Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Echocardiographic Protocol in the CBHS

View	M-mode	2D	Color Doppler	Pulsed-wave Doppler	Continuous-wave Doppler	Tissue Doppler
Subxiphoid						
Situs view		x				
Abdominal long axis: IVC		x				
Atrial septum		x	x			
Long axis: SVC-RA-IVC, LA			x			
Left parasternal						
PLAX	x (AV, LA)	x	x			
PLAX with focus on aorta		x				
PSAX aorta		x	x			
PSAX pulmonary trunk		x	x	x		
PSAX LV		x				
Apical						
Coronary sinus view		x	x			
Four chamber view (LV center)		x	x	x		x
Four chamber view (RV center)	x (TAPSE)	x	x	x	x	
Five chamber view		x	x	x (LVOT)	x	
Suprasternal						
Aortic arch		x	x		x	

AV: aortic valve; IVC: inferior vena cava; LA: left atrium; LV: left ventricle; LVOT; left ventricular outflow tract; PLAX: parasternal long-axis; PSAX: parasternal short-axis; RA: right atrium; RV: right ventricle; SVC: superior vena cava; TAPSE: tricuspid annular plane systolic excursion.

eTable 2. Views and Modalities Employed for the Quantitative Echocardiographic Parameters

	Parameter	View	Modality	Timing
Left ventricle and left ventricular outflow tract	Interventricular septal end-diastolic thickness	Parasternal long-axis view	2D	end-diastole
	Left ventricular posterior wall end-diastolic thickness	Parasternal long-axis view	2D	end-diastole
	Left ventricular end-diastolic diameter	Parasternal long-axis view	2D	end-diastole
	Left ventricular end-systolic diameter	Parasternal long-axis view	2D	end-systole
	Ejection fraction	Parasternal long-axis view	2D	
	Fractional shortening	Parasternal long-axis view	2D	
	Left ventricular outflow tract diameter	Parasternal long-axis view	2D	mid-systole
	Left ventricular outflow tract velocity time integral	Apical 5-chamber view	PW Doppler	systole
	Left ventricular outflow tract max pressure gradient	Apical 5-chamber view	PW Doppler	systole
	Left ventricular outflow tract mean pressure gradient	Apical 5-chamber view	PW Doppler	systole
	Left ventricular outflow tract peak velocity	Apical 5-chamber view	PW Doppler	systole
	Left ventricular outflow tract mean velocity	Apical 5-chamber view	PW Doppler	systole
Aortic root, tubular ascending aorta, and descending aorta	Aortic valve annulus diameter	Parasternal long-axis view	2D	mid-systole
	Sinuses of Valsalva diameter	Parasternal long-axis view	2D	mid-systole
	Sinotubular junction diameter	Parasternal long-axis view	2D	mid-systole
	Tubular ascending aortic diameter, 1cm from aortic valve annulus	Parasternal long-axis view	2D	mid-systole
	Tubular ascending aortic diameter, widest part visualized	Parasternal long-axis view	2D	mid-systole
	Aortic outflow* velocity time integral	Apical 5-chamber view	CW Doppler	systole
	Aortic outflow* peak velocity	Apical 5-chamber view	CW Doppler	systole
	Aortic outflow* mean velocity	Apical 5-chamber view	CW Doppler	systole
	Aortic outflow* max pressure gradient	Apical 5-chamber view	CW Doppler	systole
	Aortic outflow* mean pressure gradient	Apical 5-chamber view	CW Doppler	systole
	Descending aorta peak velocity	Suprasternal view	CW Doppler	systole
	Descending aorta max pressure gradient	Suprasternal view	CW Doppler	systole
Main pulmonary artery	Main pulmonary artery diameter, 0.5 cm from pulmonary valve annulus	Parasternal short-axis view	2D	mid-systole
	Main pulmonary artery velocity time integral	Parasternal short-axis view	PW Doppler	systole
	Main pulmonary artery flow peak velocity	Parasternal short-axis view	PW Doppler	systole
	Main pulmonary artery flow mean velocity	Parasternal short-axis view	PW Doppler	systole
	Main pulmonary artery flow max pressure gradient	Parasternal short-axis view	PW Doppler	systole
	Main pulmonary artery flow mean pressure gradient	Parasternal short-axis view	PW Doppler	systole

