome*

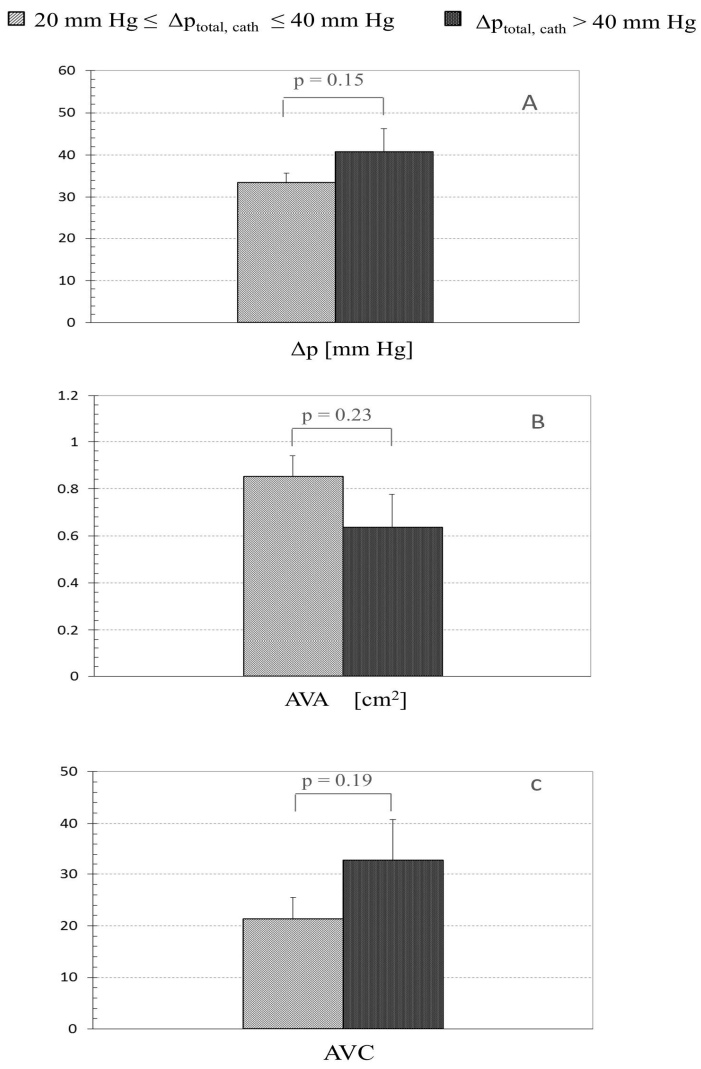


**Fig. 4. Comparison of mean values of Doppler measured time-averaged (A) pressure drop (Δp), (B) aortic valve area (AVA) and (C) aortic valve coefficient (AVC) between moderate (20 mm Hg ≥ $\Delta p_{total, cath}$ ≥ 40 mm Hg) and severe ($\Delta p_{total, cath}$ > 40 mm Hg) aortic stenosis based on the catheterization measured time-averaged pressure drop ($\Delta p_{total, cath}$)**

Variability was analyzed using the intra-class correlation coefficient (ICC). The degree of concordance was high for both the inter-observer and the intra-observer measurements, with ICC 0.82 and 0.9 respectively.

AVC is a combined pressure-velocity parameter that includes the recovery corrected pressure drop ($\Delta p_{total}$) and $V_{LVOT}$ (Equation 1). Thus, AVC is expected to correlate independently with the $\Delta p$ and the $V_{LVOT}$. The feasibility of this combined parameter was tested by performing a multiple linear regression analysis to simultaneously correlate AVC with $\Delta p$ and $V_{LVOT}$. The statistically significant improvement in the combined correlation when compared to the independent correlations (Table 2) indicates that both $\Delta p$ and $V_{LVOT}$ contribute appreciably to the variation in the AVC. Since AVC is calculated from the $\Delta p$ and $V_{LVOT}$ obtained by averaging their instantaneous values over the ejection period, it also takes into account the pressure and flow measurements throughout the systole. Further, the results presented in Fig. 4 illustrate that the mean values of AVC can improve the delineation of moderate and severe stenosis (Fig. 4C; 54%

difference) when compared to the mean values of $\Delta p$ (Fig. 4A; 22% difference) and AVA (Fig. 4B; 25% difference), when the patients were classified based on only the functional time-averaged pressure drop measurement by invasive catheterization. The functional data is considered as the gold standard.

