ECHOCARDIOGRAPHY UNDERESTIMATES STROKE VOLUME AND AORTIC VALVE AREA: IMPLICATIONS FOR PATIENTS WITH SMALL-AREA LOW-GRADIENT AORTIC STENOSIS

ONLINE SUPPLEMENTAL DATA

TABLE S1. CHARACTERISTICS OF PATIENTS WITH AORTIC STENOSIS CLASSIFIED BASED ON AORTIC VALVE AREA ESTIMATED USING DOPPLER-DERIVED STROKE VOLUME

	Non-severe (n=44)	Small-area low-gradient (n=56)	Severe (n=28)	P value
Clinical Characteristics				
Age, years	65±13	72±10	68±11	0.02[a]
Males, n (%)	32 (72)	34 (61)	19 (68)	0.44
Height, cm	169±9	163±8	168±8	<0.01[a,b]
Body mass index, kg/m^2	29±5	29±5	27±4	0.13
Body surface area, m^2	1.9±0.2	1.8±0.2	1.9±0.2	0.07
Hypertension, n (%)	27 (61)	40 (71)	16 (57)	0.36
Diabetes Mellitus, n (%)	9 (20)	6 (11)	3 (11)	0.32
Coronary artery disease, n (%)	14 (32)	15 (27)	12 (43)	0.33
Atrial fibrillation, n (%)	0	3 (5)	0	-
Systolic blood pressure, mmHg	147±20	154±20	147±22	0.19
Echocardiography				
Left ventricular outflow tract (LVOT) diameter, cm	2.19±0.21	1.96±0.19	2.08±0.24	<0.01[a,b]
LVOT cross-sectional area, cm^2	3.79±0.75	3.05±0.57	3.43±0.78	<0.01[a]
LVOT velocity time integral, cm	24.5±4.2	23.0±4.5	22.7±4.3	0.15
Doppler stroke volume, mL	92±18	70±13	78±19	<0.01[a,c]
Doppler stroke volume (indexed), mL/m^2	48±10	38±7	42±10	<0.01[a,c]
Aortic valve area, cm^2	1.38±0.38	0.79±0.15	0.69±0.17	<0.01[a,c]
Aortic valve area (indexed), cm^2/m^2	0.72±0.20	0.43±0.08	0.37±0.09	<0.01[a,c]
Mean pressure gradient, mmHg	20±8	29±9	54±17	<0.01[a,b,c]
Peak aortic velocity, m/s	3.0±0.5	3.7±0.5	4.8±0.6	<0.01 [a,b,c]
Dimensionless index	0.36±0.09	0.26±0.05	0.20±0.04	<0.01 [a,b,c]
Aortic valve calcium score	3 [2,3]	3 [3,4]	4 [4,4]	<0.01 [a,b,c]
Valvuloarterial impedance, mmHg•ml^{-1}•m^{-2}	3.6±0.8	4.9±1.1	5.0±1.2	<0.01[a,c]

End-diastolic volume, mL[¶]	94±21	82±26	83±23	0.03[a]
End-diastolic volume (indexed), mL/m^2 [¶]	49±10	45±13	44±12	0.15
End-systolic volume, mL[¶]	42±12	36±14	35±14	0.04
End-systolic volume (indexed), mL/m^2 [¶]	22±6	19±7	19±7	0.11
Stroke volume, mL[¶]	53±12	46±13	48±13	0.04[a]
Stroke volume (indexed), mL/m^2 [¶]	28±6	25±7	26±7	0.25
Ejection fraction, %[¶]	56±7	57±7	59±8	0.40
Mild mitral regurgitation, n (%)	3 (7)	9 (16)	7 (25)	0.10
Mild aortic regurgitation, n (%)	18 (41)	27 (48)	12 (43)	0.24
Cardiovascular Magnetic Resonance				
LVOT cross-sectional area, cm^2 [‡]	4.22±1.21 (n=13)	3.58±0.83 (n=14)	4.53±1.24 (n=12)	0.09
End-diastolic volume, mL	142±30	126±25	139±40	0.03[a]
End-diastolic volume (indexed) (EDVi), mL/m^2	74±13	69±13	74±19	0.17
End-systolic volume, mL	47±17	43±15	47±20	0.38
End-systolic volume (indexed), mL/m^2	25±8	23±8	25±10	0.75
Stroke volume, mL	95±19	83±16	92±26	<0.01[a]
Stroke volume (indexed), mL/m^2	49±8	45±8	49±12	0.08
Ejection fraction, %	67±7	66±7	67±7	0.84
Left ventricular mass (indexed) (LVMi), g/m^2	85±18	85±21	99±25	<0.01[b,c]
LVMi/EDVi, g/mL	1.17±0.23	1.24±0.24	1.38±0.28	<0.01[b,c]