All Doppler measurements were averaged over 3 cardiac cycles per view (if possible). All other measurements were obtained from 1 cardiac cycle.
*aortic outflow i.e. flow across the aortic valve

eTable 3. Echocardiographic Parameters for BAV and Non-BAV Groups

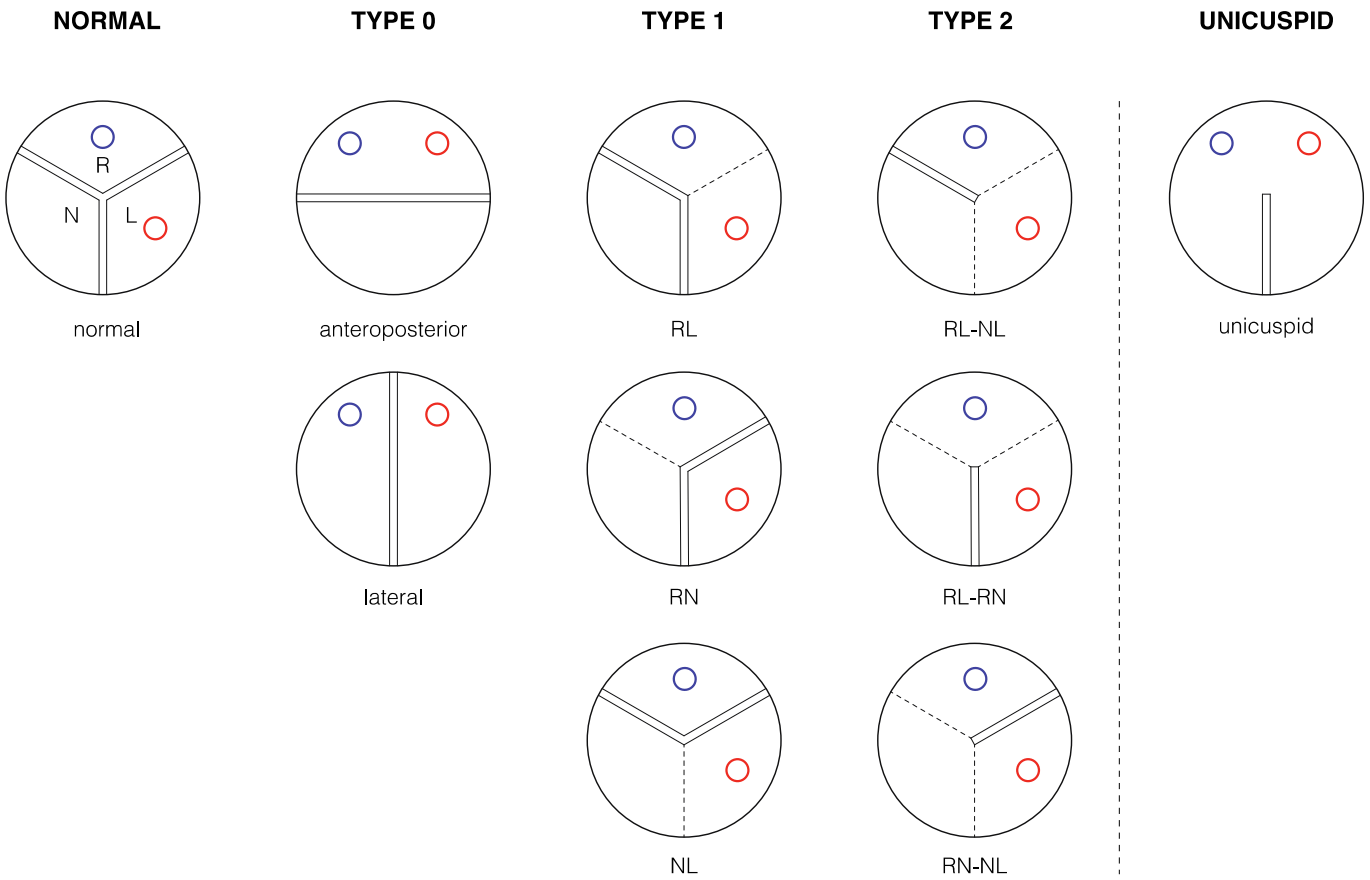
Echocardiographic parameters	BAV group n=191 [(a)]	Non-BAV group n=382	*Mean difference (continuous)*	*Absolute % difference (dichotomous)*	*95% CI*	*p-value*
Left ventricle						
Left ventricular end-diastolic diameter (mm (SD))	19.6 (1.7)	19.4 (1.6)	0.16		-0.1; 0.4	.29
Left ventricular end-systolic diameter (mm (SD))	13.3 (1.4)	13.1 (1.3)	0.20		-0.1; 0.4	.12
Ejection fraction (% (SD))	63.0 (5.4)	63.7 (5.3)	-0.70		-1.7; 0.3	.15
Aortic valve and aortic root						
AV annulus diameter (mm (SD))	7.0 (0.7)	7.0 (0.6)	0.02		-0.1; 0.1	.77
Sinuses of Valsalva diameter (mm (SD))	10.7 (1.3)	10.3 (1.0)	0.43		0.2; 0.6	**<.001***
Sinotubular junction diameter (mm (SD))	8.4 (1.1)	8.3 (0.8)	0.12		-0.1; 0.3	.19
Aortic valve area (mm^2 (SD))	34.0 (8.6)	34.5 (8.3)	-0.36		-2.3; 1.6	.72
Aortic outflow mean velocity (m/s (SD))	0.67 (0.16)	0.61 (0.08)	0.06		0.0; 0.1	**<.001***
Aortic outflow peak velocity (m/s (SD))	0.98 (0.22)	0.89 (0.12)	0.09		0.0; 0.1	**<.001***
Aortic stenosis (n (%))	1 (0.5)	0 (0)		-	-	.33
