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Simplified Bernoulli's Method Significantly Underestimates Pulmonary Transvalvular Pressure Drop

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Purpose: To determine whether neglecting the flow unsteadiness in simplified Bernoulli's equation significantly affects the pulmonary transvalvular pressure drop estimation.
Materials and Methods: 3.0T magnetic resonance imaging (MRI) 4D velocity mapping was performed on four healthy volunteers, seven patients with repaired tetralogy of Fallot, and thirteen patients with transposition of the great arteries repaired by arterial switch. Pulmonary transvalvular pressure drop was estimated based on two methods: General Bernoulli's Equation (GBE), ie, the most complete form; and Simplified Bernoulli's Equation (SBE), known as $4V^2$. More than 2300 individual pressure drop measurements were used to compare the simplified and the general Bernoulli's methods. A linear mixed-effects model was employed for statistical analyses, fully accounting for clustering of observations among the methods and systolic phases.
Results: The simplified Bernoulli's method systematically underestimated the pressure drop compared to general Bernoulli's method during the entire systolic phase ($P < 0.05$), including the peak systole, where on average $\Delta p_{SBE}/\Delta p_{\mathrm{GBE}}=78\%$.
Conclusion: The simplified Bernoulli method underestimated the pressure drop during all systolic phases in all the studied subjects. Therefore, it is necessary to take into account the flow unsteadiness for more accurate estimation of the pressure drop.

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Pulmonary valve stenosis is a common anomaly in patients with congenital heart defects. Quantitative assessment of the severity of pulmonary valve stenosis is mainly based on the pulmonary transvalvular pressure drop,[1] commonly estimated by continuous-wave Doppler[2] and recently by magnetic resonance imaging (MRI) phase contrast flow measurements.[3] The accuracy of noninvasive measurements of the transvalvular pressure drop has been debated.[4–11] Several studies have investigated the correlation between MRI measurements and echocardiography with catheterization for the estimation of the pressure drop in pulmonary circulation. The results have been inconsistent.[3,12–14] Cardiac catheterization is the current standard for estimating the transvalvular pressure drop; however, this method is not practical for routine follow-ups due to its invasive nature. A simplified version of the general Bernoulli's equation[15] is frequently used in everyday clinical practice to estimate the peak transvalvular pressure drop either by echocardiography[16,17] or MRI.[18–20] Nevertheless, the peak transvalvular pressure drop estimated by the simplified Bernoulli's equation does not always account for the net transvalvular pressure drop. This is due to the inherent limitation of the simplified Bernoulli's equation, in which the unsteady nature of the blood flow through a heart valve is ignored and only the peak jet velocity is used in the estimation.[18,21–23]

In the past, clinical use of the simplified Bernoulli equation was justifiable since Doppler echocardiography was the only available noninvasive modality to estimate the pressure drop, as Hatle et al first introduced.[15] Until recently, technological limitations

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TABLE 1. Demographics Data of the Studied Subjects Including Patients With Repaired Tetralogy of Fallot, Repaired Transposition of Great Arteries (Lecompte and Spiral Procedures), and Healthy Control Subjects

Group	Sex	Age [years]	Weight [kg]
Repaired TOF	M	1	10
	M	11	34
	F	17	59
	F	22	78
	F	29	65
	F	31	55
	M	58	100
Repaired-TGA Lecompte procedure	M	16	100
	F	18	58
	M	19	70
	M	20	65
	F	21	69
	M	22	83
	M	22	75
	M	22	85
Repaired TGA spiral procedure	M	20	76
	M	20	84
	M	20	67
	M	21	60
	M	23	81
Healthy control subjects	F	20	82
	F	23	73
	M	23	89
	F	26	52

did not allow for calculation of velocity changes in time along flow streamlines. However, flow-sensitive MRI data can nowadays provide opportunities to define the unsteady term in the general Bernoulli's equation.

In this study, we aimed to determine whether neglecting the flow unsteadiness in the simplified Bernoulli's equation significantly affects the pulmonary transvalvular pressure drop estimation. Therefore, we investigated the difference in pulmonary transvalvular pressure drop using the simplified Bernoulli equation and the general Bernoulli's equation in a mixed population of normal subjects and patients with repaired congenital heart defects by using 4D flow MRI.[24]

Materials and Methods

Study Subjects

A total of 24 subjects, including seven patients with repaired tetralogy of Fallot (r-TOF), eight patients with repaired transposition of great arteries (TGA; Lecompte procedure), five patients with repaired-TGA (spiral procedure), and four normal volunteers, were enrolled. In all, 37.5% of the subjects were female and 62.5% were male, whose age ranged from 1 to 59 with an average of 21.6, as shown in Table 1.