To test the role of biases on the combined correlation of AVC with the $\Delta p$ and $V_{LVOT}$, a multivariate linear regression analysis was performed by including age, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP) and gender as additional predictor variables. The coefficients of the additional predictor variables were not significant based on the t-test (p-values of age = 0.78, LVEF = 0.57, SBP = 0.47 and gender = 0.70). Similarly, only $\Delta p$ and $V_{LVOT}$ were selected as significant predictor variables of AVC when a model selection was performed using the stepwise selection procedure with a significance level of 0.05. Additionally, the difference in the group means of AVC were found to be marginally significant when the patients were categorized based on age (group 1 ≤ 65, group 2 > 65, p-value = 0.06) and insignificant when the patients were categorized based on LVEF (group 1 ≤ 60%, group 2 > 60%, p-value = 0.86), SBP (group 1 ≤ 140 mm Hg, group 2 > 140 mm Hg, p-value = 0.19) and gender (p-value = 0.17).

Since *pressure recovery* ($P_3$-$P_2$ in Fig. 1 and Equation A1 in the Appendix) is relatively small for mild to moderate AS cases, the effect of pressure recovery on $\Delta p_{total}$ may not be significant. However, for moderate to severe stenosis range the pressure recovery could be very high and exclusion of the pressure recovery correction may lead to inaccurate assessment (overestimation) of AS severity [13]. On a similar note, in cases of small ascending aorta the downstream pressure can be consistently lower due to increased blood velocity in the aorta while the total pressure drop is high. Such variability in pressure recovery has been accounted for improved delineation of severity of AS by including the pressure recovery correction in the definition of AVC (Equation 1). Moreover, from a physiological perspective it is the $\Delta p_{total}$ ($P_1$-$P_3$ in Fig. 1 and Equation A1 in Appendix) that represents the true hemodynamic severity of stenosis [19]. The variation of AVC observed in Fig. 3 for an AVA value is due to the fact that AVC is comprised of the total transvalvular pressure drop that includes the pressure recovery correction. Further, the total pressure drop and consequently AVC also depends on the ratio of the anatomical valve area to the LVOT cross-sectional area. In contrast, the Doppler derived AVA represents the reduced area of the flow at the *vena contracta* (Fig. 1) but not the anatomical (or geometric) valve area.

The hemodynamic parameter *pressure drop coefficient* (CDP), which is similar to AVC, has been previously evaluated by our group for assessing the severity of epicardial coronary artery stenosis [17,20]. More recent in-vivo studies [21-23] have shown that CDP correlates well with existing coronary stenosis diagnostic end-points and that CDP can independently assess the severity of epicardial stenosis. CDP has also been shown to be independent of the hemodynamic influence of heart rate or contractility [22,24] in the assessment of the severity of coronary stenosis.

The current study focuses on the feasibility of distinguishing different grades of AS severity using AVC derived only from non-invasive modalities (Doppler measurements). However, the recent retrospective study by our group [14] has evaluated the correlation between AVC derived from *invasive* (catheterization) and *non-invasive* (echocardiography) measurements. The correlation between the Doppler and catheter derived AVC exhibited improvement over the corresponding correlations of time-averaged pressure drop and aortic valve area.

The aortic valve coefficient obtained from the velocity ratio, ($AVC_{VR}$; Equation 2; Appendix, section C) is based on the pressure drop calculated from the time-averaged jet velocity at the *vena contracta* ($\Delta\bar{p} = 4\times V_{jet}^2$) rather than the time-averaged pressure drop ($\Delta p$). It may be noted that $\Delta\bar{p}$ is not the time-averaged $\Delta p$ calculated by averaging the instantaneous pressure drops over the ejection period [4]. Using $\Delta\bar{p}$ allows $AVC_{VR}$ to be computed as a function of the Doppler calculated velocity ratio (VR) [4] and the cross-sectional areas. The relationship between the values of $AVC_{VR}$ and AVC is presented in Fig. 5. Although there is a strong correlation between $AVC_{VR}$ and AVC (r = 0.99, p <.001), $AVC_{VR}$ is systemically lower than AVC (y = 0.87x + 0.49), particularly for severe AS. The inconsistency between AVC and $AVC_{VR}$ is expected due to the fact that the time-averaged $\Delta p$ used in AVC is more accurate than the calculated "Δ" "p" ¯ used in ⟦"AVC" ⟧_"VR".

