Blood Speckle Imaging Compared with Conventional Doppler Ultrasound for Transvalvular Pressure Drop Estimation in an Aortic Flow Phantom

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Abstract

Background Transvalvular pressure drops are assessed using Doppler echocardiography for the diagnosis of heart valve disease. However, this method is highly user-dependent and may overestimate transvalvular pressure drops by up to 54%. This work aimed to assess transvalvular pressure drops using velocity fields derived from blood speckle imaging (BSI), as a potential alternative to Doppler.

Methods A silicone 3D-printed aortic valve model, segmented from a healthy CT scan, was placed within a silicone tube. A CardioFlow 5000MR flow pump was used to circulate blood mimicking fluid to create eight different stenotic conditions (transvalvular flow velocities between 1.6 and 2.4 m/s and pressure drops between 9.7 and 22.7 mmHg). Eight PendoTech pressure sensors were embedded along the tube wall to record ground-truth pressures (10 KHz). The Bernoulli equation with measured probe angle correction was used to estimate pressure drop from maximum velocity values acquired across the valve using Doppler and BSI with a GE Vivid E95 ultrasound machine and 6S-D cardiac phased array transducer.

Results There were no significant differences between pressure drops estimated by Doppler, BSI and ground-truth at the lowest stenotic condition (10.4 ± 1.76 , 10.3 ± 1.63 vs. 10.7 ± 1.12 mmHg, respectively; $p > 0.05$). Significant differences were observed between the pressure drops estimated by the three methods at the greatest stenotic condition (26.4 ± 1.52 , 14.5 ± 2.14 vs. 20.1 ± 1.78 mmHg for Doppler, BSI and ground-truth, respectively; $p < 0.05$). Across all conditions, Doppler overestimated pressure drop (Bias = 3.54 mmHg), while BSI underestimated pressure drop (Bias = -3.68 mmHg).

Conclusions BSI accurately estimated pressure drops only up to 10.7 mmHg in controlled phantom conditions of low stenotic burden. Although BSI offers a number of theoretical advantages to conventional Doppler echocardiography, further refinements and clinical

studies are required with BSI before it can be used to improve transvalvular pressure drop estimation in the clinical evaluation of aortic stenosis.

Background

Doppler echocardiography is routinely used in clinical practice to assess the severity of aortic stenosis. The maximum velocity of blood flow through the aortic valve during systole is recorded, and the simplified Bernoulli equation is used to estimate the transvalvular pressure drop (a more accurate term to the widely used *gradient*) across the valve [1]. This technique is preferred to cardiac catheterisation as it is non-invasive, widely accessible and inexpensive [2].

Despite this, pressure drop estimation using Doppler echocardiography is highly user-dependent and has been shown to overestimate transvalvular pressure drops by up to 54% [3]. Taking a single peak velocity event ignores the complex haemodynamics of blood flow across the valve, where the full velocity profile at the point of maximum flow constriction is needed to estimate the actual pressure drop. In addition, if the angle of insonation is not fully aligned with the direction of blood flow, the maximum velocity will be missed [4]. Several non-invasive alternatives have been studied but are not yet applied clinically [5].

Blood speckle imaging (BSI) has recently emerged as an alternative methodology for the assessment of aortic stenosis severity [6]. By the direct measurement and visualisation of blood vector velocity fields [7, 8] it has the potential to overcome some of the limitations with conventional Doppler echocardiography. BSI utilises existing technology from tissue speckle-tracking that is commonly used to evaluate myocardial deformation [9]. A small image kernel is defined in the first image of the vessel and the same speckle signature is tracked in the following frame. This is then repeated for a grid of measurements to quantify the velocity and direction of the blood flow [10]. Acquiring blood flow velocity data in this way is advantageous

as it potentially allows pressure drop to be calculated from velocity data across 3-dimensions, rather than from a single streamline in conventional Doppler echocardiography. The principal aim of the current manuscript was to evaluate blood speckle imaging (BSI) and Doppler echocardiography for pressure drop estimations against ground-truth pressure sensors in a bespoke aortic phantom with a 3D-printed aortic valve at various flow rates.

