

**Temporal Relationship between Instantaneous Pressure Gradients and Peak-to-Peak Systolic Ejection Gradient in Congenital Aortic Stenosis**

Brian A. Boe, MD<sup>1</sup>, Mark D. Norris, MD<sup>2</sup>, MS, Jeffrey D. Zampi, MD<sup>2</sup>, Albert P. Rocchini, MD<sup>2</sup>, Gregory J. Ensing, MD<sup>2</sup>

<sup>1</sup>The Heart Center, Nationwide Children's Hospital, Columbus, OH

<sup>2</sup>University of Michigan C.S. Mott Children's Hospital Congenital Heart Center, Ann Arbor, MI

Correspondence:

Brian Boe, MD  
The Heart Center  
Nationwide Children's Hospital  
700 Children's Drive  
Columbus, OH 43205-2664  
Phone: 614-722-0494  
Fax: 614-722-3955  
Email: [brian.boe@nationwidechildrens.org](mailto:brian.boe@nationwidechildrens.org)

All authors are without conflict of interest or bias as it relates to this submission. There are no author disclosures.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version record](#). Please cite this article as [doi:10.1111/chd.12514](https://doi.org/10.1111/chd.12514).

## Abstract

### Objective

We sought to identify a time during cardiac ejection when the instantaneous pressure gradient (IPG) correlated best, and near unity, with peak-to-peak systolic ejection gradient (PPSG) in patients with congenital aortic stenosis. Non-invasive echocardiographic measurement of IPG has limited correlation with cardiac catheterization measured PPSG across the spectrum of disease severity of congenital aortic stenosis. A major contributor is the observation that these measures are inherently different with a variable relationship dependent on the degree of stenosis.

### Design

Hemodynamic data from cardiac catheterizations utilizing simultaneous pressure measurements from the left ventricle (LV) and ascending aorta in patients with congenital valvar aortic stenosis was retrospectively reviewed over the past 5 years. The cardiac cycle was standardized for all patients using the percentage of total LV ejection time (ET). Instantaneous gradient at 5 % intervals of ejection time were compared to PPSG using linear regression and Bland Altman analysis.

### Results

A total of 22 patients underwent catheterization at a median age of 13.7 years (interquartile range [IQR] 10.3-18.0) and median weight of 51.1 kg (IQR 34.2-71.6). The PPSG was  $46.5 \pm 12.6$  mmHg (mean  $\pm$  SD) and correlated sub-optimally with the maximum and mean IPG. The mid-systolic IPG (occurring at 50% of ET) had the strongest correlation with the PPSG ( $PPSG = 0.97(IPG_{50\%}) - 1.12$ ,  $R^2 = 0.88$ ), while the IPG at 55% of ET was closest to unity ( $PPSG = 0.997(IPG_{55\%}) - 1.17$ ,  $R^2 = 0.87$ ).

### Conclusions

The commonly measured maximum and mean IPG are sub-optimal estimates of the PPSG in congenital aortic stenosis. Using catheter-based data, IPG at 50-55% of ejection correlates well with PPSG. This may allow for a more accurate estimation of PPSG via noninvasive assessment of IPG.

**KEYWORDS:** congenital heart disease, aortic stenosis, catheterization, echocardiography

## INTRODUCTION

Patients with aortic valve stenosis comprise 3-8% of the congenital heart disease population<sup>1</sup>. The natural history study of this lesion revealed a high incidence of sudden cardiac death associated with the catheter measured peak-to-peak systolic ejection gradient (PPSG)<sup>2</sup>. As a result, the PPSG is utilized as the primary indication for intervention on aortic valve stenosis<sup>3</sup>. Given the improvements in ultrasound technology since publication of the natural history studies and the invasive nature of catheterization, nearly all patients with aortic valve stenosis are clinically managed using echocardiography. Current referral to the cardiac catheterization laboratory is reserved for patients with clinically significant aortic valve stenosis likely requiring intervention, and is often based on the echocardiographic estimates of the PPSG.

Echocardiography measures the velocity across the aortic valve in real-time. The instantaneous pressure gradient (IPG) is derived from the measured velocity across the valve by using the simplified Bernoulli equation:  $IPG = 4 \times \text{velocity}^2$ . Many studies have attempted to correlate aortic valve maximal and mean IPG to PPSG with variable success. The maximum IPG often overestimates the PPSG while the mean IPG has been shown to underestimate the PPSG in congenital aortic stenosis with regression equations deviating significantly from identity<sup>4-8</sup>. Mathematical models to calculate PPSG from echocardiographic measurements have been studied, but are not commonly used<sup>8-12</sup>.