MR Flow Imaging

To estimate the pressure drop using different versions of Bernoulli's equation, as described in the following sections, the velocity field in the vicinity of the pulmonary valve was quantified in all the studied subjects using 4D PC-MRI in 3D and time.[24]

Three of the r-TOF patients were studied with a 3T Siemens Magnetom Skyra system (Siemens, Erlangen, Germany). The rest of the patients and healthy volunteers were studied using a 3T Philips scanner (Achieva 3.0T X-series, Philips Medical Systems, Best, Netherlands). All the studies were approved by the local Ethics Committee and the subjects had given their informed written consent. The 3D flow field from the right ventricle through the pulmonary valve into the pulmonary artery was obtained for all the studied subjects during systole.

Segmentation of the 4D Flow Data

4D-flow MRI allowed detection of the flow-dependent phase. The pixel values of the velocity images were converted to physical velocity according to Soudah et al.[25] This velocity field was exported to Ensight (Computational Engineering International, Apex, NC) for visualization of the walls of the great arteries (Fig. 1). Using Ensight and considering the isosurfaces of the great arteries' wall, the locations of 25 streamlines passing through the pulmonary valve jet were identified for each time-step during systole (Fig. 1). For each subject, the time in systolic phase was normalized with respect to the duration of the systole over a range from 0 to 1.

Transvalvular Pressure Drop Estimation

The pressure drop through the pulmonary valve was estimated based on two methods; General Bernoulli's Equation (GBE) and Simplified Bernoulli's Equation (SBE), known as $4V^2$, schematically shown in Fig. 2. In the general Bernoulli's equation, all the terms of Bernoulli's equation are included for the estimation of the pressure drop:

$$p_1 - p_2 = \frac{1}{2}\rho\left(v_2^2 - v_1^2\right) + \rho\int_1^2 \frac{\mathrm{d}v}{\mathrm{d}t}\cdot \mathrm{d}s \qquad (1)$$

where v_2 and v_1 are downstream and upstream velocities, respectively, and the unsteady term consists of the integral of the derivative of velocity with respect to time over a flow streamline between the upstream and downstream velocity points. This is the most general form of the equation for estimating the pressure drop considering that the viscous effects of the flow are negligible compared to inertial forces.

Simplified Bernoulli's equation, as commonly used in clinical practice, only considers the downstream velocity, v_2:

$$p_1 - p_2 = \frac{1}{2}\rho v_2^2 \qquad (2)$$

when pressure drop is expressed in mmHg, it is known as $4V^2$.

In clinical settings, continuous wave echocardiography is used to compute the pressure drop using the simplified Bernoulli method, which assumes that the upstream velocity is negligible compared to the one downstream. This means that the method can be applied to evaluate the pressure drop from a point in the chamber, sufficiently upstream of the valve, to a point on the same

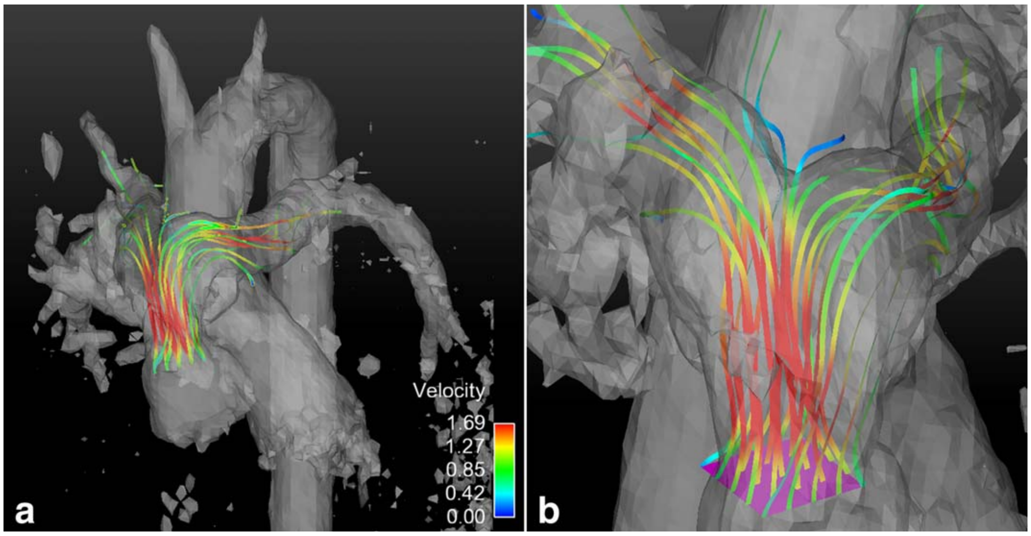

FIGURE 1: The reconstructed velocity field in one of the patients with repaired TGA (Lecompte procedure). a: The streamlines passing through the pulmonary valve. b: The locations where the streamlines originated.

