Original Article

Aortic valve leaflets are asymmetric and correlated with the origin of coronary arteries

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Background: Asymmetry of the aortic valve leaflets has been known since Leonardo Da Vinci, but the relationship between size and shape and origin of the coronary arteries has never been examined. Our aim was to evaluate this anatomy in a population of pediatric patients using a cross-sectional study design.

Methods: Consecutive pediatric patients with trans-esophageal echocardiography (TEE), with or without trans-thoracic echocardiography (TTE), were included in our study. Exclusion criteria: (I) bicuspid aortic valve; (II) aortic valve stenosis; (III) hypoplasia of aortic valve annulus, or aortic root; (IV) truncal valve; (V) coronary artery atresia; (VI) previous surgery on aortic valve and/or coronary arteries. In pre-operative TTE and intra-operative TEE inter-commissural distance and length of aortic valve leaflets were measured in short axis view in the isovolumic phase of systole. Echocardiography investigations, anonymized and randomly coded, were independently reviewed by at least two readers. Echocardiography, angiography, cardiac computed tomography (CT) scan and magnetic resonance imaging (MRI), and operative notes were reviewed to identify origin of coronary arteries.

Results: Two hundred sixty-one pediatric patients were identified, 93 excluded per our criteria, leaving 168 patients, age 2.6±4.3 years, weight 12.87±17.34 kg, 128 (76%) with normal and 40 (24%) with abnormal coronary arteries. In TTE and TEE measurements the non-coronary leaflet had larger area ($P<0.001$), while the right and left had equal areas, but different shape, with the left leaflet longer ($P<0.001$) and narrower ($P=0.005$) than the right. With the major source of blood flow from the right coronary sinus, the non-coronary leaflet was still the longest. However, there was no statically significant difference between the size and shape previously observed between the right and left leaflets.

Conclusions: Our study showed asymmetry of size and shape among aortic valve leaflets, and a relationship with coronary artery origin. The complex aortic root anatomy must be approximated to optimize function of any surgical repair. These findings also may prove useful in the pre-operative definition of coronary artery anatomy and in the recognition of coronary artery anomalies.

Keywords: Aortic valve leaflets; congenital heart defects; coronary arteries; pediatric cardiology; pediatric heart surgery

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Introduction

The aortic root has a complex three-dimensional anatomy, and its function depends upon a variety of anatomic and physiologic factors. Within the aortic root complex, the asymmetry of the three aortic valve leaflets has been known since the time of Leonardo Da Vinci, whose anatomical drawings showed three leaflets of different size and shape (*Figure 1*) (1-3), a finding confirmed by recent studies in adults (4-6).

A complete understanding of the anatomy of the aortic root and its leaflets, together with the potential correlations between the origin of the coronary arteries and the aortic valve leaflets, has two major important surgical implications. One is for the surgical repair of the aortic valve (7-10). The second is for repair of trunco-conal congenital heart defects associated with anomalous origin of the coronary arteries, or requiring reimplantation of the coronary arteries such as an arterial switch, aortic translocation, or Ross procedure (11-13).

Identification of abnormal coronary artery origin and course can also be important for the prevention of sudden cardiac death, since echocardiography may fail to identify the coronary anatomy in up to 10% of asymptomatic patients, potentially missing cases of anomalous coronary arteries (14-16).

To the best of our knowledge the precise quantitative relationship between the leaflets size and shape has not yet been well defined in large studies in pediatric populations, and the correlation of normal or abnormal origin of the coronary arteries with the aortic valve leaflets has never been investigated, as previous studies have used anatomic positioning to define the leaflets (4-6,17-23).

With these considerations in mind, we conducted this retrospective study to examine the size and shape of the aortic valve leaflets using echocardiography, and to investigate if there is a potential relationship between leaflets size and shape and coronary artery anatomy. We formulated the hypothesis that the relative size and shape of the aortic valve leaflets is related to the coronary artery anatomy. We also hypothesized that abnormal origin of the coronary arteries would be associated with deviations from the typical pattern of aortic valve geometry. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-369/rc).

Highlight box

Key findings

- Aortic valve leaflets are asymmetrical as measured by echocardiography in 168 children. The non-coronary leaflet is the largest and longest. The right and left coronary leaflets have equal areas, but the left coronary leaflet is longer and narrower.
- When the right coronary artery is the major source of blood flow, the right and left leaflets have similar morphology, without differences in size or shape.

What is known and what is new?

- Aortic valve leaflet asymmetry is well known, but their relationship to the coronary arteries has not been examined.
- Our study shows a relationship, not previously recognized, between coronary arteries and leaflet size; this is altered by anomalous coronary artery origin.

What is the implication, and what should change now?

- The relationship of aortic valve leaflets and coronary arteries has important implications for surgical repair of the aortic valve and for identifying coronary artery abnormalities.

Methods

Study population

All consecutive pediatric patients (age <18 years) who underwent trans-esophageal echocardiography (TEE) as a part of a cardiac surgery with or without prior trans-thoracic echocardiography (TTE) in our system from January 1st to December 31st, 2021, were included in our retrospective study. Patients were identified by querying our echocardiography database for patients undergoing TEE.