Aortic regurgitation (n (%))	28 (14.7)	5 (1.3)		13.4	7.8; 18.9	**<.001***
Tubular ascending aorta and descending aorta						
Tubular ascending aortic diameter, 1 cm from AV (mm	9.8 (1.2)	9.4 (0.9)	0.46		0.3; 0.7	**<.001***
Tubular ascending aortic diameter, widest part (mm (SD))	10.7 (1.3)	9.9 (1.0)	0.81		0.6; 1.0	**<.001***
Descending aortic flow peak velocity (m/s (SD))	1.31 (0.22)	1.24 (0.19)	0.08		0.0; 0.1	**.002***
Coarctation (n (%))	3 (1.6)	0 (0)		-	-	**.04**
Other						
Main pulmonary artery diameter (mm (SD))	9.2 (1.1)	8.6 (1.0)	0.59		0.4; 0.8	**<.001***
Main pulmonary artery flow mean velocity (m/s (SD))	0.56 (0.09)	0.58 (0.09)	-0.02		0.0; 0.1	**.006**
Ventricular septal defect (n (%))	8 (4.2)	16 (4.2)		0	-3.5; 3.5	1

Bonferroni corrected statistically significant *p*-values are indicated with *. Results from a sensitivity analysis, excluding all newborns with coexisting cardiac structural or functional abnormal findings (ventricular septal defect, coarctation, congenital aortic stenosis, reduced left ventricular systolic function requiring follow-up) showed no clinically important differences compared to results for the total cohort. AV: aortic valve; BAV: bicuspid aortic valve; CBHS: Copenhagen Baby Heart Study; CI: Confidence Interval; SD: Standard Deviation.