flow streamline just downstream of the valve where the velocity is high. In our study, we followed the same procedure. To measure the pressure drop, we considered Point 1 (starting point) inside the right ventricle where the velocity was at a minimum along the streamline and Point 2 (end point) on the point of peak velocity on the same transpulmonary streamline (Fig. 2). The unsteady term of the Bernoulli equation, ie, $\int_1^2 \frac{\mathrm{d}v}{\mathrm{d}t} \cdot \mathrm{d}s$, was integrated over each streamline. We used a first-order forward finite difference scheme to compute the time derivative of the velocity for the calculation of the unsteady term.

$$\frac{\mathrm{d}v^n}{\mathrm{d}t} = \frac{v^{n+1} - v^n}{t^{n+1} - t^n} \tag{3}$$

where v is the velocity magnitude on the streamline between Points 1 and 2, as illustrated in Fig. 1. Integration was performed using the trapezoidal rule. An in-house computer program (4DFloWorks, University of California, Irvine) was developed to automatically perform the calculation of the unsteady term without the need for any manual input other than demarcating the location of the pulmonary valve.

Statistical Analyses

Phases of systole were grouped into early (0–30%), middle (30–60%), and end (60–100%) phases. Since GBE is the most analytically accurate form of the Bernoulli equation, it was considered a reference for SBE. Therefore, SBE measurements were normalized by the corresponding value of the pressure drop estimated by GBE. In this study, deviation from normalized GBE, which is equal to unity, was an indication of relative error. In all, 2324 pressure drop measurements were used to perform the statistical analyses, which were drawn from all the subjects, systolic phases, and streamline locations. Similarly, at peak systole, 546 measurements

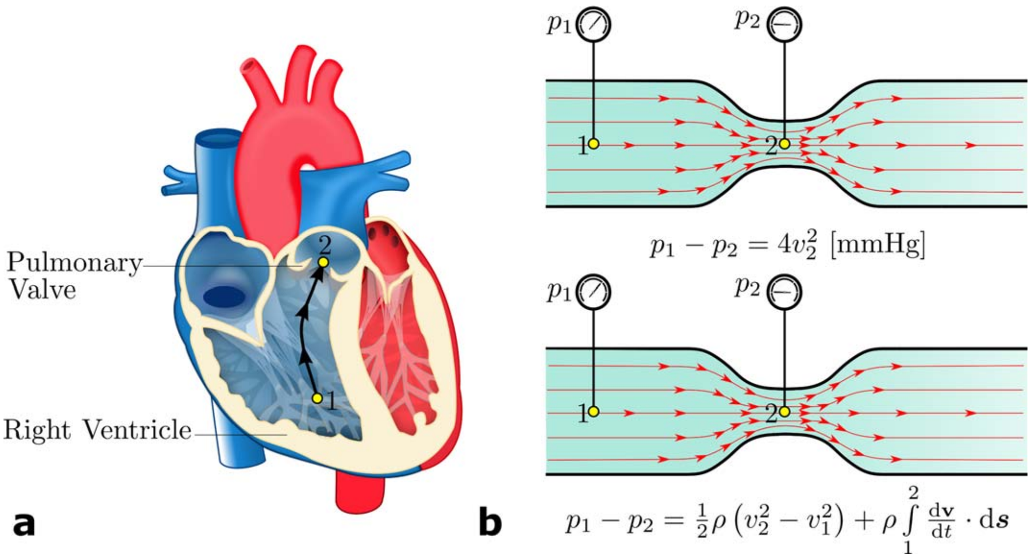

FIGURE 2: a: The schematic of the streamline passing through the pulmonary valve over which the pressure drop is estimated. Points 1 and 2 are the locations for which the pressure drop was calculated. b: The two methods of simplified Bernoulli's equation, known as $4V^2$, and general Bernoulli's equation in a simple tube.