Criteria for exclusion were the following: (I) malformation of the aortic valve, i.e., anatomical or functional bicuspid aortic valve; (II) aortic valve stenosis; (III) hypoplasia of the aortic valve annulus, aortic root, or ascending aorta, as defined by Z score less than −2; (IV) presence of truncal valve; (V) atresia of the origin of one of the coronary arteries; (VI) any previous type

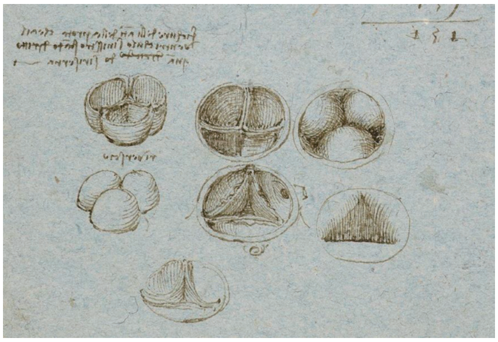

Figure 1 Several of Leonardo Da Vinci's drawings of the aortic valve. Reproduced with permission of Windsor Castle, Royal Library, copyright reserved by His Majesty King Charles III.

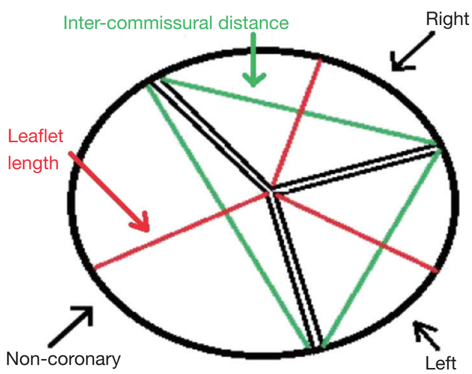

Figure 2 Schematic for measurements of aortic valve leaflets.

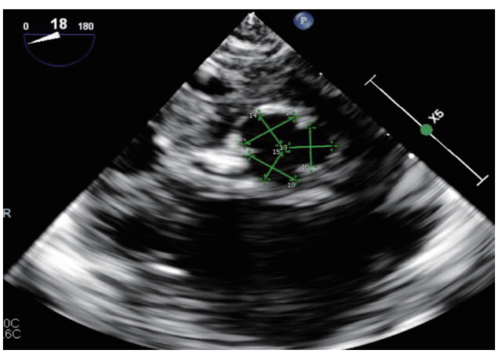

Figure 3 Representative transesophageal echocardiogram measurements.

of surgery on aortic valve and/or coronary arteries. The intra-operative TEE, performed after the induction of general anesthesia and/or the pre-operative TTE, were used for measurements. If the pre-operative TEE images

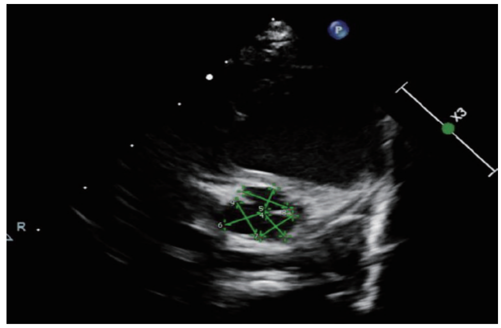

Figure 4 Representative transthoracic echocardiogram measurements.

were inadequate, the measurements were based on the post-operative TEE, unless surgery required any type of procedure on the aortic root. Patients were excluded if there were inadequate TTE and TEE images for the required measurements.

A variety of machines and probes were used as were available for the sonographer at the time of the study. The echocardiography machines used during the study were iE33, EPIQ7 and EPIQ CVx (Phillips Healthcare, Bothell, WA, USA), VIVID E9 and VIVID E95 (GE Healthcare, Horten, Norway), and ACUSON SC2000 (Siemens Healthcare, Mountain View, CA, USA). The probes used for TTE were S12-4, S8-3, X7-2, X5-1, D2cwc (Phillips Healthcare), 12S-D, 6S-D, M5S-D, 2PD, 6Vc-D, 4Vc-D (GE Healthcare, Horten, Norway), 10V4, 8V3, 4V1c (Siemens Healthcare). The probes used for TEE were X8-2t, X7-2t, S7-3t, S8-3t (Phillips Healthcare), and Z6Ms, V7M (Siemens Healthcare).

Measurements of the aortic valve leaflets

A pre-operative TTE and the pre/post-operative TEE for each patient were reviewed to perform measurements of the aortic valve leaflets in the short axis view, at the isovolumic phase of the systole just prior to their opening, as this period was identified by all investigators involved as the best time to yield reproducible measurements.

The following measurements were performed of the inter-commissural distance and of the length of each leaflet, as illustrated in *Figures 2-4*.

(I) Inter-commissural distance = distance between the interface between the two commissures on the aortic wall, considered as a fair assessment of the width of each leaflet;

(II) Length = maximum distance from the central interface of the leaflets to the aortic wall, considered as the assessment of the length of the respective aortic sinus.

Each echocardiography investigation, anonymized and coded at random, was independently reviewed, with the measurements being performed on the same clip and frame, by at least two independent readers among a group of six (T.S.K., T.C., M.E.M., M.C., L.S.T., R.M.K.) with varying experience and blinded to their own responses, other readers' responses, and the patients' clinical data and outcomes. To minimize bias, readers performed measurements separately. Once all patient's studies had been reviewed, all discordant measurements, defined as >1 mm difference in any measurement, were identified. These studies were then reviewed simultaneously by two measurers, in the case of doubts with a senior expert (T.C., R.M.K.), until a consensus measurement was obtained for all measurements on that study. Once all measurements were completed and validated, the average of two measurements was taken if there was no disagreement or the consensus measurement was used.