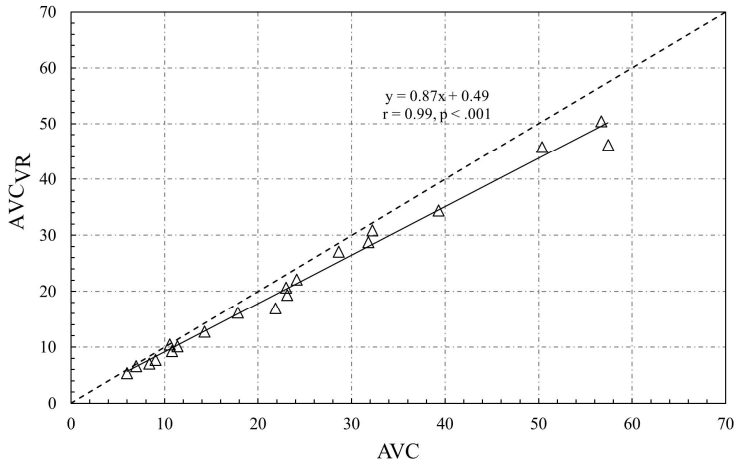


**Fig. 5. Relationship between Aortic Valve Coefficient calculated from the velocity ratio ($AVC_{VR}$) and Aortic Valve Coefficient calculated from the time-averaged pressure gradient (AVC). The solid and dotted lines represent the regression and identity lines respectively.**

Therefore, AVC is a more accurate diagnostic parameter from a fluid dynamics perspective when compared to $AVC_{VR}$. Nevertheless, $AVC_{VR}$ is a potential diagnostic parameter for assessment of AS severity in patients with cardiac dysrhythmia and can only be used after further evaluation.

## 4.1 Study Limitations

The data was not obtained from a well-controlled prospective patient pool and the number of patients who underwent both Doppler echocardiography and catheterization assessment of AS during the study period was relatively small. Hence, a smaller number of patients could be enrolled in this retrospective study. Moreover, an initial analysis revealed that data obtained for 16 of the 36 patients initially enrolled were either incomplete or had clinical inconsistencies. The retrospective nature of this study presented a limitation in obtaining complete and consistent clinical data. Based on the mean values presented in Table 1 the study population is probably biased towards large patients with lower flow. However, it is expected that the findings of this retrospective study will apply to patients with normal LV function and high gradients since AVC is a non-dimensional parameter that accounts for the non-linear pressure drop and velocity in a single diagnostic index. Further, a complete assessment of concomitant disease conditions that could have impacted the Doppler measurements and a comparison with a control group with mild AS could not be included in this study. The inherent potential errors in the calculation of the cross-sectional area of the LVOT and the aortic root could also add to the variability of the results presented in this study. With the advent of techniques like 3D echocardiography we anticipate that the accuracy of measurements of LVOT and aortic root diameters will also improve. This retrospective study is an important step in testing the feasibility of AVC before proceeding to a prospective study for evaluating the specificity and sensitivity of AVC in delineating the severity of AS.

## 5. CONCLUSION

This retrospective study has confirmed the feasibility of using both pressure drop and flow in a single combined non-dimensional non-invasive diagnostic index, AVC, for assessment of the severity of AS. AVC correlates moderately with existing Doppler derived diagnostic parameters and has the potential to better delineate moderate and severe AS than by the time-averaged pressure drop or by the aortic valve area only. In the future, it is of interest to conduct a controlled prospective study with a larger patient pool to evaluate the specificity and sensitivity of AVC and to establish cut-off points for delineating different levels of AS severity.

## CONSENT

The informed consent requirement was waived by the Institutional Review Board at University of

Cincinnati, Cincinnati, Ohio, USA for the retrospective chart reviews conducted in this study.