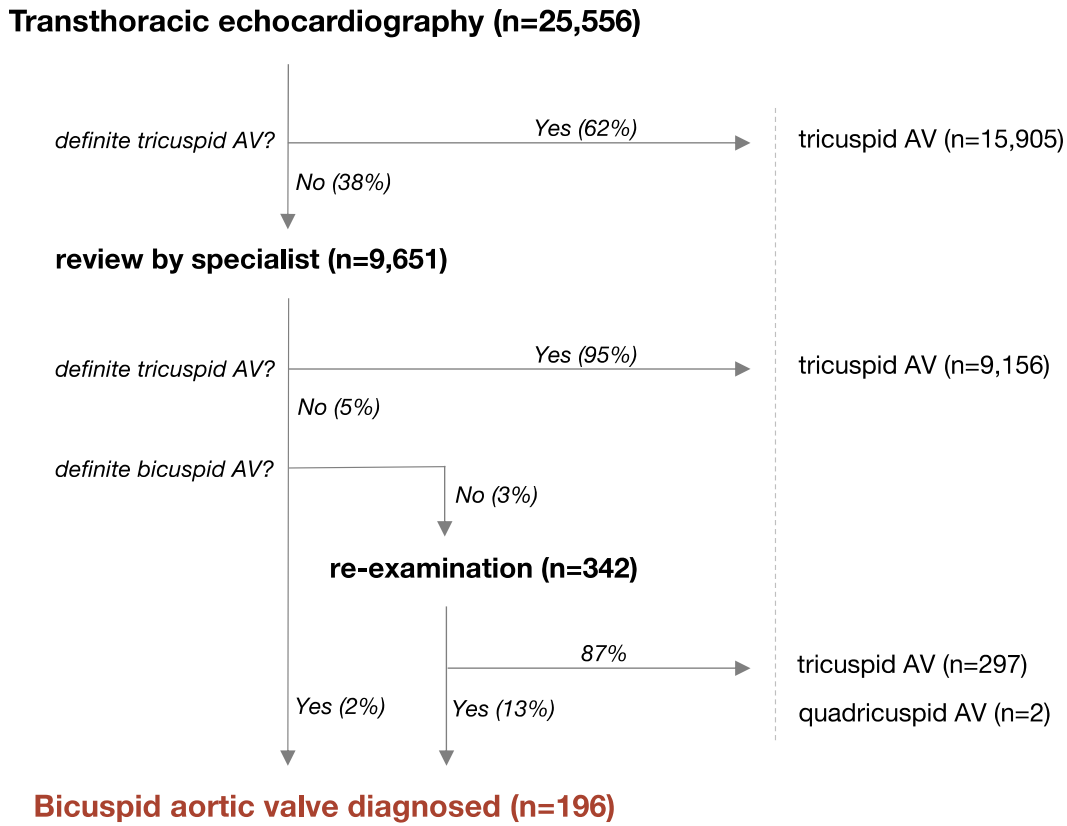
[(a)] Matching criteria for five newborns with BAV were not fulfilled and they were excluded (three newborns from twin pregnancies and two from single pregnancies; they all deviated considerably in gestational age, weight [2.1-2.9 kg and 4.0 kg] and/or age [15-47 days old] from average at time of examination).

eFigure 1. Schematic Illustration of BAV Subtypes, Classified According to Sievers and Schmidtke[1]

NL: non- and left-coronary sinuses; RL: right- and left-coronary sinuses; RN: right- and non-coronary sinuses.