With all measurements of inter-commissural distance and length available and validated, the area of all the leaflets was calculated using the principles of trigonometry, where area = Sin-1[(0.5 × inter-commissural distance)/leaflet length] × leaflet length (24).

Origin of the coronary arteries

In all patients the medical records were reviewed to identify the origin of the main branches of the coronary arteries, without observations on their course, if intra-mural or intra-arterial. The purpose was to correlate the morphology of the aortic valve leaflets with the source of the major blood flow, either from the left or from the right sinus. The reports of echocardiography, cardiac catheterization and angiography, cardiac computed tomography (CT) scan and MRI, and operative notes were analyzed, and when there were discrepancies among the description of the coronary artery origin obtained with the various modalities, preference was assigned, in order of importance, to operative notes, followed by cardiac CT or MRI, cardiac catheterization and angiography.

For patients with transposition or malposition of the great arteries, known to have a relatively high incidence of abnormal coronary artery origin, the left-facing, right-facing and non-facing coronary leaflets were assigned as the left, right, and non-coronary leaflets respectively.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of UTHealth Science Center, McGovern Medical School approved this study (IRB# HSC-MS-20-1346) and waived the need to obtain written informed consent from the families of the patients, because this study involved only the retrospective analysis of clinically acquired data.

Patients with anomalous coronary arteries

Following our initial observation of discrepancy between the shape of right and left coronary leaflets, we investigated if there was a correlation between the morphology of the aortic leaflets in patients with the major source of coronary blood flow from the right coronary sinus. This included all patients with the right coronary sinus giving origin not only to right coronary artery, but also to left main coronary artery, or one of the main left branches, either left anterior descending coronary artery or circumflex artery, or if the left main coronary artery and its branches originated from the right sinus and the right coronary artery from the left sinus. Once these patients were identified, we analyzed the same measurements as described above, regardless of the different incidence of anomalous origin among the various congenital heart defects.

Statistical analysis

The normality of the data was checked by using histograms. Since the distributions of the values were skewed to the right, nonparametric tests were used. Wilcoxon signed rank test was used for testing the difference between the values measured by transthoracic echocardiogram and those by transesophageal echocardiogram. Friedman rank sum test was used for testing whether the three aortic value leaflets were symmetrical or asymmetrical. Then pairwise Wilcoxon signed rank test with multiple testing adjustment was used to decide which two groups were significantly different. Intraclass correlation coefficient and its corresponding 95% confidence interval (CI) were computed to examine the inter-reader agreement.

Results

Between January 1st and December 31st, 2021, 261 patients were identified from the echocardiography database with

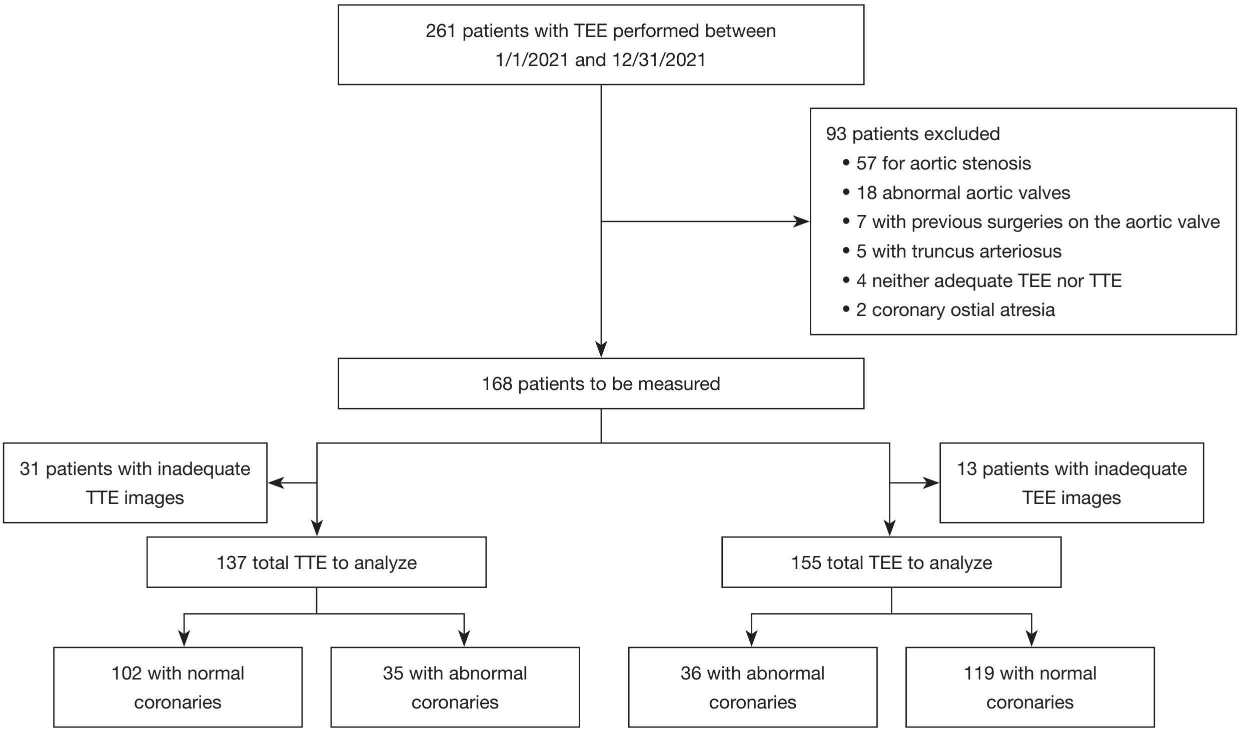

Figure 5 Patient selection process. TEE, trans-esophageal echocardiography; TTE, trans-thoracic echocardiography.

an age <18 years at the time of surgery with TEE, with or without TTE.