## ETHICAL APPROVAL

The study protocol (Study #:2012-492*711121312)* was approved by the Institutional Review Board at University of Cincinnati, Cincinnati, Ohio, USA.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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## APPENDIX

### A. Derivation of Aortic Valve Coefficient

Referring to Fig. 1, the Aortic Valve Coefficient (AVC) is defined as:

$$AVC = \frac{P_1 - P_3}{ProximalDynamicPressure} = \frac{(P_1 - P_2) + (P_2 - P_3)}{0.5 \times \rho \times V_{LVOT}{}^2} = \frac{(P_1 - P_2) - (P_3 - P_2)}{0.5 \times \rho \times V_{LVOT}{}^2} \quad \text{(Eq. A1)}$$

where $P_1 - P_3$ represents the total pressure drop that is typically measured during invasive catheterization and $P_3 - P_2$ represents the pressure recovery in the ascending aorta (AA). Here, $P_2 < P_3$, and hence $P_3 - P_2$ is a positive value. Considering that $P_1 - P_2$ represents the Doppler derived time-averaged pressure drop ($\Delta$p in mm Hg) Equation A1 simplifies to:

$$AVC = \frac{\Delta p - (P_3 - P_2)}{0.5 \times \rho \times V_{LVOT}{}^2} = \frac{\Delta p_{total}}{0.5 \times \rho \times V_{LVOT}{}^2} \quad \text{(Eq. A2)}$$

where $\Delta p_{total}$ is the Doppler measured pressure drop with the recovery correction. Substituting the value of the density of blood ($\rho$ = 1060 kg/m$^3$), and the conversion factor to mm Hg in Equation A2 yields the following:

$$AVC = \frac{\Delta p_{total}}{0.5 \times 106 \times \frac{1}{133.33} \times V_{LVOT}{}^2} = \frac{\Delta p_{total}}{4 \times V_{LVOT}{}^2} \quad \text{(Eq. A3)}$$

It may be noted that the $V_{LVOT}$ in Equation A3 is in m/s. $P_3 - P_2$ has been previously calculated as a function of $\Delta$p, the valve area (AVA) and the AA cross-sectional area ($CSA_{aorta}$) based on modified Bernoulli equation [4, 11-13].

$$P_3 - P_2 = \Delta p \left( 2 \frac{AVA}{CSA_{aorta}} \left( 1 - \frac{AVA}{CSA_{aorta}} \right) \right) \quad \text{(Eq. A4)}$$

Therefore, the recovery corrected time-averaged pressure drop is calculated as:

$$\Delta p_{total} = \Delta p - (P_3 - P_2) = \Delta p \left( 1 - \left( 2 \frac{AVA}{CSA_{aorta}} \left( 1 - \frac{AVA}{CSA_{aorta}} \right) \right) \right) \quad \text{(Eq. A5)}$$

### B. Example Calculation of AVC for One Patient

The two-dimensional images and the Doppler spectral displays for one of the patients enrolled in this study are shown in Fig. A1. This patient has a peak pressure drop of 41 mm Hg and time-averaged transvalvular pressure drop ($\Delta$p) of 20 mm Hg indicating moderate stenosis, while the AVA was 0.73 cm$^2$ indicating severe stenosis. The ejection fraction for this patient was 54%. The discordance between $\Delta$p and AVA is representative of "*low-flow, low-gradient AS*". The $CSA_{aorta}$ was calculated to be 6.61 cm$^2$.

The calculation of AVC using Doppler measured parameters of this patient is described here as an example.

$$\Delta p_{total} = \Delta p \left( 1 - \left( 2 \frac{AVA}{CSA_{aorta}} \left( 1 - \frac{AVA}{CSA_{aorta}} \right) \right) \right) = 20 \left( 1 - \left( 2 \frac{0.7}{6.61} \left( 1 - \frac{0.7}{6.61} \right) \right) \right) = 16.1 \; mmhg$$

$$AVC = \frac{\Delta p_{total}}{4 \times V_{LVOT}{}^2} = \frac{16.1}{4 \times 0.43^2} = 21.8$$

The AVC value of 21.8 accounts for the variation in pressure drop and flow in a single non-invasive hemodynamic index.

