Morphologic variability of the arterial valve in common arterial trunk and the concept of normality

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ABSTRACT

OBJECTIVE: To date, no study established a morphometric evaluation of the truncal valve dysplasia and a description of its different presentation patterns. Thus, authors conducted an anatomopathological study describing the gross features and histological findings of the truncal valve. METHODS: Fifty common arterial trunk specimens were examined. The number of valvar leaflets was determined and valvar dysplasia was classified as absent, mild, moderate or severe. Selected leaflets were sectioned and submitted to histological analysis and linear measurements (thickness, length, and area), besides quantification of collagen area fraction. RESULTS: Twenty-eight (56%) valves presented three, 15 (30%) four and 7 (14%) two leaflets. Valvar dysplasia was absent in 13 (26%) cases, mild in 19 (38%), moderate in 6 (12%) and severe in 12 (24%). A significant association was found between the presence of four leaflets and valvar dysplasia ($p<0.001$). Single coronary ostium was more common in two-leaflet than in three-leaflet cases ($p=0.037$). Leaflets medial thirds were thicker in the more dysplastic valves ($p=0.006$) and in those presenting anarchic collagen distribution ($p=0.002$). CONCLUSION: Common arterial trunk semilunar valves present two main patterns. The first characterized by three leaflets and absent or mild dysplasia and the second by four leaflets and severe dysplasia. Still, great variability regarding thickness, microscopic organization of the extracellular matrix and proportions of leaflets' dimensions exists, which may impact on the surgical outcomes.

KEY MESSAGES

What is already known about this subject?

It is known that there is huge variability on the morphology of the arterial valves in common trunk regarding number of leaflets and dysplasia, but no morphometric or histological analysis of them.

What does this study add?

The study shows that a categorization is possible for such valves, combining features of dysplasia with the number of leaflets. Besides that, it also describes the relative position of the coronary arteries ostia to the valvar sinuses and, further, an association of single coronary ostium and two-leaflet valves.

How might this impact on clinical practice?

The categorization of the valve should potentially allow correlations between the valvar dysplasia patterns and the surgical indication and outcomes. The study brings also a new perspective to guide the surgeon and echocardiographer in regard to the morphology of the valve, the valvar sinuses and position of the coronary ostia.

INTRODUCTION

The single arterial valve found in hearts with common arterial trunk is known to show great morphological variability, with different numbers of leaflets and presenting frequently as dysplastic and insufficient or, more rarely, stenotic. Marked valvar malformations prove to be an important causal factor in the early deaths of children with common arterial trunk[1, 2]. The additional burden caused by the anomalous valve may worsen heart failure, leading to a reduced cardiac output, which over time may become refractory.

The quantitative review of eleven studies, in regard to the number of valvar leaflets and prevalence of valvar dysplasia, totaling 432 heart specimens, resulted in the data summarized in Tables 1 and 2. In summary, moderate or severe valvar dysplasia were more common in valves with two or four leaflets than in those with three, with a relative risk of 1.934 (95%CI: 1.317-2.839; $p=0.004$) for the two-leaflet valves and of 2.417 (95%CI: 1.765-3.310; $p<0.001$) for the four-leaflet valves, when compared with three-leaflet valves. Table 3 summarizes the findings of retrospective studies of patients undergoing truncal valve surgery, reviewed from literature. Complete literature review can be found in supplementary material.