One of the fundamental flaws with the comparison of PPSG and IPG lies in the inherent differences between the two measured gradients (Figure 1). The gold-standard measurement for aortic stenosis, PPSG, is a single gradient which does not occur at any one time during the cardiac cycle. Pressure in the left ventricle (LV) peaks before the pressure in the ascending aorta (AAo) during systole. PPSG is calculated by subtracting the peak systolic LV pressure from the peak systolic AAo pressure. The IPG is a continuous and variable measurement and is dependent on the flow across the aortic valve. At the onset and completion of LV ejection, the IPG is zero. IPG increases rapidly during early LV ejection until it reaches a maximum value near the peak systolic LV pressure. As the LV pressure decreases, the aortic pressure continues to rise to the peak systolic AAo pressure. This leads to the gradual decline of the IPG. As a result, the maximum IPG is greater than the PPSG. Given the curvilinear relationship, the IPG must equal the PPSG twice during the cardiac cycle. The timing of the maximum IPG varies with disease severity. As the severity of aortic stenosis increases, the peak LV pressure occurs later in systole. Thus, the maximum IPG occurs sooner in milder disease as is evidenced by the early peaking murmur and earlier peaking

Doppler signal. We sought to identify a time during cardiac ejection when IPG correlates best, and near unity, with PPSG in patients with congenital aortic stenosis.

## METHODS

The purpose of this study was to correlate an IPG during ejection with PPSG using catheterization data. All cardiac catheterizations performed at the University of Michigan Congenital Heart Center for isolated, congenital valvular aortic stenosis between 2010 and 2015 were identified using our internal catheterization database. Cases were excluded if the hemodynamic assessment of the aortic valve stenosis was not measured via a simultaneous LV and AAO pressure recording (i.e. via pullback, or simultaneous LV and femoral arterial pressure recording). Patient and procedural details from identified cases were recorded using the electronic medical record.

All pressure tracings were recorded using Xper Hemodynamic Monitoring System (Philips Healthcare, Andover, MA). Hemodynamic measurements were obtained during steady-state conditions, prior to intervention (if an intervention was performed), with the patient in sinus rhythm. Simultaneous pressure measurements were obtained using either a single (6 French Langston® Dual Lumen Pigtail Catheter [Aquilant Interventional, Basingstoke, Hampshire, UK]) or two fluid-filled catheters (one catheter antegrade via a patent foramen ovale or transeptal puncture into the LV, and a second pigtail catheter placed retrograde in the AAO). Simultaneous pressures were recorded over two separate cardiac cycles for each patient at end expiration during the respiratory cycle. Pressure measurements are captured every 4 milliseconds during active recording. The tracings were synced by aligning the systolic upstrokes of both pressure waveforms on the hemodynamic software system.

The PPSG was calculated by subtracting the maximum AAO pressure from the maximum LV pressure.

$$PPSG = LV_{MAX} - AAO_{MAX}$$

The IPG at each recorded time point (t) throughout the cardiac cycle was calculated by subtracting the AAO pressure from the LV pressure.

$$IPG_t = LV_t - AAO_t$$

Time throughout LV ejection was standardized to the percent of LV ejection time (%ET) in order to compare the IPG across multiple cardiac cycles with different rates. LV ejection was defined at any point when the IPG > 0. Individual data points at every 5% of ejection time were used for analysis.

Descriptive demographics were calculated. Categorical variables are reported as number (percentage). Continuous variables are expressed as mean  $\pm$  standard deviation or median (interquartile range) as appropriate. Correlations between IPG and PPSG were assessed using linear regression and Bland-Altman analysis.

## RESULTS

From January 1<sup>st</sup>, 2010 through December 31<sup>st</sup>, 2015, 22 patients met study criteria (Table 1). One study patient had undergone an aortic valve replacement with a 19 mm bioprosthetic Freestyle® valve (Medtronic, Minneapolis, MN). Pre-procedural echocardiograms measured maximum and mean gradients of  $77.1 \pm 18.1$  and  $45.1 \pm 11.9$ , respectively. General anesthesia with endotracheal intubation was used in 45.5% of cases. Patients were spontaneously breathing under conscious sedation in 54.5% of cases. Simultaneous pressures were measured using a single catheter in 13 patients (59%) and two catheters in 9 patients (41%). Based on the PPSG, balloon aortic valvuloplasty was performed in 12 patients (55%).

Figure 2 depicts the linear regression analyses comparing the maximum and mean IPG to PPSG which vary from unity. As expected, the maximum IPG ( $60.8 \pm 13.0$  mm Hg) overestimated the PPSG and mean IPG ( $36.7 \pm 8.8$  mm Hg) over and underestimated the PPSG ( $46.5 \pm 12.6$  mm Hg).