Materials and Methods

Pressure Drop Phantom

In order to investigate the accuracy and utility of novel techniques for pressure drop estimation, a bespoke aortic phantom was developed [11]. The phantom was designed to simulate the human aorta, able to deform with pulsatile and constant flow conditions, allowing for comparison of novel pressure drop estimation techniques to ground-truth pressure drop data from pressure sensors across a 3D-printed aortic valve.

A silicone 3D-printed aortic valve model was placed within a semi-compliant silicone tube, suspended in an acrylic box (**Fig. 1**). The valve was designed to resemble a healthy aortic valve, segmented from patient CT scans. The valve design was converted to a mould, before degassed Ecoflex 0030 silicone (Smooth-On Inc., Macungie, PE, USA) was poured in and left to cure. Valve mounts were also 3D printed using poly-lactic acid.

8 PendoTech pressure sensors (PRESS-S-000 sensor, PendoTech, Princeton, NJ, USA) were embedded along the tube wall, 1 situated before the valve and 7 downstream. The position of each pressure sensor was decided aiming to both capture the event of maximum constriction (i.e. location of the vena contracta) and the distal net pressure drop (i.e. characterisation of the pressure recovery). The sensors were calibrated and validated using a pressure catheter (Mikro-Cath, Millar Inc, Houston, TX, USA). The pressure sensors were wired to input modules of a

data acquisition USB chassis (National Instruments, Austin, TX, USA) to record ground-truth pressures for the 8 locations along the silicone tube at a sampling frequency of 10 KHz (**Fig. 2**).

A 20 L external reservoir containing blood mimicking fluid [12] was connected to a CardioFlow 5000MR flow pump (Shelley Medical Imaging Technologies, Ontario, Canada). The pump was programmed, via control unit, to circulate approximately 15 L of blood mimicking fluid at eight different flow rates (100, 150, 200 and 250 mL/s, constant and pulsatile flows). These flow rates were programmed to generate maximum velocities of flow across the valve between 1.6 and 2.4 m/s and pressure drops between 9.7 and 22.7 mmHg. Flow was maintained at a constant rate throughout each acquisition in the constant flow conditions. The pulsatile flow conditions were programmed to closely resemble the flow waveforms produced by the human heart, with fluctuations in pressure corresponding to systole and diastole.

Velocity and ground truth pressure data acquisition and analysis

Continuous wave Doppler and BSI data were acquired using a Vivid E95 ultrasound machine and 6S-D cardiac phased array transducer (GE Healthcare, Oslo, Norway) across the valve for each flow condition. Ground-truth pressure drop data were calculated using the methods outlined below. A metal clamp held the probe in position. The tilt angle between the tube and probe was recorded and used for angle correction calculations (**Fig. 3**). Each experimental condition was repeated on a second day of experiments.

Pressure data in pulsatile conditions was enhanced with a Butterworth filter that reduced the random peaks and noise on the raw temporal transients of pressure data from each sensor. For each experimental condition and flow rate, pressure data were recorded over 5 seconds and captured 4-5 cycles. The cycles were then segmented before the mean and standard deviation

of the pressure transient, across 3 cycles, were calculated. The instant of peak pressure difference between channels 1 and 2 or 3 was selected for further analysis. The mean and standard deviation values from each pressure sensor were then plotted against their physical position in the phantom, relative to the valve at point 0 cm. Spline interpolation was performed between the valve and channel 4, the region of the vena contracta, to estimate the maximum pressure drop and its location, relative to the valve (**Fig. 4A**). In constant flow conditions, a Butterworth filter was applied to the pressure signals before the mean and standard deviation values from each pressure sensor were then plotted against their physical position in the phantom. (**Fig. 4B**).