Table 1. Number of leaflets and prevalence of valvar dysplasia								
	number of leaflets					valvar dysplasia		
	1	2	3	4	5	present	mild	moderate to severe
Van Praagh et al. [3]	0 (0.0%)	4 (7.1%)	38 (67.9%)	14 (25.0%)	0 (0.0%)	not available	not available	not available
Fuglestad SJ et al.[4]	1 (8.3%)	2 (16.7%)	8 (66.7%)	1 (8.3%)	0 (0.0%)	12 (100.0%)	7 (58.3%)	5 (41.7%)
Deshpande J et al.[5]	0 (0.0%)	4 (25.0%)	12 (75.0%)	0 (0.0%)	0 (0.0%)	6 (37.5%)	0 (0.0%)	6 (100.0%)
Suzuki A et al.[6]	0 (0.0%)	7 (8.4%)	53 (63.9%)	22 (26.5%)	1 (1.2%)	83 (100.0%)	62 (74.7%)	21(25.3%)
Butto F et al.[7]	2 (3.8%)	17 (32.1%)	26 (49.1%)	8 (15.1%)	0 (0.0%)	39 (73.6%)	12 (30.8%)	27 (69.2%)
Gerlis LM et al.[8]	0 (0.0%)	7 (30.4%)	10 (43.5%)	6 (26.1%)	0 (0.0%)	15 (65.2%)	4 (26.7%)	11 (73.3%)
Ceballos R et al.[9]	0 (0.0%)	1 (4.5%)	11 (50.0%)	10 (45.5%)	0 (0.0%)	15 (68.2%)	0 (0.0%)	15 (100.0%)
Crupi G et al.[10]	0 (0.0%)	4 (6.1%)	46 (69.7%)	15(22.7%)	1 (1.5%)	64 (97.0%)	44 (68.8%)	20 (31.3%)
Thiene G et al.[11]	0 (0.0%)	2 (16.7%)	8 (66.7%)	2 (16.7%)	0 (0.0%)	12 (100.0%)	2 (16.7%)	10 (83.3%)
Calder L et al.[12]	0 (0.0%)	6 (7.8%)	47 (61.0%)	24 (31.2%)	0 (0.0%)	52 (67.5.0%)	17 (32.7%)	35 (67.3%)
Gelband H et al.[1]	0 (0.0%)	0 (0.0%)	11 (91.7%)	1 (8.3%)	0 (0.0%)	7 (58.3%)	0 (0.0%)	7 (100.0%)
TOTAL	**3 (0.7%)**	**54 (12.5%)**	**270 (62.5%)**	**103 (23.8%)**	**2 (0.5%)**	**305 (81.1%)**	**148 (48.5%)**	**157 (51.5%)**
Liguori et al.	0 (0.0%)	7 (14.0%)	28 (56.0%)	15 (30.0%)	0 (0.0%)	37 (74.0%)	19 (51.4%)	18 (48.6%)

Table 2. Distribution of cases (in literature and current series) according to the number of leaflets and the degree of dysplasia										
number of leaflets	1 leaflet		2 leaflets		3 leaflets		4 leaflets		5 leaflets	
valvar dysplasia	absent to mild	moderate to severe	absent to mild	moderate to severe	absent to mild	moderate to severe	absent to mild	moderate to severe	absent to mild	moderate to severe
Deshpande J et al.[5]	0 (0.0%)	0 (0.0%)	2 (12.5%)	2 (12.5%)	8 (50.0%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Suzuki A et al.[6]	0 (0.0%)	0 (0.0%)	7 (8.4%)	0 (0.0%)	47 (56.6%)	6 (7.2%)	8 (9.6%)	14 (16.9%)	0 (0.0%)	1 (1.2%)
Butto F et al.[7]	0 (0.0%)	2 (3.8%)	4 (7.5%)	13 (24.5%)	8 (15.1%)	18 (34.0%)	2 (3.8%)	6 (11.3%)	0 (0.0%)	0 (0.0%)
Gerlis LM et al.[8]	0 (0.0%)	0 (0.0%)	4 (17.4%)	3 (13.0%)	7 (30.4%)	3 (13.0%)	1 (4.3%)	5 (21.7%)	0 (0.0%)	0 (0.0%)
Crupi G et al.[10]	0 (0.0%)	0 (0.0%)	1 (1.5%)	3 (4.5%)	39 (59.1%)	7 (10.6%)	6 (9.1%)	9 (13.6%)	0 (0.0%)	1 (1.5%)
Gelband H et al.[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (41.7%)	6 (50.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
TOTAL	**0 (0.0%)**	**2 (0.8%)**	**18 (7.1%)**	**21 (8.3%)**	**114 (45.1%)**	**44 (17.4%)**	**17 (6.7%)**	**35 (13.8%)**	**0 (0.0%)**	**2 (0.8%)**
Liguori et al.	0 (0.0%)	0 (0.0%)	5 (10.0%)	2 (4.0%)	24 (48.0%)	4 (8.0%)	3 (6.0%)	12 (24.0%)	0 (0.0%)	0 (0.0%)