[¶] Estimated using the Teichholz formula
[‡] Planimetered left ventricular outflow tract area was performed in 40 patients. One patient was classified with large-area high-gradient aortic stenosis

[a] P<0.05 between non-severe and small-area low-gradient aortic stenosis
[b] P<0.05 between small-area low-gradient and severe aortic stenosis
[c] P<0.05 between non-severe and severe aortic stenosis

TABLE S2. CHARACTERISTICS OF PATIENTS WITH DISCORDANT SMALL-AREA LOW-GRADIENT AORTIC STENOSIS AFTER CORRECTION FOR STROKE VOLUME UNDERESTIMATION AND INCONSISTENT THRESHOLDS

	Non-severe (n=61)	Small-area low-gradient (n=29)	Severe (n=33)	P value
Clinical Characteristics				
Age, years	66±13	73±9	72±9	<0.01[a,c]
Male, n (%)	44 (72)	15 (52)	20 (61)	0.15
Height, cm	168±9	161±9	165±8	<0.01[a]
Body mass index, kg/m^2	29±5	30±5	27±3	0.09
Body surface area, m^2	1.9±0.2	1.8±0.2	1.8±0.2	0.02
Hypertension, n (%)	38 (62)	21 (72)	22 (67)	0.64
Diabetes mellitus, n (%)	11 (18)	3 (10)	4 (12)	0.56
Coronary artery disease, n (%)	18 (30)	7 (24)	17 (52)	0.04
Atrial fibrillation, n (%)	-	3 (10)	-	-
Systolic blood pressure, mmHg	149±21	151±22	151±23	0.91
Echocardiography				
Left ventricular outflow tract (LVOT) diameter, cm	2.14±0.21	1.94±0.21	2.02±0.25	<0.01[a,c]
LVOT cross-sectional area, cm^2	3.64±0.73	3.01±0.63	3.28±0.82	<0.01[a]
LVOT velocity time integral, cm	23.6±4.2	23.3±5.1	23.7±4.4	0.93
Doppler stroke volume, mL	86±19	69±14	77±20	<0.01[a]
Doppler stroke volume (indexed), mL/m^2	45±10	38±8	42±10	<0.01[a]
Aortic valve area, cm^2	1.24±0.41	0.76±0.16	0.71±0.19	<0.01[a,c]
Aortic valve area (indexed), cm^2/m^2	0.65±0.22	0.42±0.10	0.39±0.10	<0.01 [a,c]
Mean pressure gradient, mmHg	21±8	30±5	55±24	<0.01[a,b,c]
Peak aortic velocity, m/s	3.1±0.6	3.7±0.3	4.8±0.9	<0.01[a,b,c]
Dimensionless index	0.34±0.09	0.26±0.05	0.21±0.05	<0.01[a,b,c]
Aortic valve calcium score	3 [2,3]	4 [3,4]	4 [4,4]	<0.01[a,b,c]
Valvuloarterial impedance, mmHg•ml^{-1}•m^{-2}	4.0±1.0	4.8±1.2	4.9±1.3	<0.01[a,c]