The difference between the IPG and PPSG throughout left ventricular ejection is shown in Figure 3. As the PPSG is a constant value, the y-axis represents the IPG throughout LV ejection as it relates to PPSG. During early systole, the IPG is highly variable among the patient population. IPG first equals PPSG around 20% of LV ejection, with a difference between the two values of  $1.2 \pm 10.3$  mm Hg. The IPG peaks at 30-40% ejection time and there is less disparity between the individual patient values as it slowly decreases. Between 50-60% of LV ejection time, the IPG equals PPSG for the second time in the cardiac cycle. The mean difference between the IPG and PPSG at 50%, 55%, and 60% ejection time is  $2.8 \pm 4.1$ ,  $1.3 \pm 4.3$ , and  $-2.6 \pm 4.4$  mm Hg, respectively.

Figure 4 shows the linear regression and Bland-Altman plots comparing PPSG and IPG at every 5% between 45% and 60% of ejection time. The IPG at these times during mid-systole were nearly analogous to the PPSG, with the greatest correlation occurring at 50% of ejection time ( $\text{PPSG} = 0.97(\text{IPG}_{50\%}) - 1.12$ ,  $R^2 = 0.88$ ) and slope closest to unity at 55% of ejection ( $\text{PPSG} = 0.997(\text{IPG}_{55\%}) - 1.17$ ,  $R^2 = 0.87$ ).

## DISCUSSION

The management of aortic valve stenosis can be challenging for congenital cardiologists. With the exception of critical aortic valve stenosis, patients are often asymptomatic and are at risk for sudden cardiac death<sup>2</sup>. Stratification of risk and guidelines for intervention are based upon the invasively measured PPSG<sup>2,3</sup>. Currently, the non-invasively measured maximum and mean IPG are used to estimate the PPSG when referring a patient for cardiac catheterization. Given the inconsistent relationship between IPG and PPSG, patients sometimes undergo cardiac catheterization only to evaluate a mild aortic valve gradient. The majority of the 22 study patients referred for cardiac catheterization in our study had high pre-procedural echocardiographic measured mean IPG (median 48 mmHg [IQR 34.3-55.5]) and maximum IPG (median 79.5 mmHg [IQR 59-94.3]). While not all patients were referred for intervention, 16 study patients (73%) had generous Doppler gradients with substantially lower catheter measured PPSG. These patients are clinical challenges with significant discrepancy between the echocardiographic and catheterization measured aortic valve gradients. Clearly, improvement of correlation between echocardiographic measured gradients and PPSG at catheterization would reduce the number of diagnostic catheterizations in patients not meeting criteria for intervention.

Hatle et al. first described the Doppler measurement of aortic stenosis gradient in 1980, and also described the physiologic differences between mean IPG and PPSG<sup>13</sup>. In 1985, Currie et al. described a correlation between maximum IPG measured simultaneously via Doppler and catheterization<sup>14</sup>. The authors went on to further correlate the Doppler-measured maximum IPG with the catheter-measured PPSG using the following equation ( $PPSG = 0.84(\text{maximum IPG}) - 13.7, r=0.94$ ). Beekman et al. devised a model accounting for pulse pressure ( $PPSG = 6.02 + 1.49(\text{mean IPG}) - 0.44(\text{pulse pressure}), r^2=0.97$ ) to correlate these gradients which was verified by the Toronto group<sup>9,10</sup>. More recent studies have demonstrated lesser correlations between these measured gradients in congenital aortic stenosis with slopes deviating from unity<sup>5-8</sup>. Discrepancies between Doppler measurements of aortic valve gradients and catheterization measured PPSG have been attributed to four major factors:

1. Angle and signal quality affecting the Doppler gradient measurement.
2. The effect of pressure recovery as potential energy is converted into kinetic energy across a stenotic aortic valve. As a result, the Doppler measured IPG from the LV to the vena contracta is greater than the catheter measured PPSG from the LV to the downstream ascending aorta.
3. The differences in gradient measurements. Specifically, there is a significant difference between maximum IPG and mean IPG measured by echocardiography and PPSG measured at catheterization.

4. The baseline patient hemodynamic differences between echocardiography and catheterization.

Echocardiograms are typically performed with the patient under no sedation while catheterizations are performed using some sedation and with the patient NPO.