Table 3. Summary of the retrospective studies of patients undergoing truncal valve surgery reviewed from literature

reference	number of patients	pre-operative						surgery				post-operative			
		regurgitation (moderate or severe)	stenosis	number of leaflets				concomitance with CAT repair		repair vs. replacement		absent or mild regurgitation*	follow-up (months)	reoperation	survival
				2	3	4	5	at CAT repair	after CAT repair	repair	replacement				
De Leval MR et al (1974) [13]	19	19 (100.0%)	NA	4 (21.1%)	13 (68.4%)	2 (10.5%)	0 (0.0%)	NA	NA	13 (84.2%)	3 (15.8%)	NA	9.0***	0 (0.0%)	13 (68.4%)
Elami A et al. (1994) [14]	5	3 (60.0%)	2 (40.0%)	0 (0.0%)	2 (40.0%)	3 (60.0%)	0 (0.0%)	2 (40%)	3 (60%)	5 (100.0%)	0 (0.0%)	5 (100.0%)	12.6±6.4	1 (20.0%)	4 (80.0%)
McElhinney DB et al. (1998)[2]	33	24 (72.8%)	7 (46.7%)**	NA	NA	NA	NA	15 (45.4%)	18 (54.6%)	5 (15.1%)	28 (84.9%)	10 (100.0%)**	120.9***	6 (18.1%)	23 (69.7%)
Black MD et al. (1998) [15]	3	3 (100.0%)	NA	0 (0.0%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	2 (66.7%)	1 (33.3%)	3 (100.0%)	NA	0 (0.0%)	3 (100.0%)
Imamura M et al. (1999) [16]	4	4 (100.0%)	NA	0 (0.0%)	1 (25.0%)	3 (75.0%)	0 (0.0%)	4 (100.0%)	0 (0.0%)	4 (100.0%)	0 (0.0%)	3 (75.0%)	9.2±10.3	1 (25.0%)	4 (100.0%)
Jahangiri M et al. (2000) [17]	6	6 (100.0%)	NA	1 (20.0%)**	0 (0.0%)**	3 (60.0%)**	1 (20.0%)**	NA	NA	5 (83.3%)	1 (16.7%)	5 (100.0%)	14.0***	0 (0.0%)	4 (66.7%)
Mavroudis C et al. (2001) [18]	8	8 (100.0%)	NA	1 (12.5%)	2 (25.0%)	5 (62.5%)	0 (0.0%)	3 (37.5%)	5 (62.5%)	5 (62.5%)	3 (37.5%)	7 (100.0%)	28.7±26.2	1 (12.5%)	7 (87,5%)
Henaine R et al. (2008) [19]	31	9 (100.0%)**	1 (11.1%)**	1 (11.1%)**	3 (33.3%)**	5 (55.6%)**	0 (0.0%)**	9 (29.0%)	22 (71.0%)	9 (29.0%)	22 (71.0%)	NA	NA	5 (16.1%)	24 (77.4%)
Kaza AK et al. (2010)[20]	17	14 (82.4%)	5 (29.4%)	NA	NA	NA	NA	14 (82.4%)	3 (17.6%)	17 (100.0%)	0 (0.0%)	NA	48.0±33.0	5 (29.4%)	17 (100.0%)
Russell HM et al. (2012)[21]	16	16 (100.0%)	2 (12.5%)	0 (0.0%)	4 (25.0%)	12 (75.5%)	0 (0.0%)	5 (31.3%)	11 (68.7%)	15 (93.3%)	1 (6.7%)	NA	89.1±44.1	2 (12.5%)	14 (87.5%)
Russell HM et al. (2012) [22]	27	NA	NA	NA	NA	NA	NA	25 (92.6%)	2 (7.4%)	24 (88.9%)	3 (11.1%)	NA	NA	2 (7.4%)	15 (55.5%)
Perri G et al (2013) [23]	11	NA	NA	0 (0.0%)	4 (36.4%)	7 (63.6%)	0 (0.0%)	3 (27.3%)	8 (72.7%)	11 (100.0%)	0 (0.0%)	NA	52.2***	1 (9.0%)	9 (81.8%)
Myers PO et al. (2013) [24]	36	NA	9 (25.0%)	1 (2.8%)	13 (36.1%)	22 (61.1%)	0 (0.0%)	11 (30.6%)	25 (69.4%)	36 (100.0%)	0 (0.0%)	27 (75.0%)	38.3±44.9	16 (44.4%)	32 (88.9%)
Patrick WL et al. (2016)[25]	20	19 (95.0%)	4 (20.0%)	NA	NA	NA	NA	16 (80.0%)	4 (20.0%)	20 (100.0%)	0 (0.0%)	NA	NA	NA	18 (90.0%)
TOTAL	**236**	**125 (89.3%)**	**30 (25.4%)**	**8 (6.9%)**	**42 (36.2%)**	**65 (56.0%)**	**1 (0.9%)**	**110 (52.1%)**	**101 (47.9%)**	**171 (73.4%)**	**62 (26.6%)**	**60 (85.7%)**	**42.2±76.7**	**40 (18.5%)**	**187 (79.2%)**