To estimate maximum velocity using Doppler, a continuous wave acquisition was acquired with the cursor placed at the valve opening. Once acquired, the E95 machine was used to manually select the maximum velocity observed in the acquisition (**Fig. 5A**). To estimate maximum velocity using BSI, the blood speckle imaging setting was used on the Vivid E95 machine to acquire BSI velocity data. A movie containing examples of BSI acquisitions at the different flow rates can be viewed in the additional files (**Additional File 1**). Offline analysis was performed to extract the maximum velocity observed across the acquired frames. Secondary validation was performed by an observer, using the interface shown in **Fig. 5B** to confirm that the maximum velocity vector was indeed observed within the expected region of interest where the jet after the valve is observed.

Pressure drop values were estimated from Doppler and BSI acquisitions by applying an angle correction, using the measured probe angle (**Fig. 3**), to the maximum velocity (m/s) value measured by each technique. Following this, the Bernoulli formulation was applied to the angle-corrected velocity value to convert to transvalvular pressure drop (mmHg).

Data and Statistical Analysis

Pressure sensor data were extracted and analysed offline using MATLAB (Mathworks, Natick, MA, USA). To calibrate the pressure sensors for random error, the mean pressure across the 8 pressure sensors was calculated with static fluid in the phantom, before and after each experimental condition. For each condition, a correction was applied to each pressure sensor based on its deviation from this set mean. Pressure drop and flow velocity data are presented as the mean $\pm$ standard deviation. To calculate the significance level of the values estimated by each technique, a paired two-tailed distribution t-test was used with a significance level of $p < 0.05$ (Microsoft Excel, Microsoft Office Version 2102, Microsoft Corporation, Redmond, Washington, USA).

Results

The probe angles were 24° and 40° on two days of experiments, respectively. The mean pressure drops across the valve, recorded by the ground-truth pressure sensors, were 9.75 ± 0.07 , 12.4 ± 0.00 , 16.4 ± 0.21 and 19.3 ± 0.14 mmHg under constant flow conditions and 11.6 ± 0.57 , 14.9 ± 0.49 , 18.5 ± 0.57 and 23.6 ± 1.23 mmHg under pulsatile conditions, at the flow rates investigated (100, 150, 200, 250 mL/s, respectively). There was no significant difference between the mean pressure drop values acquired under constant vs. pulsatile conditions ($p > 0.05$). The pressure drop values measured by the sensors were converted to velocity using:

$$Velocity = \frac{\sqrt{Pressure\ Drop}}{4}$$

The mean flow velocities across the valve were 1.6 ± 0.0 , 1.8 ± 0.0 , 2.0 ± 0.0 and 2.2 ± 0.0 m/s under constant flow conditions and 1.7 ± 0.0 , 1.9 ± 0.0 , 2.2 ± 0.0 and 2.4 ± 0.1 m/s under pulsatile conditions, at the flow rates investigated (100, 150, 200, 250 mL/s, respectively). There was no significant difference between the mean velocity values acquired under constant vs. pulsatile conditions ($p > 0.05$).

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164 The pressure drop values estimated across the 4 flow rates by the ground-truth pressure sensors,
165 BSI and Doppler methods are presented in **Fig. 6**. No significant differences were observed
166 between pressure drops estimated by Doppler, BSI and ground-truth sensors at the 100 mL/s
167 pump flow rate (10.4 ± 1.76 , 10.3 ± 1.63 vs. 10.7 ± 1.12 mmHg, respectively; $p > 0.05$).

168 Nevertheless, under the 150, 200 and 250 mL/s pump flow rates, pressure drops estimated by
169 BSI (10.5 ± 1.47 , 13.7 ± 2.27 and 14.5 ± 2.14 mmHg, respectively) were significantly lower
170 than ground-truth pressure drops (13.6 ± 1.44 , 17.4 ± 1.29 and 20.1 ± 1.78 mmHg, respectively;
171 $p < 0.05$). On the other hand, pressure drops estimated from Doppler velocity data were
172 significantly higher than ground-truth pressure drop under 250 mL/s pump flow conditions
173 (26.4 ± 1.52 vs. 20.1 ± 1.78 mmHg, respectively; $p < 0.05$).