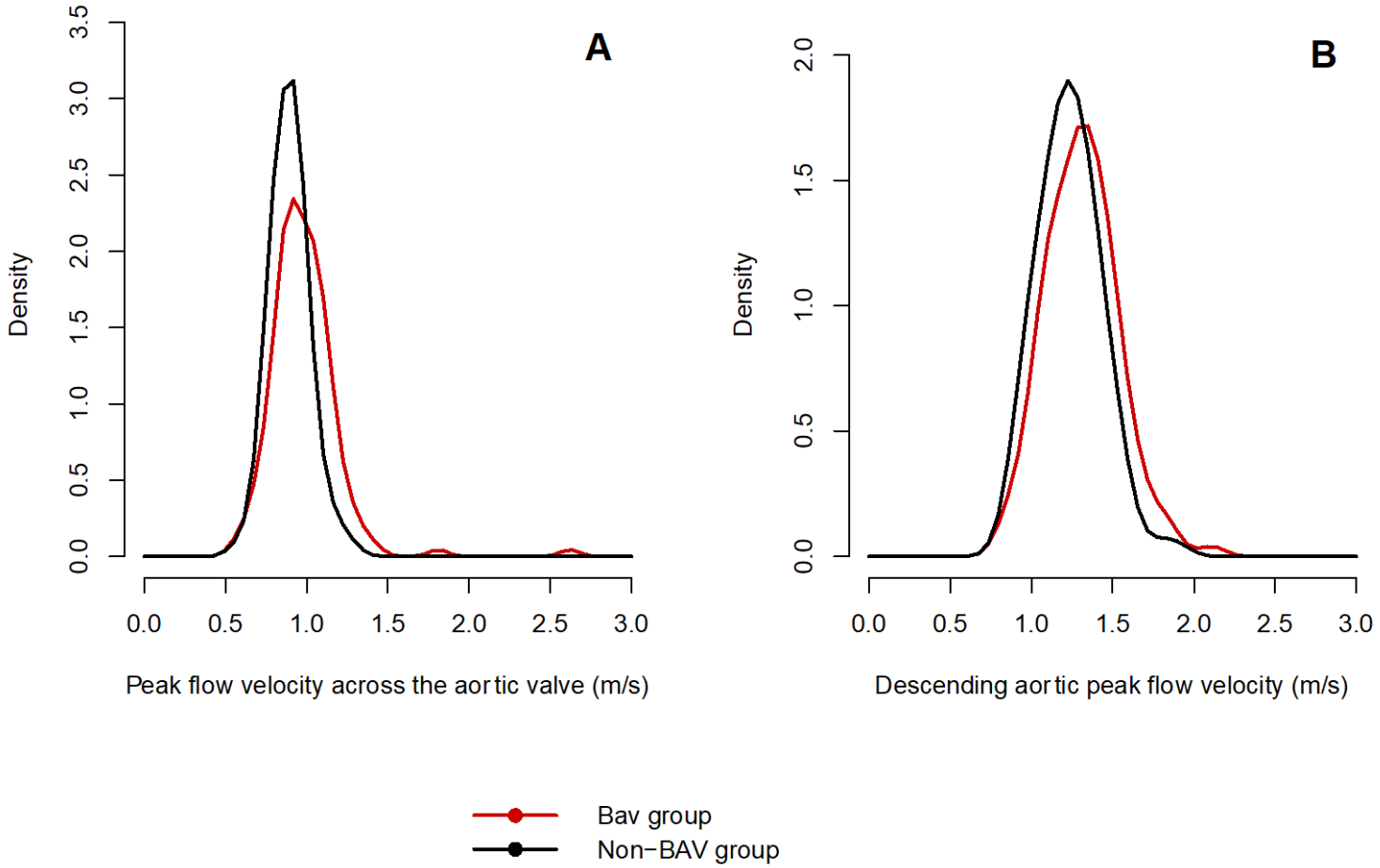


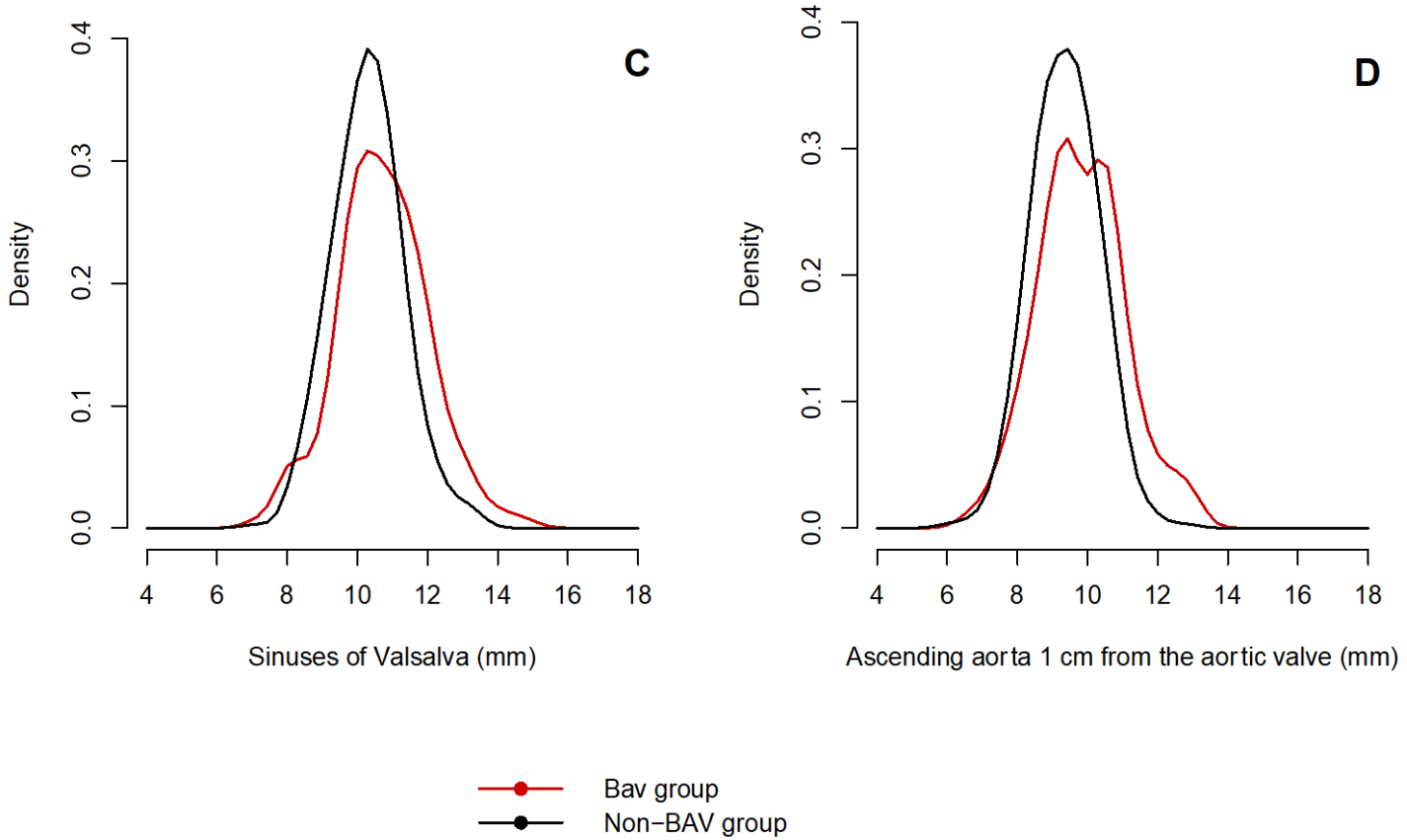
eFigure 2. Flowchart for the Identification of Newborns With BAV on Transthoracic Echocardiography
AV: aortic valve.



eFigure 3. Overlapping Kernel Density Plots for the BAV (Red Line) and Control (Black Line) Groups