### C. AVC as a Function of the Average Velocity Ratio and Cross-sectional Areas

We pursued an expression for AVC as a function of the Doppler measured velocity ratio (VR) and cross-sectional areas. Substituting the time-averaged $\Delta$p, which is calculated by averaging the instantaneous pressure drop over the ejection period [4], in Equation A5 with the pressure drop calculated from the time-averaged jet velocity at the *vena contracta* ($\Delta\bar{p} = 4 \times V_{jet}^2$) and combining with Equation A3 we obtain the following relationship.

$$AVC_{VR} = \frac{4 \times V_{jet}{}^2}{4 \times V_{LVOT}{}^2} \left( 1 - \left( 2 \frac{AVA}{CSA_{aorta}} \left( 1 - \frac{AVA}{CSA_{aorta}} \right) \right) \right) \quad \text{(Eq. A6)}$$

The continuity equation between the LVOT and the aortic valve yields the following:

$$AVA = \frac{CSA_{LVOT} \times V_{LVOT}}{V_{jet}} \quad \text{(E. A7)}$$

Equations A6 and A7 can be combined to give the following equation.

$$AVC_{VR} = \frac{{V_{jet}}^2}{{V_{LVOT}}^2} - 2\frac{V_{jet} \times CSA_{LVOT}}{V_{LVOT} \times CSA_{aorta}} + 2\left(\frac{CSA_{LVOT}}{CSA_{aorta}}\right)^2 \quad \text{(Eq. A8)}$$

The velocity ratio (VR) [4], is defined as the ratio of time-averaged velocities.

$$VR = \frac{V_{LVOT}}{V_{jet}} \quad \text{(Eq. A9)}$$

By using Equation A9, $AVC_{VR}$ can be reduced to the following:

$$AVC_{VR} = \frac{1}{VR^2} - \frac{2}{VR}\frac{CSA_{LVOT}}{CSA_{aorta}} + 2\left(\frac{CSA_{LVOT}}{CSA_{aorta}}\right)^2 \quad \text{(Eq. A10)}$$

$AVC_{VR}$ is also calculated for one patient described in Appendix, section B as an example.

$$AVC_{VR} = \frac{1}{0.215^2} - \left(\frac{2}{0.215} \times \frac{3.8}{6.61}\right) + 2\left(\frac{3.8}{6.61}\right)^2 = 16.94$$

For this patient example $AVC_{VR}$ (16.94) is significantly lower than AVC (21.8) which is expected due to the fact that the time-averaged $\Delta p$ used in AVC is more accurate than the calculated $\Delta\bar{p}$ used in $AVC_{VR}$.

## D. Comparison of AVC with Existing Diagnostic Parameters

Recent studies have evaluated the parameter *energy loss coefficient* (ELCo) to account for the pressure recovery phenomenon [25,26]. Both the theoretical energy loss and $\Delta p_{total}$ represent the total pressure drop, that is $(P_1 - P_3)$. However, the ELCo, which is developed from the modified Bernoulli's equation, is a *dimensional* parameter with an *atypical* unit of $cm^2$ and is very similar to the valve area derived from catheterization data using the Gorlin equation [25]. On the contrary,