174 The mean percentage errors in pressure drop estimation for each flow rate investigated,
175 compared to the ground-truth pressure sensors, were -2.26 ± 17.7 , 13.8 ± 22.2 , 17.4 ± 12.3 and
176 32.5 ± 14.9 % by Doppler and -2.00 ± 22.8 , -22.5 ± 8.01 , -21.5 ± 11.3 and -26.9 ± 13.9 % by
177 BSI at the flow rates investigated (100, 150, 200, 250 mL/s, respectively; **Fig. 7**). The
178 percentage error in pressure drop estimation by Doppler at the highest flow rate (32.5 ± 14.9
179 %) was significantly greater than the percentage error at the lowest flow rate (-2.26 ± 17.7 %;
180 $p < 0.05$).

181 Bland-Altman analysis of the Doppler and BSI techniques, compared to ground-truth pressure
182 drop are presented in **Fig. 8** [13]. **Fig. 8A**, shows that the bias of pressure drop estimations
183 made using Doppler, when compared to ground-truth pressure drop was 3.54 mmHg. The range
184 of the limits of agreement was 20.31 mmHg (**Fig. 8A**). **Fig. 8B** shows that the bias of pressure
185 drop estimations made using BSI, when compared to ground-truth pressure drop was -3.68
186 mmHg. The range of the limits of agreement was 13.2 mmHg (**Fig. 8B**).

Intra-technique reproducibility of the pressure drop estimations made across the two days of experiments by the three methods are presented in **Fig. 9**. Bland-Altman analysis produced intra-technique bias values of 0.56, 5.19 vs. 1.61 mmHg for ground-truth, Doppler and BSI, respectively. The range of the limits of agreement within each technique were 2.40, 22.19 vs. 10.24 mmHg for ground-truth, Doppler and BSI, respectively (**Fig. 9**).

Discussion

This study provides evidence to show that both BSI and Doppler techniques can make accurate estimations of low pressure drops in a controlled and reproducible aortic phantom. However, for stenotic conditions of clinical relevance in the setting of aortic stenosis, BSI underestimates while Doppler overestimates the pressure drop.

The assessment of the pressure drop by echocardiography in conventional clinical practice is subject to important methodological limitations that cannot be solved by current BSI technology. Significantly different pressure drop estimations, large percentage errors, bias values and wide limits of agreement exist for Doppler and BSI when compared with ground-truth pressure drop estimations. This is coupled with poor intra-technique reproducibility across two days of experiments. These findings illustrate that despite its theoretical advantages, further development of BSI or alternative novel and more comprehensive methods for pressure drop estimation are required to improve clinical practice.

Pressure drop estimation

A good agreement between pressure sensors, Doppler and BSI was found at low stenosis levels (10.7 ± 1.12 mmHg) but differences onset at the next stenotic condition tested (13.6 ± 1.44 mmHg; **Fig. 6**). BSI would likely be accurate in the diastolic estimations of trans-mitral valve pressure drop and intra-cardiac pressure drops. When comparing Doppler and BSI to ground-

truth pressure drop estimations, the limits of agreement are wide for both methods (20.31 mmHg for Doppler vs. 13.20 mmHg for BSI; **Fig. 8**). Over/underestimations of transvalvular pressure drop by these margins are clinically significant.