End-diastolic volume, mL[¶]	93±25	77±25	83±24	<0.01[a]
End-diastolic volume (indexed), mL/m^2 [¶]	49±12	42±13	45±13	0.09
End-systolic volume, mL[¶]	42±14	31±13	35±14	<0.01[a]
End-systolic volume (indexed), mL/m^2 [¶]	22±7	17±7	20±7	0.02[a]
Stroke volume, mL [¶]	52±13	45±13	45±11	0.02
Stroke volume (indexed), mL/m^2 [¶]	27±6	25±7	25±7	0.27
Ejection fraction, % [¶]	56±6	60±7	57±9	0.05[a]
Mild mitral regurgitation, n (%)	7 (11)	4 (14)	7 (21)	0.44
Mild aortic regurgitation, n (%)	24 (39)	16 (56)	16 (48)	0.34
Cardiovascular Magnetic Resonance				
LVOT cross-sectional area, cm^2 [‡]	4.30±1.05 (n=16)	3.40±0.90 (n=8)	4.10±1.36 (n=12)	0.20
End-diastolic volume, mL	142±28	117±18	127±35	<0.01[a,c]
End-diastolic volume (indexed) (EDVi), mL/m^2	74±14	65±9	70±17	0.01[a]
End-systolic volume, mL	47±16	39±10	45±22	0.12
End-systolic volume (indexed), mL/m^2	25±8	22±5	25±11	0.28
Stroke volume, mL	95±18	78±13	83±21	<0.01[a,c]
Stroke volume (indexed), mL/m^2	50±9	43±7	45±10	<0.01[a]
Ejection fraction, %	67±7	67±6	66±9	0.63
Left ventricular mass (indexed) (LVMi), g/m^2	86±21	81±18	93±20	0.06
LVMi/EDVi, g/mL	1.18±0.22	1.25±0.23	1.37±0.30	<0.01[c]

[¶] Estimated using the Teichholz formula
[‡] Planimetered left ventricular outflow tract area was performed in 40 patients. Four patients were classified with large-area high-gradient aortic stenosis

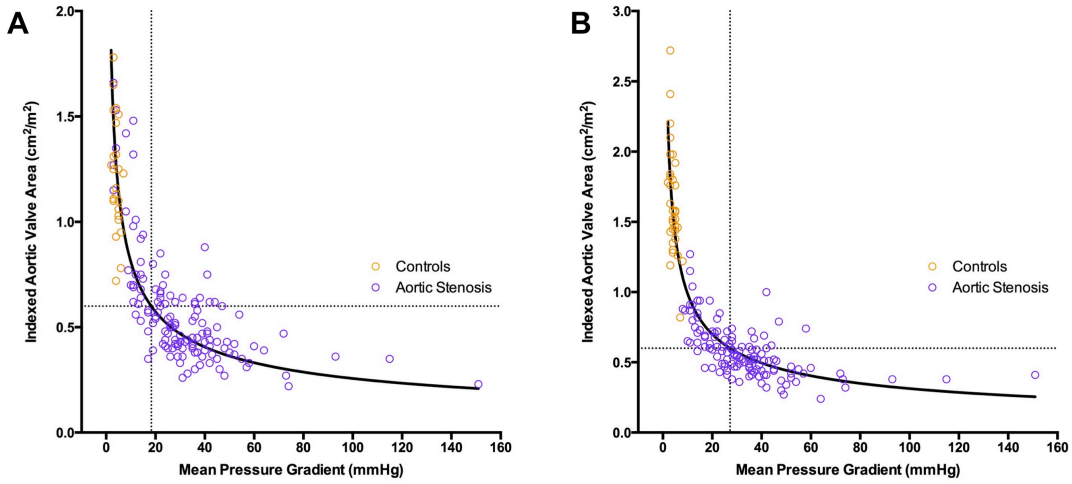
[a] P<0.05 between non-severe and small-area low-gradient aortic stenosis
[b] P<0.05 between small-area low-gradient and severe aortic stenosis
[c] P<0.05 between non-severe and severe aortic stenosis

EVALUATION OF AORTIC STENOSIS CLASSIFICATION USING INDEXED AORTIC VALVE AREA

We investigated thresholds of severe aortic stenosis using indexed aortic valve area, and the effects on classification using an indexed aortic valve area of 0.6 cm^2/m^2, and mean pressure gradient of 40 mmHg.

Using Doppler stroke volume, an indexed aortic valve area of 0.6 cm^2/m^2 corresponded to a mean pressure of 18 mmHg (Figure S1A) while an indexed aortic valve area of 0.6 cm^2/m^2 corresponded to a mean pressure gradient of 27 mmHg with MRI-derived stroke volume (Figure S1B). The use of indexed aortic valve area did not reduce the number of patients with discordant small-area low-gradient aortic stenosis with either Doppler stroke volume [61 patients (46%) compared with the 56 patients (42%) using non-indexed aortic valve area] or MRI-derived stroke volumes [52 patients (39%) compared with the 36 patients (27%) using non-indexed aortic valve area]. These results are also consistent with recent studies (Minners et al., Heart 2010; Jander et al., Heart 2013).