The first factor was evaluated by Vlahos who measured aortic valve gradients from multiple transthoracic echocardiograms windows and found the echocardiographic measurements did not accurately estimate the PPSG measured during catheterization<sup>7</sup>. The authors discovered a maximum IPG measured from the right parasternal window > 90 mmHg and mean IPG measured from the apical window > 50 mmHg correlated with catheter intervention. These echocardiographic parameters can support a referral for cardiac catheterization, however are not surrogates for the PPSG based on current guidelines<sup>3</sup>. Several reports have demonstrated the inclusion of estimation of pressure recovery improves correlation of Doppler measured gradients to those at catheterization<sup>8,11,12,15</sup>. Pressure recovery (PR) is calculated using the equation below ( $v$  = velocity across the aortic valve, AVA = aortic valve area, AoA = cross sectional area of the aorta).

$$PR = 4v^2 \times 2(AVA/AoA) \times (1 - AVA/AoA)$$

Most recently, Schlingmann demonstrated incorporating pressure recovery estimate into Doppler measurements for aortic stenosis improves correlation with PPSG measured at subsequent catheterization<sup>8</sup>. All of these previously studied approaches address the first two of the factors listed above, and can provide additional clinical value when estimating PPSG from Doppler measurements.

This study uses direct hemodynamic measurements to understand and optimize adjustment of the third factor: the differences between the measured Doppler IPG and PPSG. Using catheterization data, we found the PPSG correlated well with the IPG during mid-systole (50-55% of LV ejection time) with regression nearest unity at 55% of ejection PPSG. This data suggest that Doppler measurement of the IPG at 50-55% of ejection, rather than using maximal or mean IPG, may provide a more accurate estimate of the PPSG.

The IPG at mid-systole is relatively easy to measure during an echocardiogram from an apical 5 chamber or suprasternal notch view. The duration of the ejection is measured as the width of the Doppler envelope. A vertical line is drawn from the baseline to the edge of the envelope at 50-55% of ejection to measure the IPG (Figure 5).

This has been reported and compared to the PPSG in an animal model of aortic stenosis<sup>16</sup>. The model consisted of a band placed around the aorta in canines. An echocardiogram was performed with the probe directly on

the AAO during cardiac catheterization. The mid-systolic IPG accurately correlated with the PPSG in the animal model; however, this finding has not been verified in human subjects.

As the purpose of this study was to correlate IPG during ejection with PPSG using catheterization data, additional study is needed to compare Doppler measured mid systolic IPG with catheterization measured PPSG. This should assess and account for contribution of other potential sources of discrepancy noted above. In addition to guiding intervention, further correlation of these measurements will provide cardiologists with a better understanding of gradients while patients are at their physiologic baseline during echocardiogram with the patient awake and hydrated versus when sedated and NPO for a cardiac catheterization. We would then be able to more accurately address the hemodynamic discrepancies between the two studies.

There are multiple limitations in this study. Echocardiographic measured IPG were not performed during the catheterization. The purpose of this study was to evaluate the relationship between the IPG and PPSG using the same catheter measurements. Echocardiographic measurements obtained simultaneously with catheterization measurements would allow us to further correlate invasive and non-invasive assessment of aortic stenosis. Fluid-filled catheters were used in this study to measure pressures, which are subject to multiple sources of error (i.e. height of transducer compared to the body, bubbles within the tubing, catheter fling/whip on the tracings). The use of micromanometer catheters may have provided a more accurate pressure measurement but given the expense, these catheters are not routinely used in our catheterization laboratory. Therefore the use of fluid-filled catheters provides data that is more consistent with how these measurements are made and could be used in clinical practice. The exact placement of the catheters within the LV and AAO were not standardized in all catheterizations. A catheter placed in the ascending aorta relatively close to the aortic valve may overestimate the PPSG secondary to pressure recovery. Despite these limitations, the accuracy of the catheter measured gradients were optimized by measuring simultaneous LV and AAO pressures using dual lumen pigtailed or transseptal access.

## CONCLUSIONS

The aortic valve IPG at 50-55% of systole correlates well, and at near unity, with the PPSG using catheterization data. This suggests that Doppler measured aortic valve IPG at 50-55% of systole should decrease discrepancies between Doppler and catheterization measured gradients for patients with aortic stenosis. Further studies using high quality Doppler-measured mid systolic IPG at optimal angles during similar hemodynamic



conditions, with and without estimate of pressure recovery have potential to maximize echocardiographic-catheterization data correlation. Cardiac catheterization will continue to be the gold-standard for assessing aortic valve stenosis until this correlation can be well demonstrated.

#### **AUTHOR CONTRIBUTIONS**

All authors contributed significantly to the research study and article as follows:

Brian Boe: Study concept/design, data collection, data analysis/interpretation, drafting article, critical article revision, and approval of article.