Among these patients, 93 were excluded per our criteria: 57 with aortic valve stenosis, 18 with other abnormalities of the aortic valve (13 bicuspid valve, 3 valve dysplasia, 1 with leaflet prolapse, 1 partial fusion of commissures), 7 with previous surgery on aortic root, 5 truncal valve, 2 coronary artery ostial atresia; 4 additional patients were excluded because of inadequate TTE and TEE images.

This gave a total of 168 pediatric patients, age 2.6± 4.3 (mean ± standard deviation) years, weight 12.87± 17.34 kg, to include in our measurements.

In 31/168 (18.5%) patients the TTE images were inadequate, therefore only 137 TTE were included in the statistical analysis. In 13/168 (7.7%) patients the TEE images were inadequate, therefore only 155 TEE were included in the statistical analysis.

Within the TTE group there were 102/137 (74%) patients with normal and 35/137 (26%) with abnormal origin of the coronary arteries, while in the TEE group there were 119/155 (77%) patients with normal and 36/155 (23%) with abnormal coronary arteries.

The selection process is detailed in *Figure 5*.

Agreement between measurements

Our study group was composed of 168 patients, 128 (76%) with normal coronary arteries and 40 (24%) with abnormal coronary arteries. Patient characteristics are given in *Table 1*.

Over 137 TTE investigations, a total of 822 measurements were taken (6 measurements for each TTE), 66 (8%) of which had a discrepancy between the two measurers. This represented 35 (26%) of the total TTEs. Over 155 TEE investigations, a total of 930 measurements were taken (6 measurements for each TTE), 130 (14%) of which had a discrepancy between the two measurers. This represented 56 (36%) of the total TEE. Despite the need to remeasure, we had strong inter-observer correlation with intraclass correlation coefficients >0.95 for all length and inter-commissural distance measurements on transthoracic and transesophageal echocardiograms. These full results are presented in *Table 2*.

Comparison of measurements between TTE and TEE

A comparison of the leaflet measurements between TTE

Table 1 Patient characteristics

Characteristics	Number of patients	Age, days (average ± SD)	Weight, kg (average ± SD)	Percentage male
All patients	168	954±1,575	12.87±17.34	57%
Normal coronary anatomy	128	863±1,433	11.98±16.45	54%
All anomalous coronaries	40	1,245±1,954	15.72±19.9	73%
Normal coronary anatomy + major left	140	924±1,509	16.48±20.61	54%
Left coronary cusp major flow source	12	1,647±2,144	19.94±21.96	50%
Right coronary cusp major flow source	28	1,073±1,881	13.91±19.09	82%

SD, standard deviation.

Table 2 Intraclass correlation coefficients for transthoracic and transesophageal echocardiograms

Imaging modality	Measurement	Leaflet	Intraclass correlation coefficient (95% CI)
Transthoracic echocardiogram	Aortic valve leaflet length	Left (mm)	0.966 (0.953–0.976)
		Right (mm)	0.952 (0.933–0.965)
		Non (mm)	0.979 (0.97–0.985)
	Inter-commissural distance	Left (mm)	0.964 (0.95–0.974)
		Right (mm)	0.963 (0.948–0.973)
		Non (mm)	0.971 (0.959–0.979)
Transesophageal echocardiogram	Aortic valve leaflet length	Left (mm)	0.964 (0.951–0.974)
		Right (mm)	0.966 (0.953–0.975)
		Non (mm)	0.984 (0.978–0.988)
	Inter-commissural distance	Left (mm)	0.97 (0.959–0.978)
		Right (mm)	0.951 (0.933–0.964)
		Non (mm)	0.972 (0.962–0.98)

CI, confidence interval.

and TEE for patients with normal coronary arteries showed a statistically significant difference between the two modalities. For each of the respective leaflets, the median values of length, inter-commissural distance, and areas were larger on the TEE than the TTE, with P<0.001 for every measurement except for the length of the non-coronary leaflet (P=0.002) (*Tables 3,4*). For the 85 patients whose TTE and TEE both commented on origin of the coronary arteries, only 4 (4.7%) showed a discrepancy between the origin of the coronary arteries. All four of these patients had advanced imaging performed with the TEE correctly identifying the origin of the coronary arteries.

Comparison of measurements of the three leaflets for patients with normal origin of the coronary arteries

For the TTE measurements, the non-coronary leaflet was longer and had a larger area than the left and right and coronary leaflets (P<0.001 for all). The estimated median difference (95% CI) for non-coronary versus left length was 0.44 mm (0.25–0.63), and area 3.39 mm^2 (2.09–4.83); non-coronary versus right length 0.98 mm (0.75–1.24), area 2.14 mm^2 (1.01–3.61). The non-coronary leaflet had a longer inter-commissural distance than the left, estimated median difference of 0.61 mm (0.41–0.8) (P<0.001) but there was no statistically significant difference between the non-coronary and right inter-commissural distance, estimate