NA: not available; CAT: Common Arterial Trunk; * immediate results, excluding early deaths; ** information only partially available; *** standard deviation not available

To date, no study sought to establish a comprehensive description of the gross and histological morphology of the truncal valve dysplasia, and its different presentation patterns. In the present article, the authors conduct an anatomopathological study, describing the morphometric features of the arterial valve in the context of common arterial trunk.

METHODS

From the anatomical archives of the Cardiac Morphology Unit of the Royal Brompton Hospital, London, United Kingdom, and the Laboratory of Pathology of the Heart Institute (InCor), University of Sao Paulo Medical School, Brazil, we identified 77 postnatal hearts with common arterial trunk. In 27 hearts the analysis was not possible, either because of previous dissection or previous surgery; the remaining 50 hearts were examined.

Gross Analysis

Firstly, specimens were described according to the three different common arterial trunk classification methods: Collett and Edwards[26], Van Praagh[3], and Russell and co-workers[27]. Then, the number of valvar leaflets was determined and the maximal height and width were measured for each semilunar leaflet. The ratio between width and height was determined for each leaflet as a reference measure for evaluating its symmetry. The perimeter percentage occupied by each leaflet within the truncal valve circumference was defined as the ratio between the leaflet width at the level of the sinutubular junction and the perimeter of the

common trunk. The relative position of the coronary arteries ostia to the truncal valvar sinuses was noted.

Finally, valves were analyzed according to the thickness and similarity of the semilunar leaflets, being classified as: 1) mildly dysplastic, in the presence of mild diffuse thickening and uniform involvement of the leaflets with no variation among their dimensions; 2) moderately dysplastic, in the presence of mild to moderate thickening and uneven involvement of the leaflets, with focal enhancement in the form of nodules but no significant differences among the leaflets' dimensions; and 3) severely dysplastic, in the presence of moderate to severe thickening and non-uniform involvement of the leaflets, with frequent nodules and excrescences and significant differences among the leaflets' dimensions. If there was no involvement of the valvar thickness and similarity, we considered the valve as non-dysplastic.

Additionally, the origin of the arterial trunk root – and valve – relative to the ventricles and also the nature of the postero-inferior border of the interventricular communication were evaluated.