FIGURE S1



EVALUATION OF USING THE DIMENSIONLESS INDEX IN AORTIC STENOSIS CLASSIFICATION

Using a dimensionless index (DI) threshold of <0.25 and mean pressure gradient of <40mmHg, 26 patients were classified with discordant low-DI low-gradient aortic stenosis (20%). This appears to support our conclusion that discordant small-area low-gradient aortic stenosis is largely influenced by left ventricular outflow tract area ($LVOT_{area}$) estimation.

However, this result has to be interpreted with caution. The use of DI has major limitations precisely because it does not take into account the left ventricular outflow tract area ($LVOT_{area}$), which is the key factor to consider when determining the severity of aortic stenosis (Michelena et al., Heart 2012; Baumgartner et al., JASE 2009). This is perhaps best illustrated with an example:

$$\textbf{Aortic valve area} = \textbf{LVOTd}^2 \times 0.785 \times \textbf{DI};\ \textbf{DI} = \textbf{LVOT}_{\textbf{VTI}}/\textbf{AV}_{\textbf{VTI}}$$

In a patient with a LVOT diameter (LVOTd) of 2.0 cm and DI of 0.25 (severe aortic stenosis), this would translate to an aortic valve area of 0.79 cm^2 (severe aortic stenosis). However, in another patient with LVOTd of 2.5 cm and the same DI of 0.25, this increases the aortic valve area to 1.23 cm^2 (moderate aortic stenosis). This example illustrates that a DI threshold of 0.25 may not be appropriate in all patients: in patients with large LVOT, a smaller DI threshold for severe disease may be needed (Michelena et al., Heart 2012). Indeed, amongst the 26 patients with discordant low-DI low-gradient aortic stenosis, 9 patients (35%) had an aortic valve area > 1.0cm^2 and they had larger mean LVOTd (measured on 2D echocardiography) compared to the other 17 patients (2.2±0.2 versus 1.9±0.2 cm, P=0.03).

Accurate estimation of the $LVOT_{area}$ is therefore critical in assessing aortic stenosis severity. Our study highlights the limitations that echocardiography has in making such measurements and how improved stroke volume estimation can have important implications in the grading of aortic stenosis.

BASELINE CHARACTERISTICS OF THE 40 PATIENTS WITH PLANIMETERED LEFT VENTRICULAR OUTFLOW TRACT AREA ON CARDIOVASCULAR MAGNETIC RESONANCE

In this study, 40 patients with mild to severe aortic stenosis were randomly selected and planimetry of the left ventricular outflow tract area ($LVOT_{area}$) was performed on cardiovascular magnetic resonance. The purpose is to investigate the effects of accurate $LVOT_{area}$ measurement on stroke volume estimation.

The characteristics of these 40 patients were similar to the entire cohort of patients with aortic stenosis (Table S3).

TABLE S3

Characteristics	Subgroup (n=40)	All patients with aortic stenosis (n=133)	P value
Age, years	68±12	69±12	0.64
Males, n (%)	27 (68)	83 (63)	0.56
Body surface index, m^2	1.9±0.2	1.9±0.2	1.00
Systolic blood pressure, mmHg	151±21	150±21	0.79
Heart rate, per min	64±10	64±11	1.00
Mean pressure gradient, mmHg	37±24	32±16	0.13
Peak aortic jet velocity, m/s	4.0±1.1	3.7±0.8	0.06
Aortic valve area, cm^2	1.0±0.3	1.0±0.4	1.00
Indexed end-diastolic volume (EDV), mL/m^2	75±21	72±16	0.34
Indexed end-systolic volume, mL/m^2	25±12	24±9	0.57
Indexed stroke volume, mL/m^2	50±12	48±10	0.29
Ejection fraction, %	67±8	67±7	1.00
Indexed left ventricular mass (LVM), g/m^2	95±28	88±21	0.09
LV mass/EDV, g/mL	1.29±0.28	1.25±0.26	0.40