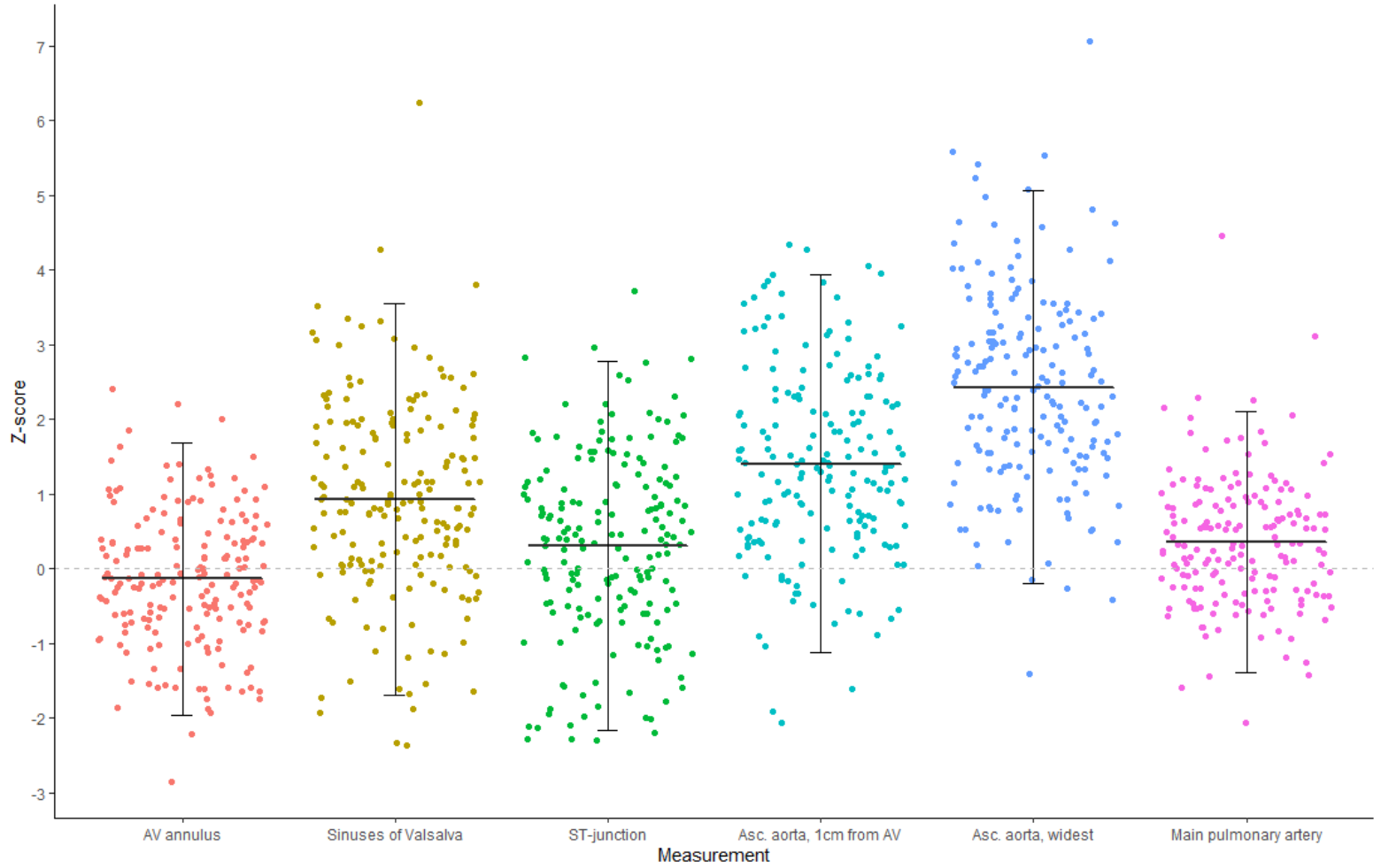
A. Peak velocity across the aortic valve. B. Descending aortic peak flow velocity. C. Sinuses of Valsalva. D. Ascending aorta 1 cm from the aortic valve.