Table 3 Comparison of measurements of leaflets between TTE and TEE

Measurement	Transthoracic measure, mm (n=102)		Transesophageal measure, mm (n=119)		Estimate of median difference mm (95% CI)	P value of median difference
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Left leaflet length	5.6 (2.14)	5 (4.26, 6.23)	6.2 (2.2)	5.65 (4.57, 7.14)	−0.52 (−0.83 to −0.21)	<0.001
Right leaflet length	5.03 (2.14)	4.62 (3.79, 5.62)	5.67 (2.46)	5.26 (4.35, 6.4)	−0.58 (−0.85 to −0.32)	<0.001
Non-coronary leaflet length	6.1 (2.32)	5.39 (4.66, 6.73)	6.69 (2.69)	5.94 (4.87, 7.93)	−0.44 (−0.76 to −0.18)	0.002
Left inter-commissural distance	7.06 (2.88)	6.46 (5.24, 7.44)	8.05 (3.47)	7.22 (5.68, 9.38)	−0.82 (−1.22 to −0.48)	<0.001
Right inter-commissural distance	7.62 (3.00)	6.93 (5.79, 8.42)	8.5 (3.11)	7.77 (6.38, 9.52)	−0.86 (−1.25 to −0.48)	<0.001
Non-coronary inter-commissural distance	7.61 (3.25)	6.67 (5.75, 8.45)	8.46 (3.38)	7.46 (6.38, 9.8)	−0.78 (−1.15 to −0.43)	<0.001

TTE, trans-thoracic echocardiography; TEE, trans-esophageal echocardiography; SD, standard deviation; IQR, interquartile range; CI, confidence interval.

Table 4 Comparison of measurement of areas of the leaflets between TTE and TEE

Measurement	Transthoracic measure, mm^2		Transesophageal measure, mm^2		Estimate of median difference mm^2 (95% CI)	P value of median difference
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Left leaflet area	24.62 (24.4), n=102	17.27 (12.77, 24.3), n=102	31.49 (28.94), n=119	22.05 (14.58, 35.49), n=119	−4.54 (−7.61 to −2.3)	<0.001
Right leaflet area	26.08 (25.88), n=91	18.84 (13.32, 27.22), n=91	32.41 (28.77), n=109	22.89 (16.72, 34.6), n=109	−5.02 (−7.95 to −2.49)	<0.001
Non-coronary leaflet area	29.16 (29.32), n=102	19.38 (15.14, 30.85), n=102	35.27 (31.33), n=118	23.12 (16.68, 41.81), n=118	−4.53 (−7.29 to −2.3)	<0.001

TTE, trans-thoracic echocardiography; TEE, trans-esophageal echocardiography; SD, standard deviation; IQR, interquartile range; CI, confidence interval.

Table 5 Comparison of leaflet measurements from TTE of normal patients

Measurement	Median of left (IQR)	Median of right (IQR)	Median of non-coronary cusp (IQR)	P value of overall difference	Left *vs.* right		Non-coronary *vs.* left		Non-coronary *vs.* right	
					Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P
Leaflet length (mm), n=102	5.02 (4.26, 6.28)	4.68 (3.79, 5.64)	5.38 (4.65, 6.85)	<0.001	0.53 (0.33 to 0.73)	<0.001	0.44 (0.25 to 0.63)	<0.001	0.98 (0.75 to 1.24)	<0.001
Inter-commissural distance (mm), n=102	6.48 (5.26, 7.67)	6.97 (5.94, 8.54)	6.97 (5.83, 8.62)	<0.001	−0.61 (−0.8 to −0.41)	<0.001	0.61 (0.41 to 0.84)	<0.001	−0.01 (−0.19 to 0.23)	>0.99
Leaflet area (mm^2)	17.97 (12.78, 26.86), n=102	19.09 (13.27, 29.16), n=91	19.83 (16.38, 34.91), n=102	<0.001	−0.94 (−1.93 to −0.01)	0.14	3.39 (2.09 to 4.83)	<0.001	2.14 (1.01 to 3.61)	<0.001

TTE, trans-thoracic echocardiography; IQR, interquartile range; CI, confidence interval.

median difference −0.01 mm (−0.19 to 0.23) (P>0.99). When the left coronary leaflet was compared with the right, the left had a greater length, estimated median difference 0.53 mm (0.33–0.73), and narrower inter-commissural distance −0.61 mm (−0.8 to −0.41) (P<0.001 for both) while there was no statistically significant difference between the area of right and left coronary leaflets, estimated medial difference −0.94 mm^2 (−1.93 to −0.01) (P=0.14) (*Table 5*).

For the TEE measurements, the non-coronary leaflet was longer and had a larger area than the other two leaflets (P<0.001 for both). The estimated median difference (95% CI) for non-coronary versus left length was 0.52 mm (0.29–0.74), and area 3.6 mm^2 (2.06–5.27); non-coronary versus right length 0.99 mm (0.74–1.26), area 3.2 mm^2 (1.5–4.85). The non-coronary leaflet had a longer inter-commissural distance than the left, estimated median difference of 0.39 mm (0.15–0.61) (P=0.005) but there was no statistically significant difference between the non-coronary and right inter-commissural distance, estimate median difference −0.01 mm (−0.25 to 0.21) (P>0.99). When the left coronary leaflet was compared with the right, the left had a greater length, estimated median difference 0.43 mm (0.19–0.66) (P=0.002), and narrower inter-commissural distance −0.44 mm (−0.66 to −0.23) (P<0.001) while there was no statistically significant difference between the area of right and left coronary leaflets, estimated medial difference −0.35 mm^2 (−1.77 to 1.01) (P>0.99) (*Table 6*).