COMPARISON OF DOPPLER, MRI VOLUMETRIC AND PHASE CONTRAST STROKE VOLUME ESTIMATION

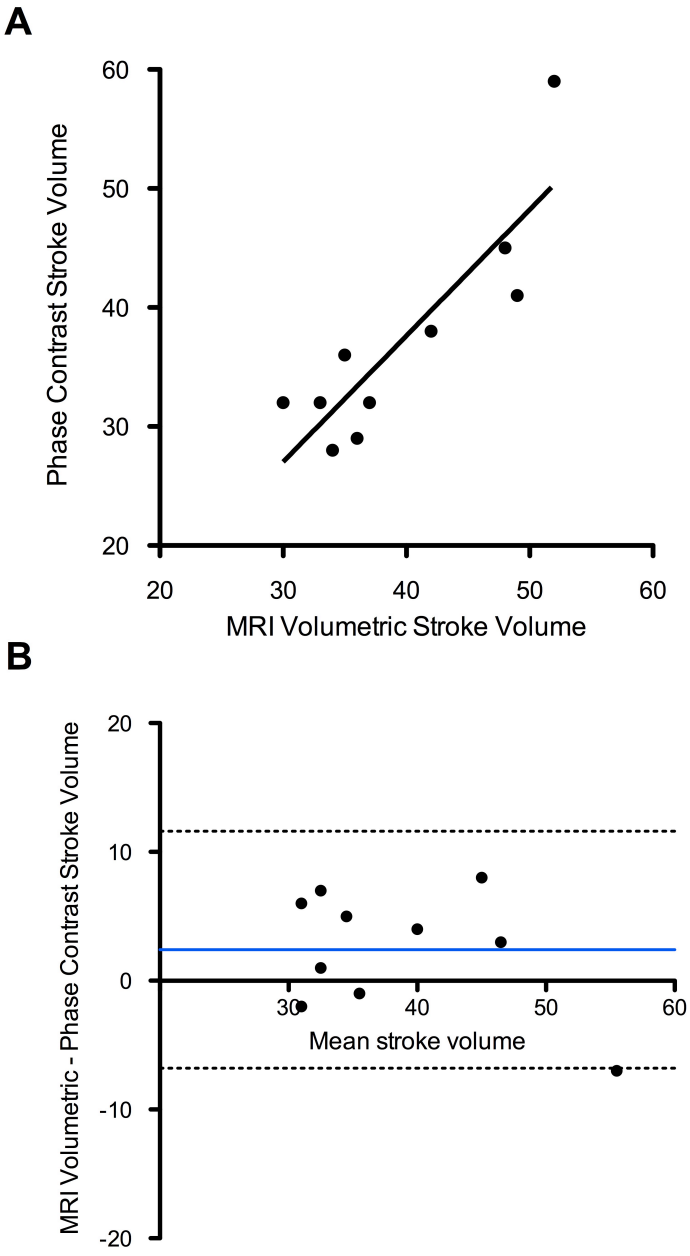
An exploratory analysis was performed in 10 patients with aortic stenosis to compare Doppler, MRI volumetric (cine) and phase contrast stroke volume. Through plane phase contrast velocity mapping was positioned orthogonal to the ascending aorta at the level of the bifurcation of the main pulmonary artery. An initial velocity encoding level of 100 cm/s was selected and increased in increments of 50 cm/s if aliasing occurs. The total forward flow during systole is computed using the Argus software (Siemens AG Healthcare Sector, Erlangen, Germany).

The results are shown in Table S4. In these 10 patients, there was no correlation between Doppler indexed stroke volume and MRI-derived indexed stroke volume (r=0.32; P=0.37) and between Doppler indexed stroke volume and MRI phase contrast indexed stroke volume (r=0.20; P=0.58). On the other hand, MRI-derived stroke volume and MRI phase contrast demonstrated excellent correlation (r=0.87; P=0.001; Figure S2A) and agreement (2.4mL/m^2; 95% CI -6.8 to 11.6 mL/m^2; Figure S2B).

TABLE S4

Patient S/N	Echocardiographic indexed stroke volume (mL/m^2)	MRI-derived indexed stroke volume (mL/m^2)	Phase contrast indexed flow volume (mL/m^2)	Aortic stenosis severity
#1	34	49	41	Severe
#2	33	33	32	Severe
#3	45	34	28	Moderate
#4	35	35	36	Moderate
#5	46	37	32	Severe
#6	54	36	29	Severe
#7	50	48	45	Mild
#8	45	42	38	Moderate
#9	36	30	32	Severe
#10	49	52	59	Mild

FIGURE S2


A
Phase Contrast Stroke Volume
60
50
40
30
20
20
30
40
50
60
MRI Volumetric Stroke Volume
B
MRI Volumetric - Phase Contrast Stroke Volume
20
10
0
-10
-20
30
40
50
60
Mean stroke volume