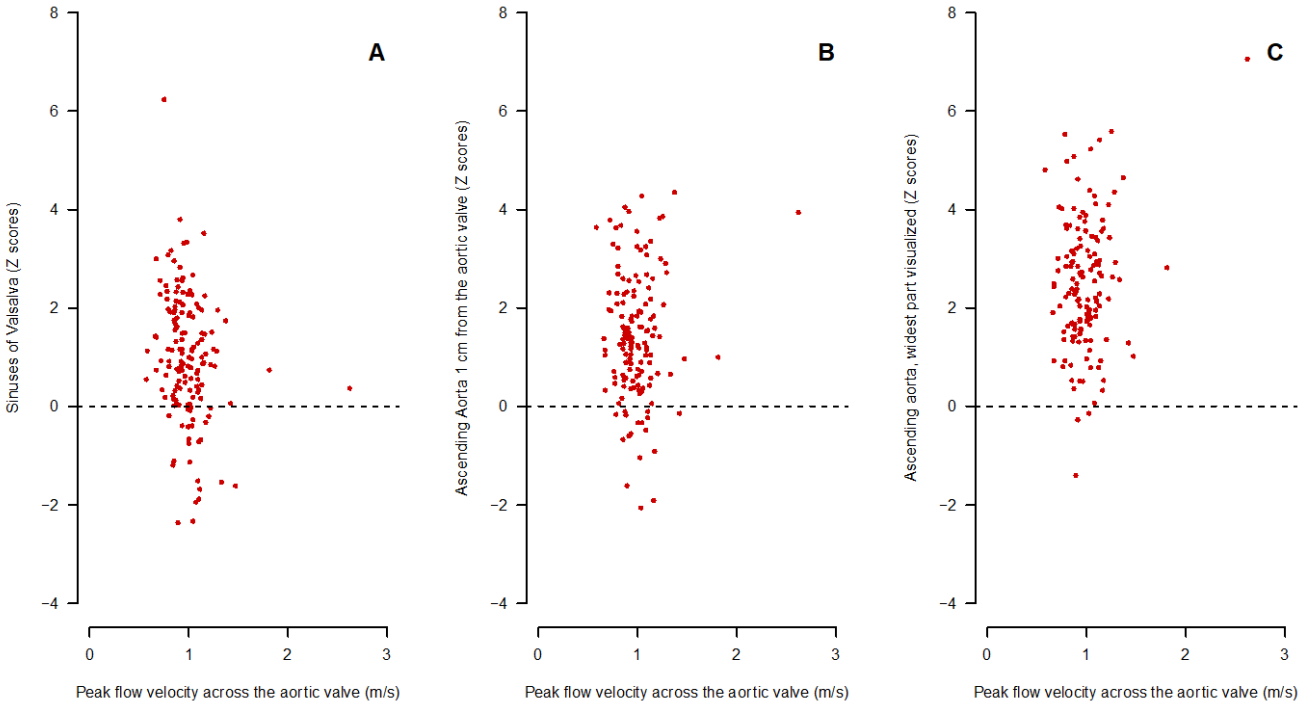
eFigure 4. Z scores for Ascending Aortic Dimensions and Main Pulmonary Artery Diameter in Newborns With BAV According to the Pediatric Heart Network Normal Echocardiogram Database

Each dot represents the measurement at a given point in each newborn with BAV. Horizontal lines and error bars represent mean and standard deviations for each measurement.



eFigure 5. Scatter Plots Displaying Ascending Aortic Diameter Expressed as Z score and the Peak Flow Velocity Across the Aortic Valve for Newborns in the BAV Group

A. Sinuses of Valsalva, B. Tubular Ascending Aorta 1 cm From the Aortic Valve, and C. Tubular Ascending Aorta at Widest Part Visualized



eReferences

1. Sievers H-H, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg*. 2007;133(5):1226–33.