TABLE 2. Pressure Drop (mmHg) Based on Estimation Method and Systolic Phase

Systolic phase	SBE/GBE ($n = 2{,}324$)	SBE [mmHg] ($n = 2{,}324$)	GBE [mmHg] ($n = 2{,}324$)
Early	0.52 ± 0.33	21.60 ± 32.66	29.14 ± 31.96
Mid	0.83 ± 0.30	37.07 ± 35.83	39.56 ± 33.44
End	0.80 ± 0.30	21.14 ± 29.67	23.88 ± 29.09
	SBE/GBE ($n = 284$)		
Peak Systole	0.78 ± 0.32	35.47 ± 38.57	39.51 ± 36.06

Reporting mean ± SD for both the ratio of SBE/GBE and the actual pressure drop. The standard deviation of actual pressure drop is associated with the heterogeneity of the sample size including sex, age, and heart condition.

were used for analyses, which were also drawn from all the subjects and streamline locations.

We calculated the mean and standard deviation of the pressure drop using each method, reported in Table 2. In addition, we calculated estimates of the regression model for the pressure drop as a function of the predictors given by the methods (SBE and GBE) and systolic phases (early, mid, end). Interactions among the terms were included in the model, including second- and third-order interactions among the method and phase. In our analyses, the data related to mid-systole and the general Bernoulli equation were considered as the reference categories.

A linear mixed-effects model[26] was fitted taking into account the clustering of observations among the methods and systolic phases. The dependent variable was the pressure drop measurement and the independent variables were methods (SBE, GBE) and time (early, mid, end). At peak systole, the independent variables were only SBE and GBE. Estimates of parameters for the predictors were calculated with 95% confidence intervals. A generalized covariance structure and robust standard errors were also used to guard against model misspecification. An analysis of variance (ANOVA) was calculated for the main effects and interactions, and a summary of the variance components (VARCOMP) was calculated for the error terms in the model. These analyses were investigated with and without adjustments for the patient mix.

Pressure-drop values were analyzed using the same linear mixed effects model that involves method, time, and their interaction. A set of six treatment contrasts were implemented,[27] given by a set of six specified comparisons among the methods at different times within the systole. These comparisons included: simplified Bernoulli's ($4V^2$) versus general Bernoulli's at 1) early systole, 2) mid systole, 3) end systole, and (4) peak systole.

To investigate whether SBE versus GBE pressure drop estimations differed in the heterogeneous groups of our study, we also performed a one-way ANOVA among the following groups: 1) all the studied subjects ($n = 24$), 2) all normal subjects ($n = 4$), 3) all subjects with repaired congenital heart defects (CHD; $n = 20$), 4) pediatric subjects with repaired CHD ($n = 4$), 5) adult subjects with repaired CHD ($n = 16$), 6) all adult subjects regardless of their status ($n = 20$) during all studied phases of cardiac cycle. It should be noted that in our study all the pediatric subjects were patients with repaired CHD.

Results

4D Flow MRI

Figure 1 shows the streamlines passing through the pulmonary valve of a patient with repaired TGA (Lecompte procedure).

Pulmonary Transvalvular Pressure Drop

During the entire systole, the mean pressure drops calculated by the SBE method underestimated the pressure drop calculated by GBE. This observation was also corroborated at peak systole (see Table 2), which reports the mean response surface of all the principal combinations of the studied parameters during early, mid, peak, and end systole. On average and compared to GBE, SBE underestimated the pressure drop with a ratio of SBE to GBE of 52%, 83%, 80%, and 78% in early, mid, end, and peak systole, respectively. Summaries were based on all the subjects and repeated measures within the conditions, and were broadly indicative of the effects of the linear models reported below. Table 3 reports the results of the comparisons between SBE and GBE during systole as well as the peak systole. The differences between SBE and GBE were statistically significant (P-value < 0.05) during the entire systole (including at peak systole).

The ANOVA resulted in a statistically significant difference among these six groups of studied subjects, as described in the Materials and Methods section. The P-value was found to be much smaller than 0.001. The boxplot of the ratio of SBE to GBE is shown in Fig. 3. As can be seen in the figure, the mean of the ratio of SBE to GBE for each individual group was less than 1, indicating that SBE underestimated pressure drop compared to GBE.