Histological Analysis

Eighteen valvar specimens from the Laboratory of Pathology of the Heart Institute (InCor), University of Sao Paulo Medical School, Brazil, were submitted to microscopic analysis.

After conventional histological processing of the thickest semilunar leaflet of each truncal valve, 5µm sections were obtained and stained with Hematoxylin-Eosin, for general analysis, and Sirius Red, for collagen identification. Using Axiovision-Zeiss image analysis system, dimension measurements (larger proximal, medial and distal thickness, length from the hinge point to the free edge and area) of the sectioned leaflets were determined. Thickness and area were indexed by the leaflet length and plotted as fold-change of the average values in non-dysplastic valves, for comparison purposes. To complete the histological analysis, collagen area fraction was quantified by means of identification by color and collagen distribution was analyzed.

Statistical Analysis

Data was expressed as the mean and standard deviation. Comparisons for the quantitative variables were made through Student's t-test or One-way ANOVA with *post hoc* Student-Newman-Keuls test. To assess qualitative associations, chi-square test or Fisher's exact test was conducted. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using SigmaPlot 13 (Systat, Chicago, IL, USA).

RESULTS

Gross Findings

In the present series, there were only valves with two, three or four leaflets. Among the 50 specimens, 28 (56%) presented three, 15 (30%) four and 7 (14%) two leaflets. Mild dysplasia was found in 19 (38%), moderate in 6 (12%) and severe in 12 (24%); in 13 there was no gross leaflet dysplasia. The distribution of cases according to the number of leaflets and the degree of dysplasia is shown in Table 4 and was included in Tables 1 and 2 for comparison with the literature. A significant association was found between the presence of four leaflets and the presence of moderate to severe degree of truncal valve dysplasia, when compared with three-leaflet valves, with a relative risk of 5.600 (95%CI: 2.183-14.363; $p<0.001$). Valves with two leaflets did not show the same association.

Table 4. Distribution of cases (in this study) according to the number of leaflets and the degree of dysplasia

	2 leaflets	**3 leaflets**	**4 leaflets**	**TOTAL**
absent	2 (4%)	11 (22%)	0 (0%)	**13 (26%)**
mild	3 (6%)	13 (26%)	3 (6%)	**19 (38%)**
moderate	2 (4%)	1 (2%)	3 (6%)	**6 (12%)**
severe	0 (0%)	3 (6%)	9 (18%)	**12 (24%**
TOTAL	**7 (14%)**	**28 (56%)**	**15 (30%)**	**50 (100%)**

Among the 50 specimens evaluated, 5 (10%) presented a single coronary ostium; 3 of them associated with two-leaflet valves and the other 2 with three-leaflet valves. Thus, single coronary ostium was more common in valves with two leaflets than in those with three, with a relative risk of 6.429 (95%CI: 1.312-31.487; $p=0.037$). Of all the three-leaflet valve cases, one presented both right and left coronary ostia leaving from the same truncal sinus; another four presented a supracomissural ostium, two right and two left; all the remaining presented coronary origins from adjacent valvar sinuses. For the four-leaflet valves, two presented the right and left

coronary ostia leaving from adjacent truncal sinuses; all the remaining presented the right and left coronary ostia leaving from truncal sinuses that were intercalated by non-coronary sinuses.

The perimeter percentage occupied by each leaflet within the truncal valve circumference at the sinutubular junction was compared among specimens with absent or mild dysplasia and those with moderate or severe dysplasia. For three-leaflet valves, those presenting absent or mild dysplasia showed leaflets of virtually equal dimensions, while those with moderate or severe dysplasia presented a smaller right coronary leaflet and a larger left coronary leaflet. As to the four-leaflet valves, it was the opposite; those with moderate or severe dysplasia had a larger right coronary leaflet and a smaller left coronary leaflet, when compared to their counterparts without or with mild dysplasia (Fig. 1).