Mark Norris: Data interpretation, critical article revision, and approval of article.

Jeffrey Zampi: Data interpretation, critical article revision, and approval of article.

Albert P. Rocchini, MD: Data interpretation, critical article revision, and approval of article.

Gregory J. Ensing, MD: Study concept/design, data analysis/interpretation, critical article revision, and approval of article.

Accepted Article

## REFERENCES

1. Hoffman JI, Christianson R. Congenital heart disease in a cohort of 19,502 births with long-term follow-up. *Am J Cardiol.* Oct 1978;42(4):641-647.
2. Keane JF, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with aortic valvar stenosis. *Circulation.* Feb 1993;87(2 Suppl):116-27.
3. Feltes TF, Bacha E, Beekman RH, 3rd, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation.* Jun 7 2011;123(22):2607-2652.
4. Wright SB, Wienecke MM, Meyer KB, McKay CA, Wiles HB. Correlation of pediatric echocardiographic Doppler and catheter-derived valvar aortic stenosis gradients and the influence of aortic regurgitation. *Am J Cardiol.* Mar 15 1996;77(8):663-665.
5. Smith MD, Dawson PL, Elion JL, et al. Systematic correlation of continuous-wave Doppler and hemodynamic measurements in patients with aortic stenosis. *Am Heart J.* Feb 1986;111(2):245-252.
6. Bengur AR, Snider AR, Serwer GA, Peters J, Rosenthal A. Usefulness of the Doppler mean gradient in evaluation of children with aortic valve stenosis and comparison to gradient at catheterization. *Am J Cardiol.* Oct 1 1989;64(12):756-761.
7. Vlahos AP, Marx GR, McElhinney D, Oneill S, Goudevenos I, Colan SD. Clinical utility of Doppler echocardiography in assessing aortic stenosis severity and predicting need for intervention in children. *Pediatric cardiology.* May 2008;29(3):507-514.
8. Schlingmann TR, Gauvreau K, Colan SD, Powell AJ. Correction of Doppler Gradients for Pressure Recovery Improves Agreement with Subsequent Catheterization Gradients in Congenital Aortic Stenosis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* Dec 2015;28(12):1410-1417.
9. Lima VC, Zahn E, Houde C, Smallhorn J, Freedom RM, Benson LN. Non-invasive determination of the systolic peak-to-peak gradient in children with aortic stenosis: validation of a mathematical model. *Cardiol Young.* Mar 2000;10(2):115-119.
10. Beekman RH, Rocchini AP, Gillon JH, Mancini GB. Hemodynamic determinants of the peak systolic left ventricular-aortic pressure gradient in children with valvar aortic stenosis. *Am J Cardiol.* Mar 15 1992;69(8):813-815.
11. Barker PC, Ensing G, Ludomirsky A, Bradley DJ, Lloyd TR, Rocchini AP. Comparison of simultaneous invasive and noninvasive measurements of pressure gradients in congenital aortic valve stenosis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* Dec 2002;15(12):1496-1502.
12. Niederberger J, Schima H, Maurer G, Baumgartner H. Importance of pressure recovery for the assessment of aortic stenosis by Doppler ultrasound. Role of aortic size, aortic valve area, and direction of the stenotic jet in vitro. *Circulation.* Oct 15 1996;94(8):1934-1940.
13. Hatle L. Noninvasive assessment and differentiation of left ventricular outflow obstruction with Doppler ultrasound. *Circulation.* Aug 1981;64(2):381-387.

4. Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation*. Jun 1985;71(6):1162-1169.
5. Kobayashi D, Humes RA. Pressure Recovery in Congenital Aortic Stenosis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. Dec 2015;28(12):1418-1419.
6. Smith MD, Dawson PL, Elion JL, et al. Correlation of continuous wave Doppler velocities with cardiac catheterization gradients: an experimental model of aortic stenosis. *J Am Coll Cardiol*. Dec 1985;6(6):1306-1314.

Accepted Article

**Table 1: Patient Demographics (n=22)**

Demographics	
Age (years)	13.7 (10.3-18.3)
Weight (kg)	51.1 (34.2-71.6)
Male Gender	13 (59%)
Valve Morphology	
Bicuspid	17 (77.3%)
Unicuspid	3 (13.6%)
Tricuspid	1 (4.5%)
Other	1 (4.5%)
Pre-procedural echocardiographic gradients	
Maximum IPG	77.1 ± 18.1
Mean IPG	45.1 ± 11.9
Sedation	
General Anesthesia	10 (45.5%)
Conscious Sedation	12 (54.5%)

Values reported in n (%), mean ± standard deviation, median (Interquartile Range), as appropriate.