Discussion

The adult normal size of the pulmonary valve area is about 2.0 cm^2 per square meter of body surface area, with a zero

TABLE 3. Comparisons for the Main Inference: Pressure Drop in Method-by-Time Model Comparison of Methods Within Systole as Well as at the Peak

	Time	Point est.	SE	95% Lower	95% Upper	*P*-value	*n*
SBE/GBE vs. GBE/GBE	Early	0.53	0.055	0.424	0.640	2.90×10^{-17}	2324
	Mid	0.84	0.056	0.727	0.945	3.27×10^{-3}	2324
	End	0.80	0.055	0.696	0.913	4.14×10^{-4}	2324
	Peak	0.82	0.062	0.700	0.943	4.20×10^{-3}	284

The ratio of SBE/GBE was found to be statistically significant (P-values$\ll$0.05) among all the systolic phases.

to minimal pressure drop across the valve during systole.[28] In pulmonary valve stenosis, right ventricular systolic pressure increases, creating a pressure drop across the valve. Potential energy conversion to kinetic energy across the stenotic pulmonary valve leads to a higher velocity and a transpulmonary pressure drop whose magnitude is an indicator of the severity of pulmonary stenosis. According to the most recent EAE/ASE guideline, systolic pressure drop derived from the transpulmonary velocity flow curve is estimated using the simplified Bernoulli's equation.[1] The guideline refers to the work done by Lima et al in 1983 that validated the simplified Bernoulli's equation in 16 children with pulmonary valve stenosis ranging from mild to severe on the basis of pulsed and continuous-wave Doppler echocardiography.[29] However, prior to Lima et al, another study by Holen et al[30] indicated that the pressure drop estimated by the simplified Bernoulli equation does not always predict the actual pressure drop; for example, they independently showed that the pressure drop is underestimated when velocities are low. Alternatively, Yoganathan et al showed that the simplified Bernoulli's equation reflects the maximal drop, which overestimates the measured drop across a valve or downstream of an obstruction.[31] Overestimation or underestimation of the true pressure drop would misrepresent the conditions under which the flow circulates and consequently affect diagnoses (e.g., grading the valvular stenosis) and follow-up. Nowadays, advanced MRI systems, equipped with phase contrast technology, can provide the required information to calculate GBE, for more accurate estimations of pressure drop in a completely noninvasive way.

The simplified version of Bernoulli's equation only considers a single velocity for pressure drop estimation, implying that the entire pressure drop is due to the convective acceleration of blood, thus neglecting losses resulting from inertial acceleration and viscous drag.[32] While viscous drag is usually negligible due to high Reynolds numbers in the vicinity of the transvalvular jet,[†] the use of the simplified Bernoulli's equation for pressure drop estimation may be justifiable only in situations where blood acceleration is minimal, such as in particular cases of valvular insufficiency where there is not much change in temporal and spatial blood velocity.

The results of this study suggest that, overall, a statistically significant discrepancy exists among the pressure drops estimated by the two different versions of Bernoulli's equation. Accordingly, we found that the simplified Bernoulli method underestimates the pulmonary transvalvular pressure drop compared with the most complete form of Bernoulli equation during all systolic phases, including at peak systole. This study corroborates that the flow unsteadiness—as represented by the unsteady term of Bernoulli's equation—plays a significant role in the transvalvular pressure drop and neglecting it, as in the simplified Bernoulli's equation, misrepresents the transvalvular pressure drop.

The results of this study indicate that the simplified Bernoulli's method significantly underestimated the pressure drop compared to general Bernoulli's method during the entire systolic phase, including the peak systole. This discrepancy may result in confusing situations for grading the stenosis when the pressure drop is within a borderline range. The American College of Cardiology/American Heart Association guidelines define mild, moderate, and severe pulmonic valvular stenosis based on peak transvalvular gradient with mild equaling less than 30 mmHg, moderate in range of 30–50 mmHg, and severe equaling greater than 50 mmHg.[33,34] Considering the most recent guidelines, we anticipate that, for example, a pressure drop of 25 mmHg (mild) estimated by SBE is actually equal to 32.1 mmHg if properly calculated by GBE, which clinically represents moderate stenosis. Alternatively, a 29 mmHg (mild grade) calculated by SBE may become 37.2 mmHg (moderate grade), and a moderate stenosis estimated by SBE may even become severe if the pressure gradient is properly estimated by the GBE method. Our study suggests that SBE and GBE are statistically different and SBE can systematically underestimate the pressure drop values.