In summary, in both our TTE and TEE measurements the non-coronary leaflet always has a statistically larger area, while right and left have equal areas, but different shape, with the left leaflet longer and narrower (smaller inter-commissural distance) than the right.

Aortic valve leaflets geometry and relationship with abnormal coronary artery origin

The analysis in this group of patients with major source of coronary artery blood flow from the right coronary sinus provided the following results. For the TTE measurements the non-coronary leaflet was longer than both other leaflets, estimated median difference (95% CI) for non-coronary versus left 0.55 (0.15–1.03) (P=0.025) and non-coronary versus right 1.05 mm (0.51–1.62) (P=0.002). In contrast to the group with normal origin of the coronary arteries, there was no longer a statistically significant difference in the inter-commissural distance and area of between any of the leaflets, and no longer a difference in the length of the left and right coronary leaflets (*Table 7*).

Table 6 Comparison of leaflet measurements from TEE of normal patients

Measurement	Median of left (IQR)	Median of right (IQR)	Median of non-coronary cusp (IQR)	P value of overall difference	Left *vs.* right		Non-coronary *vs.* left		Non-coronary *vs.* right	
					Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P
Leaflet length (mm), n=119	5.99 (4.94, 7.94)	5.46 (4.46, 7.18)	6.23 (5.08, 8.9)	<0.001	0.43 (0.19 to 0.66)	0.002	0.52 (0.29 to 0.74)	<0.001	0.99 (0.74 to 1.26)	<0.001
Inter-commissural distance (mm), n=119	7.54 (6.24, 10.61)	8.33 (6.7, 11.13)	7.89 (6.5, 10.69)	<0.001	−0.44 (−0.66 to −0.23)	<0.001	0.39 (0.15 to 0.61)	0.005	−0.01 (−0.25 to 0.21)	>0.99
Leaflet area (mm^2)	25.18 (15.88, 46.71), n=119	25.57 (16.97, 47.46), n=109	28.7 (18.95, 55.59), n=118	<0.001	−0.35 (−1.77 to 1.01)	>0.99	3.6 (2.06 to 5.27)	<0.001	3.2 (1.5 to 4.85)	0.001

TEE, trans-esophageal echocardiography; IQR, interquartile range; CI, confidence interval.

Table 7 Comparison of leaflet measurements from TTE of patients with a primary source of coronary artery blood flow from the right

Measurement	Median of left (IQR)	Median of right (IQR)	Median of non-coronary cusp (IQR)	P value of overall difference	Left *vs.* right		Non-coronary *vs.* left		Non-coronary *vs.* right	
					Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P
Leaflet length (mm), n=26	5.54 (4.65, 7.24)	5.16 (3.91, 7.42)	5.88 (4.82, 7.84)	<0.001	0.43 (−0.08 to 0.85)	0.35	0.55 (0.15 to 1.03)	0.025	1.05 (0.51 to 1.62)	0.002
Inter-commissural distance (mm), n=26	6.92 (5.54, 9.48)	7.11 (5.73, 10.31)	7.25 (6.21, 9.22)	0.459	−0.29 (−0.75 to 0.41)	0.87	0.01 (−0.63 to 0.61)	>0.99	0.3 (−0.31 to 0.84)	0.839
Leaflet area (mm^2)	20.58 (13.03, 34.8), n=26	20.06 (13.26, 41.75), n=25	22.46 (17.77, 37.97), n=26	0.008	−0.57 (−2.27 to 4.61)	>0.99	1.41 (−1.25 to 5.12)	0.298	3.2 (0.91 to 7.59)	0.087

TTE, trans-thoracic echocardiography; IQR, interquartile range; CI, confidence interval.

Table 8 Comparison of leaflet measurements from TEE of patients with a primary source of coronary artery blood flow from the right

Measurement	Median of left (IQR)	Median of right (IQR)	Median of non-coronary cusp (IQR)	P value of overall difference	Left *vs.* right		Non-coronary vs. left		Non-coronary *vs.* right	
					Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P	Estimated median difference (95% CI)	P
Leaflet length (mm), n=20	6.02 (4.77, 7.73)	5.64 (4.39, 6.7)	6.1 (4.94, 8.34)	0.044	0.49 (−0.06 to 0.96)	0.164	0.44 (0.17 to 0.83)	0.021	0.99 (0.39 to 1.59)	0.005
Inter-commissural distance (mm), n=20	7.76 (6.11, 11.12)	7.93 (6.54, 11.25)	7.9 (6.58, 9.95)	0.097	−0.34 (−0.84 to 0.15)	0.609	0.01 (−0.63 to 0.61)	>0.99	−0.56 (−1.33 to 0.26)	0.503
Leaflet area (mm^2), n=20	25.22 (16.36, 50.19)	24.03 (16.38, 44.26)	29.39 (18.97, 44.48)	0.717	0.18 (−3.18 to 2.68)	>0.99	1.41 (−1.25 to 5.12)	0.609	0.81 (−2.15 to 4.7)	>0.99

TEE, trans-esophageal echocardiography; IQR, interquartile range; CI, confidence interval.

The same was true for all TEE measurements, with no statistical difference among the three leaflets regarding area and inter-commissural distance. The non-coronary leaflet remained longer than the both other leaflets, estimated median difference (95% CI) for non-coronary versus left 0.44 mm (0.17–0.83) (P=0.021) and versus the right 0.99 mm (0.39–1.59) (P=0.005) (*Table 8*).