Accepted

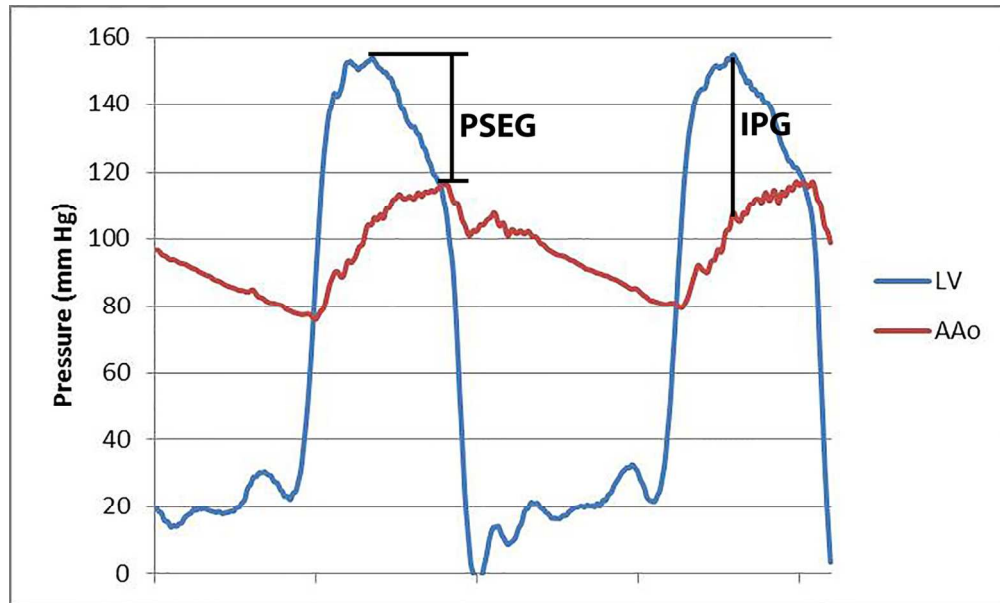


Fig 1. Simultaneous left ventricle (LV) and ascending aorta (AAo) pressure tracings from a patient with aortic valve stenosis showing the PSEG and maximum IPG.

127x76mm (300 x 300 DPI)

Accepte

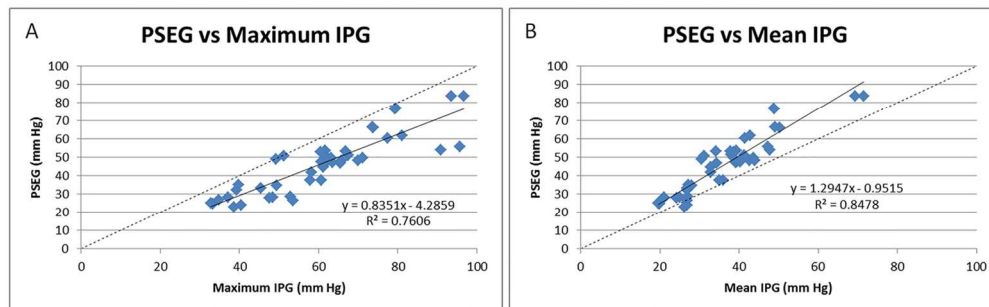


Fig 2. Linear regression plots comparing PSEG to the maximum IPG (A) and mean IPG (B). The trendline for the data is solid black and the dotted line represents perfect unity of gradient measurements.

127x40mm (300 x 300 DPI)