There are several possible limitations to our study. Invasive cardiac catheterization has been the gold standard for pressure measurement. In this work, catheterization data

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[†] The Reynolds number computed for all subject was in the proper range to ensure that the general Bernoulli's equation would provide a desired estimation for the pressure drop in the present study (Re = 14,000 ± 3840).

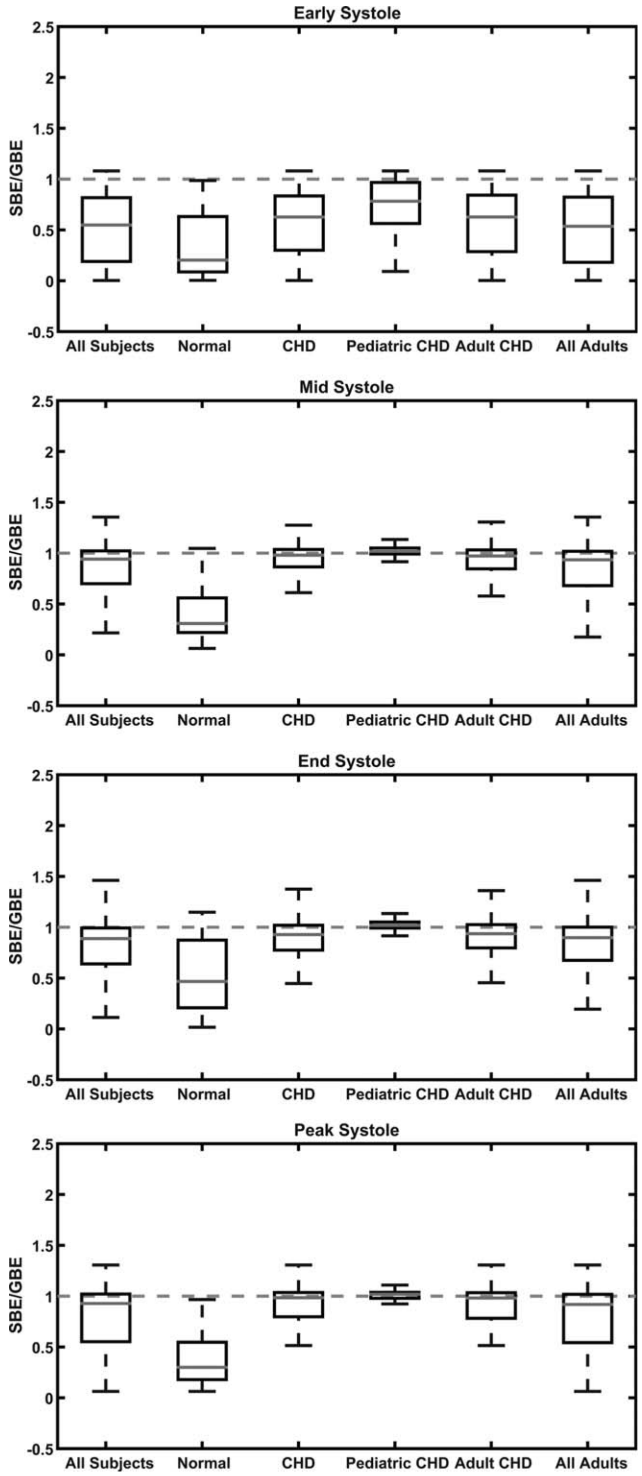

FIGURE 3: The boxplots for the comparison of the SBE to GBE ratio in different systolic phases for (1) all the subjects, (2) all normal subjects, (3) all subjects with repaired CHD, (4) pediatric subjects with repaired CHD, (5) adult subjects with repaired CHD, (6) all adult subjects. Furthermore, *t*-test between all the subjects and the pediatric group showed there is a statistically significant difference (*P*-value < 0.05) in all the systolic phases.

were not available for comparison with the measured pressure drops using the MRI data. Computations of the unsteady term of the Bernoulli equation were performed accurately according to 4D-flow MR data, and therefore, the only error associated with GBE method is the one related to inherent limitations of 4D-flow MR, since the GBE equation is the most general form inferred from Navier-Stokes equation for inertia-dominant flow regimes.

In conclusion, the results of this study suggest that, overall, a statistically significant difference exists between the pressure drops estimated by simplified and general Bernoulli equations. Accordingly, we found that the simplified Bernoulli method systematically underestimates the pulmonary transvalvular pressure drop compared with the most complete form of Bernoulli equation during all systolic phases, including at peak systole. Therefore, the unsteady term plays a significant role in the transvalvular pressure drop estimation.

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