At the higher pressure drops, with higher flow velocities, BSI significantly underestimates pressure drop (**Fig. 6**). A negative linear relationship is observed for percentage error (**Fig. 7**) and agreement (**Fig. 8B**), illustrating that this underestimation is more pronounced at higher flow rates. These results are consistent with previous findings conducted *in vitro/in silico*, whereby BSI was shown to underestimate flow velocity [14, 15, 16]. The largest *in vivo* study to date was performed in 51 healthy paediatric controls, where underestimations of velocity values acquired using BSI were also observed. The same study also revealed that the difference tended to increase at higher velocities [7]. The underestimation is most likely due to the current inability of the BSI algorithm to track these greater flow velocities, even in an optimal phantom configuration with low penetration depth (tracking is more challenging in deeper regions of interests).

On the other hand, pressure drops estimated using Doppler were significantly higher than ground-truth pressure drop at the greatest level of stenosis tested (20.1 ± 1.78 mmHg). This is likely due to the error in estimation of momentum from a single velocity value: the characterisation of the pressure drop requires the full velocity profile [3, 5]. The bias of Doppler measurements across the experimental conditions was 3.54 mmHg; with peak overestimations of up to 18 mmHg (**Fig. 8A**). These findings are consistent with those reported by Donati *et al.* (2017), where pressure drop values obtained using the Simplified Bernoulli formulation were shown to overestimate the true pressure drop by 54% [4].

The peak pressure drop values measured by the pressure sensors in the phantom are different to net pressure drops measured in clinical practice during cardiac catheterisation, which

measure the pressure difference between the left ventricular outflow tract and the ascending aorta, downstream of the vena contracta [17]. The peak pressure drop measured by the pressure sensors in the phantom is at the location of the vena contracta, as is the case for the Doppler data. The effect of pressure recovery further downstream, which is the traditional understanding of the reason of pressure drop overestimation by Doppler, can therefore be excluded.

The percentage error of measurements made using Doppler increased with flow rate and a significant difference in percentage error was observed between the highest and lowest flow rates (**Fig. 7**). A linear increase in the difference between the estimated pressure drop of Doppler vs. ground-truth with increasing level of stenosis can also be observed in the respective Bland-Alman agreement plot in **Fig. 8A**.

These findings support the observation that the overestimation of pressure drop by Doppler echocardiography is more pronounced at higher flow rates. The simplified Bernoulli formulation is accurate for uniform Doppler velocity profiles, observed at low flow velocities [4]. As flow rate and pressure drop increased in our experiments, the flow profiles became more heterogenous, explaining why Doppler is less accurate under these higher flow regimes (**Fig. 7**). Further variability would be expected if different valve models and geometries were studied, or indeed if using *in vivo* data. These conditions would likely increase the degree of mismatch between true and estimated pressure drops further.

As a final minor remark, no significant difference was observed between the mean pressure drops achieved under constant and pulsatile conditions, allowing them to be grouped within each pump flow rate (**Fig. 6**; $n = 4$).

Intra-technique reproducibility

The intra-technique reproducibility analysis demonstrates the strong reproducibility of the ground-truth pressure readings (Bias 0.56 mmHg; **Fig. 9A**). Variability is greater in the pulsatile estimations since each pressure drop is calculated as the mean over 3 cycles. BSI is less variable than Doppler (Bias 1.61 vs 5.19 mmHg, respectively; **Fig. 9B-C**). However, the reproducibility of BSI may be positively influenced by its inability to track high pressures, resulting in false clustering of measurements (**Fig. 9C**).

Limitations

These experiments were performed using a single model of a healthy aortic valve. The ultrasound probe was placed directly against the phantom to make the BSI and Doppler acquisitions with low penetration depth. These two factors represent a best-case scenario for the acquisition data for pressure drop estimation. In human subjects, acquisitions would be at an increased penetration depth, thus reducing the imaging frame rate, with an increased level of attenuation. In addition, experiments in human valves would exhibit more physiological and/or pathological variation. The results, therefore, would likely be different if data were obtained *in vivo*.

Future technological advances may improve the ability of BSI to track higher flow velocities and therefore estimate greater pressure drops more accurately. Future *in vivo* studies are required before BSI can be used in the clinical setting.