Accepted A

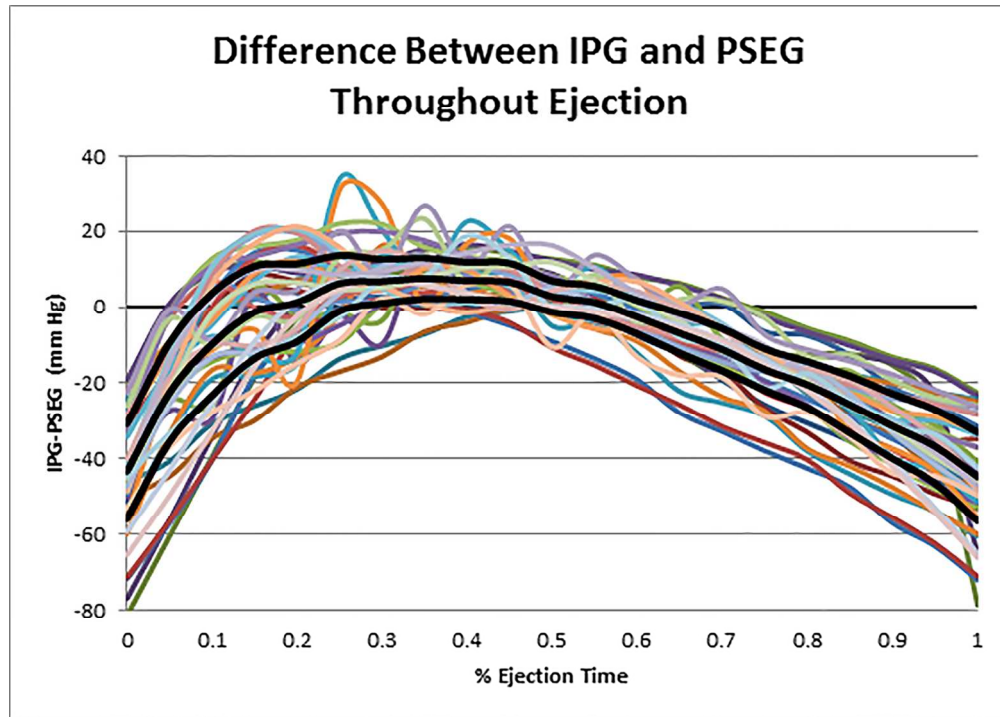


Fig 3. The difference between the IPG and PSEG in valvar AS for all study patients plotted throughout LV ejection with the mean  $\pm$  1 standard deviations highlighted in black. The IPG is equivalent to the PSEG at a value of 0 on the y-axis.

127x90mm (300 x 300 DPI)

Accep

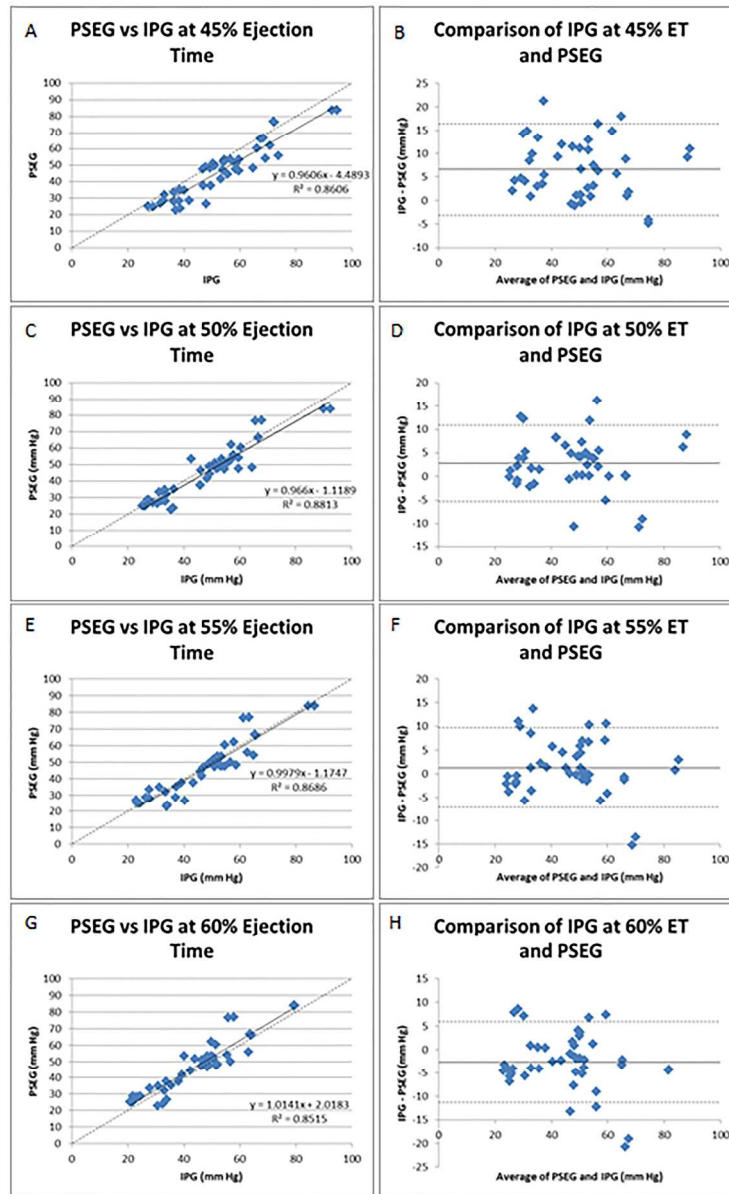


Fig 4. Linear regression and Bland-Altman plots comparing PSEG to the IPG at 45% (A,B), 50% (C,D), 55% (E,F), and 60% (G,H) of ejection time. On the Linear Regression plot, the trendline for the data is solid black and the dotted line represents perfect unity of gradient measurements. On the Bland-Altman plot, the bias (mean) and  $\pm 1.96$  standard deviations are represented by the solid black and dotted lines, respectively.