In summary, in both our TTE and TEE measurements of aortic valve leaflets of patients with major source of coronary artery blood flow from the right coronary sinus, the non-coronary leaflet was still the longest, but the differences observed between patients with normal coronary arteries origin disappeared. There was no statistical difference in the shape of right and left leaflets and the areas and inter-commissural distance between any of the three leaflets.

Discussion

Key findings

Our observations in children confirmed that the aortic valve leaflets are asymmetrical in size and morphology, with the non-coronary leaflet being largest of the three, and the right and left cusps having similar areas but different shape. Described in the context of the known ovoid shaped virtual basal ring or "annulus" of the aortic valve in diastole, the right coronary sinus is aligned with the minor axis, producing a shorter and wider shape while the left and non-coronary sinuses are aligned with the major axis, producing the longer and narrower shapes. In the presence of an anomalous major source of coronary artery blood supply originating from the right coronary sinus, the differences between the left and right leaflets are no longer found.

Strengths and limitations

To the best of our knowledge, our research study is the first with simultaneously all the following characteristics: (I) investigations accomplished in patients *in vivo*, as opposed to cadaver specimens; (II) all patients in the pediatric age group <18 years; (III) measurements of each of the three leaflets of the aortic valve performed with both TTE and TEE; (IV) statistical analysis evaluating the differences among the three leaflets; (V) analysis of the different morphology of the aortic valve leaflets in the presence of anomalous coronary artery origin.

Limitations in this study include:

(I) As the study was retrospective, the measurements performed with a quite large number of machines and probes, as well as observers. To compensate for this limit, all variations among different observers have been scrutinized to avoid possible errors.

(II) Variations in measurements between observers. We used a standardized process and measured on the same frame to minimize variation, yet 8% of the total TTE values and 14% of the TEE measurements were initially discrepant, even if only >1 mm. This required us to repeat measurements in many patients, 28% of TTE and 39% of TEE. While overall a significant number of patients needed to be remeasured, fortunately, more of the individual measurements agreed as confirmed by our calculated inter-rater intraclass correlation coefficients all being >0.95. The higher incidence of discrepancies in TEE were likely due to the lower resolution of the images obtained through TEE, especially in our neonatal patients.

(III) Our echocardiograms were often not performed to specifically measure the aortic valve leaflets in a standardized fashion and it is possible that different planes through the aortic valve may have added variation in our measurements and contributed to the differences between TTE and TEE. However, this reflects real-world echocardiography practice.

(IV) As the characteristic of the study was retrospective, multi-modality investigations were available only in a relatively small number of patients.

(V) Our calculation of the area of aortic valve leaflets assumed a circular geometry of the aortic valve, which may have introduced errors in our calculations. As we have used the same formula to calculate the area of all aortic valve leaflets, we expect that the potential error of calculation was homogenously distributed among the calculations.

(VI) There is significant variability in the rotational position of the aortic root both in normal hearts, and those with congenital heart defects. These changes impact hemodynamics, tissue biomechanics, valve function, and propensity for dilation. All of these will modify the leaflet orientation relative to the ovoid/elliptical shaped "annulus", and presumably the leaflet dimensions.

(VII) Even though children with known aortic valve and root pathology were excluded from our study, there may have been unrecognized structural and/or hemodynamic abnormalities potentially influencing the aortic root geometry. Patients with congenital defects potentially influencing size and geometry of the aortic root, such as subaortic fibromuscular ridge, subaortic ventricular septal defect, have not been excluded, considering the rare incidence of these malformation in our study population.

(VIII) The statistical tests examining patients with anomalous coronary arteries were underpowered. So, the large P values may be due to the small sample sizes.

Comparison with similar research

Evaluation of aortic leaflet anatomy utilizing autopsy specimens

Previous research studies into the anatomy of the aortic valve leaflets have yielded mixed results.

Two different investigations, respectively in 200 (5) and 50 (6) specimens of normal adult hearts, found the right coronary leaflet to be the largest, followed by the non-coronary and by the left (5,6). In contrast to these findings, a study of 100 autopsied normal hearts found no statistically significant difference between the size of the aortic valve leaflets (17). A later study investigating 100 specimens of normal adult hearts reported instead that the left coronary leaflet presented with the largest height, width, length, with the right coronary leaflet the next largest and the non-coronary leaflet as the smallest (18). However, the observed relationship was reversed when the inter-commissural distance was measured, and the non-coronary leaflet became the largest, followed by the left and right (18).

Our research study likely differs from the previous observations because of several reasons. The most probable reason is that ours are the first data examining the relationship among aortic valve leaflets using measurements performed on echocardiography images *in vivo* as opposed to measurements on heart specimens. The aortic valves in our study were under physiologic conditions, which may have influenced the relative geometry of the leaflets. We also examined pediatric patients with congenital heart defects that may have influenced the relative geometry of the leaflets.

Two studies have evaluated aortic valve leaflets *in vivo* using computer tomography scans. The first used 123 adult patients with anatomically and functionally normal aortic valve. With this method of investigation *in vivo* the right coronary and non-coronary leaflets and sinuses were the largest, while the left coronary was the smallest; the authors of this investigation attributed these differences in size to the different stress applied to the respective sinuses (19). The other study evaluated 70 adult patients with structurally normal hearts and found asymmetry of the aortic valve with the right leaflet having the largest inter-commissural distance with no difference in the left and non-coronary leaflet inter-commissural distance (20).