Conclusions

BSI accurately estimated pressure drops up to 10.7 mmHg in controlled and reproducible phantom conditions of low stenotic burden, which may be useful for diastolic estimations of trans-mitral valve pressure drop and intra-cardiac pressure drops. BSI underestimated greater pressure drops, likely due to an inability of the algorithm to track higher flow velocities.

Doppler overestimated greater pressure drops, in line with the published literature. Although BSI offers a number of theoretical advantages to conventional Doppler echocardiography, further refinements and clinical studies are required with BSI before it can be used to improve transvalvular pressure drop estimation in the clinical evaluation of aortic stenosis.

List of Abbreviations

BSI – Blood speckle imaging
CT scan - Computerised tomography scan

Figure Legends

Fig. 1. The Ecoflex 0030 silicone aortic valve used for the experiments. Pictured from the front, outside of tube (left) and from the back, in situ (right).

Fig. 2. The phantom used for the velocity-based pressure drop estimation experiments.

Fig. 3. A photograph taken during the blood speckle imaging experiments, illustrating probe orientation and tilt angle measurement.

Fig. 4. Example plots of the pressure drop measured by the pressure sensors at 250 mL/s A) pulsatile flow B) constant flow rates. Blue points and error bars represent mean $\pm$ standard deviation from the 8 pressure sensors. The red point represents the maximum pressure drop and its location, estimated using spline interpolation between the valve and sensor 4.

Fig. 5. A) Example continuous wave doppler acquisition at 250 mL/s flow rate with manual measurement shown. B) Example BSI velocity vector interface, showing the velocity of flow through the region of interest.

Fig. 6. Angle-corrected pressure drop (Bernoulli equation; mmHg) from BSI (grey dotted bars) and Doppler (light grey bars), compared to ground truth acquired by sensors (dark grey bars). Data are presented as the mean estimated drop under each flow condition, grouping constant and pulsatile flows. Error bars represent $\pm$ standard deviation.* denotes statistical significance ($p < 0.05$).

Fig. 7. Percentage error of pressure drop estimations (%) from BSI (grey dotted bars) and Doppler (light grey bars), compared to ground truth acquired by sensors. Data are presented as the mean value (cross), the median value (line), the upper and lower quartiles (box range) and the minimum and maximum values (whiskers) under each flow condition, grouping constant and pulsatile flows. * denotes statistical significance compared to the 100 mL/s flow rate ($p < 0.05$).

Fig. 8. Bland-Altman plots illustrating the agreement between A) Doppler vs. ground-truth and B) BSI vs. ground-truth pressure drop estimations ($n=16$). The solid line represents the bias between the 2 methods, while the 95% limits of agreement (± 1.96 standard deviation) are represented by the dashed lines.

Fig. 9. Bland-Altman plots illustrating the agreement between A) ground-truth B) Doppler and C) Blood Speckle Imaging estimations of pressure drop across two days of experiments (n=16). The solid line represents the bias within the methods, while the 95% limits of agreement (± 1.96 standard deviation) are represented by the dashed lines.

Additional Files

File name: Additional File 1

File type: WMV file (.wmv)

Title of data: Example BSI Acquisitions

Description: A video file containing examples of the BSI acquisitions at each of the flow rates studied

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for Publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

All authors contributed to the study design and interpretation of results. HG, JF, AN and CD were involved in phantom design and construction. HG, CD and AN performed data acquisition. AN and CD performed data analysis. CD and PL drafted the manuscript. The final version was reviewed by all authors and investigators.

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Figures

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Figure 8

Bland-Altman plots illustrating the agreement between A) Doppler vs. ground-truth and B) BSI vs. ground-truth pressure drop estimations (n=16). The solid line represents the bias between the 2 methods, while the 95% limits of agreement (± 1.96 standard deviation) are represented by the dashed lines.

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Supplementary Files

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