260x422mm (300 x 300 DPI)



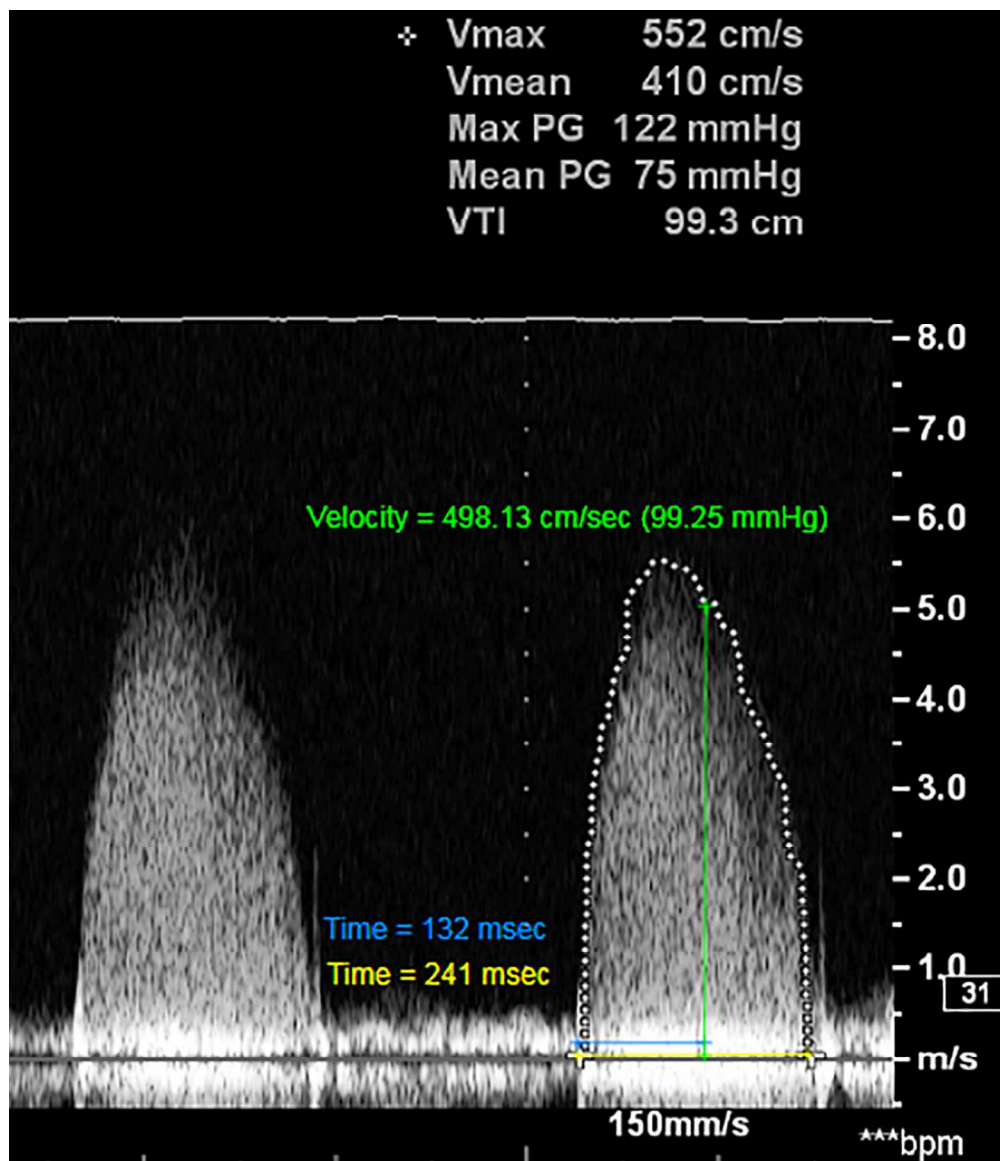


Fig 5. Measurement of mean IPG, maximum IPG and IPG at 55% ejection time from a Doppler envelope from a suprasternal notch view. The total ejection time is measured at 241 msec and 55% of ejection time (132 msec) is measured from the start of ejection. The IPG at 55% ejection time is measures 99 mmHg.

109x126mm (300 x 300 DPI)