The previously reported studies used different parameters to define the leaflets size. It is possible that if the measurements were standardized across studies, the results would have been more consistent. It is not a surprise that the results of *in vivo* echocardiographic measurements are likely influenced by the complex three-dimensional anatomy of the aortic root, as well as the means and angle of interrogation of the aortic valve within the cardiac cycle. The measurements performed under physiologic conditions, with general anesthesia for TEE, may have also influenced the relative geometry of the leaflets.

Comparison of flow mechanics of the aortic root

Computational modeling has demonstrated difference in the stress on the aortic valve leaflets, with modeling of an asymmetric root reconstructed from magnetic resonance imaging (MRI) demonstrating that the non-coronary cusp has the highest stresses and the left coronary the lowest, while strains were highest in the right coronary leaflet, followed by the non-coronary and lowest in the left (25). It is likely that these hemodynamic factors are associated with the development of valve leaflet structure resulting in the differences in leaflet size and shape our research demonstrated. The reduced strain may also be a function of the decompressing effect of the coronary arteries with the benefit of improved myocardial diastolic perfusion as well (25).

Fluid-structure interaction modeling of the aortic root provided further evidence of asymmetric forces and movement of the three aortic leaflets, which has important interactions with the hemodynamic properties of the aortic root (26). As previous reports have shown, there likely is a relationship between the hemodynamics and the structure of the leaflets; while our research was not intended to investigate this relationship, our results should prompt further studies to explore this connection.

In vivo measurements using piezoelectric crystals implanted within the aortic root of sheep demonstrated a complex asymmetric expansion and displacement of the entire root and leaflet complex facilitating blood flow, while minimizing trauma to the leaflets (27). This study found asynchronous movement of the aortic leaflets, forming a clover-shaped orifice. Interestingly, the pattern of leaflet opening was consistent within each individual sheep, but no consistent pattern was seen between the animals (27). Further research studies could evaluate how the asymmetry of the leaflets is related to movement patterns of the aortic valve and define an optimum geometry to facilitate opening.

The dynamic movements of aortic root and leaflets has important implications for aortic root surgery as the shape of the sinuses, leaflets, and root all interact with each other and these interactions can be altered if a fixed geometry is imposed by surgery (27). These interactions have implications for efficiency and longevity of the aortic valve system, particularly important in children who benefit most from long-term durability.

Explanations of findings

Relationship between aortic valve leaflets and origin of the coronary arteries

A possible explanation of the consistent finding of the non-coronary sinus always being the largest, is that leaflet size and coronary artery blood flow are interrelated. Interestingly, we found that the differences in the normal morphology of the right and left coronary leaflets were eliminated when the primary source of coronary artery blood flow originated from the right cusp. We hypothesize that this morphology suggests a potential contribution of coronary artery blood flow to the development of leaflet morphology, or conversely, that the different morphology of right and left leaflets contributes to facilitate the blood flow distribution in the respective coronary artery.

Implications and actions needed

Our observations, if confirmed by the analysis of a larger number of patients both with normal coronary artery origins and with the major source of coronary artery blood flow from the right coronary sinus, should stimulate mathematical and bioengineering modeling to examine the potential mechanisms in which leaflet morphology influences the blood flow distribution in the coronary arteries. We chose to use the absolute value of the leaflet length and inter-commissural distance rather than adjusting for body surface area as we were comparing the relative size of the leaflets in each patient. Further measurements repeated on many of patients, could possibly allow for normative indexed values of leaflet size to be determined which could be used for comparison to identify patients with abnormalities of the aortic valve size and shape and/or origin of the coronary arteries.

An ideal aortic valve repair would replicate the normal morphology as closely as possible, and an essential component is the appropriate sizing and shaping of the leaflets. Leonardo Da Vinci explored the flow mechanics of the aortic valve and sinuses, and his intuitive observations (1,2) have been confirmed by modern 4-dimensional MRI studies, proving that the aortic root geometry has important implications for the mechanism of opening and closure of the aortic valve (3). The need for appropriate sizing of the aortic valve leaflets is best illustrated by the Ozaki procedure, in which the native aortic valve leaflets are replaced with prosthetic leaflets, constructed from autologous (native or glutaraldehyde-treated) or heterologous pericardium, using templates of different sizes. Each leaflet is tailored accordingly with their asymmetrical nature (8-10).

Our findings become especially important when attempting to pre-operatively identify the coronary artery anatomy in patients, as deviation from the normal leaflet morphology could be accompanied by an anomalous coronary artery origin. The morphology of the aortic valve leaflets may be detected with echocardiography more easily than the presence of anomalous origin of the coronary arteries. Even if our observations were based on a relatively small number of patients, our findings should still prompt careful consideration for additional investigations for precise clarification of the origin of the coronary arteries when the leaflet morphology does not follow the typical pattern and the coronary arteries are not well-seen. Such investigations may yield findings essential for both surgical planning and prevention of sudden death.

Conclusions

Our original study in children adds to the understanding of the morphology of the aortic valve leaflets by showing the definitive asymmetry of size and shape among the leaflets, and a relationship between aortic valve leaflets and coronary artery origin. This relationship also may prove useful in the pre-operative definition of coronary artery anatomy, in surgical planning and techniques involving the aortic root, and in the recognition of coronary artery anomalies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of UTHealth Science Center, McGovern Medical School approved this study (IRB# HSC-MS-20-1346) and waived the need to obtain written informed consent from the families of the patients, because this study involved only the retrospective analysis of clinically acquired data.

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