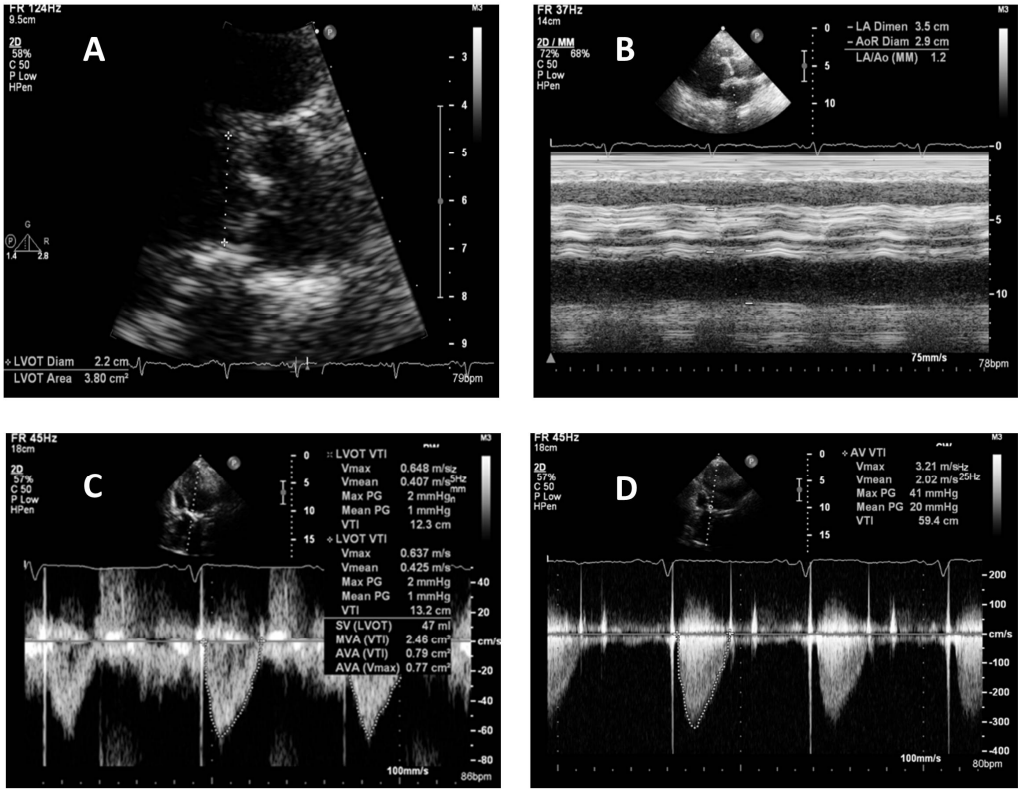


**Fig. A1. Two-dimensional images of (A) the left ventricular outflow tract (LVOT) and (B) the aortic root cross-sectional area measurements. Doppler spectral displays of (C) the LVOT and (D) the aortic valve velocity measurements**

the AVC proposed in this study (Equation A1 in the Appendix) is a non-dimensional parameter where the normalization of the total pressure drop is based on the differential mass and momentum equations [17]. Moreover, the ELCo, by definition, is calculated from Doppler measurements [25] under the assumption of the limiting high Reynolds number condition where only loss due to momentum change caused by AS is significant (Supplement A, [17]). Thus frictional loss (viscous) is not accounted for. This assumption may not be accurate for lower flow or lower Reynolds number conditions (for example, in patients with left ventricular dysfunction due to myocardial disease or hypertrophy). Whereas, the numerator in the definition of AVC can be the $\Delta p_{total}$ derived from Doppler measurements (*non-invasive*) or catheterization measurements (*invasive*). Here, by definition, $\Delta p_{total}$ includes both the frictional (viscous) loss and pressure loss due to momentum change, irrespective of the flow status (high or low Re).

AVC displays an inverse non-linear relationship with the *velocity ratio* (VR, Equations A9 and A10 in the Appendix, section C). This implies that in patients with severe AS small changes in VR can cause large changes in AVC. Thus, AVC can provide better delineation and wider range for patients with moderate to severe AS when compared to VR.

## E. Diagnosis of 'Low-Flow, Low-Gradient' AS

While dobutamine stress echo is indicated for the assessment of '*low-flow, low-gradient AS*' [4], the changes in pressure drop and valve area during stress conditions depend on various factors like the presence or absence of LV contractile reserve. The presence of coronary artery disease or previous myocardial infraction can nullify the inotropic effect of dobutamine and can result in less than expected rise in flow and pressure drop [27]. Further, calculation of the projected valve area [4,9], requires Doppler measurements at each incremental increase in dobutamine infusion. Similarly the stroke volume index can be used along with other diagnostic indices for an improved assessment of 'paradoxical low-flow, low-gradient severe AS' [9]. Nevertheless, assessment of AS severity with abnormal volume loading states either requires clinical judgment based on additional indices or carries the increased risk and complexity of dobutamine administration. In this context, the normalization and combination of the $\Delta p_{total}$ with the square of the $V_{LVOT}$ in AVC is fundamentally more accurate from a fluid dynamic perspective [22] and has the potential to improve the accuracy of assessment of AS severity in patients with 'low-flow, low-gradient AS'.



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