When comparing the four groups with different degrees of valvar dysplasia, a significant difference of the leaflet width/height ratio was found (One-way ANOVA, $p=0.007$), such that the higher the degree of dysplasia the greater was the height and the smaller was the width of the leaflet (Fig. 2). After post-test, the comparison between non-dysplastic and severely dysplastic valves showed a significant difference (1.476 ± 0.263 vs. 1.125 ± 0.223, $p=0.007$), as well as the comparison between mild dysplastic and severely dysplastic valves (1.356 ± 0.260 vs. 1.125 ± 0.223, $p=0.046$).

Concerning the classification of the common trunk, among the 50 cases 34 (68%) were type I, 11 (22%) type II and 5 (10%) type III of Collett and Edwards. According to Van Praagh classification, 33 (66%) were type 1, 11 (22%) type 2, 2 (4%) type 3 and 4 (8%) type 4. Using

Russell and co-workers` classification, 40 (80%) specimens presented aortic pattern, 6 (12%) pulmonary pattern and 4 (8%) presented a balance between the pulmonary and aortic components. The statistical analysis did not depict any significant association between truncal type and valvar dysplasia or number of leaflets.

Regarding the origin of the arterial trunk root – and valve – relative to the ventricles, it was described as being predominantly related to the right ventricle in 16 (36%), to the left ventricle in 6 (13%) and balanced in 23 (51%) specimens. Among the 50 specimens, 4 (8%) presented an atrioventricular septal defect and in one it was not possible to define the features of the border of the interventricular communication due to previous dissection. For the remaining 45 specimens, 34 (75.6%) presented a muscular postero-inferior border of the defect and in 11 (24.4%) the border reached the area of the membranous septum. Both the arterial trunk origin and the postero-inferior border nature did not show any significant association with valvar dysplasia or number of leaflets.

Histological Findings

Comparing the groups with absent or mild dysplasia with those with moderate or severe dysplasia, it was demonstrated that the medial third was thicker in the more dysplastic valves (Student's t-test; absent/mild vs. moderate/severe, 1.36±0.70 vs. 2.75±1.14; p=0.006) (Fig. 3A). The comparison among the three thirds of the leaflet showed that, while in valves with moderate or severe dysplasia the medial third was thicker than both the proximal and distal ones (One-way RM ANOVA, p=0.045; post hoc tests: medial vs. proximal, 1,650±680μm vs. 990±290μm,

p=0.045; medial vs. distal, 1,650±680μm vs. 1,150±490μm, p=0.057), in valves with absent or mild dysplasia there was no difference among the thickness of the three thirds of the leaflet (One-way RM ANOVA, p=0.223). This finding can be better visualized when the thickness values of each leaflet are plotted separately (Fig. 3B).

The area percentage occupied by collagen represented 34.22±14.70% and 26.81±13.20% of the leaflets area section, respectively, for the valves with absent or mild dysplasia and for those with moderate or severe dysplasia (Student's t-test, p=0.341). Comparisons among specimens which showed anarchic patterns of collagen distribution and those with uniform distribution of collagen suggested a trend such that the former presented higher degrees of dysplasia than the latter, as seen in Fig. 4, although not statistically significant (Fisher Exact test, p=0.118). When we compared the leaflet dimensions in regard to the two patterns of collagen distribution, all measurements - except for the proximal thickness - showed significant differences (Student's t-test; medial thickness: uniform vs. anarchic collagen distribution, 1.11±0.29 vs. 2.56±1.16, p=0.002; distal thickness: uniform vs. anarchic collagen distribution, 1.08±0.37vs. 1.73±0.48, p=0.005; total area: uniform vs. anarchic collagen distribution, 1.13±0.33 vs. 1.84±0.59, p=0.005) (Fig. 3C). When analyzing the dimensions of the three thirds of the leaflets on those with uniform and anarchic collagen distribution, it was observed that, in valves with anarchic collagen distribution, the medial and distal thirds are thicker than the proximal third (One-way RM ANOVA, p=0.027; post hoc tests: proximal vs. medial, 900±280μm vs. 1,520±650μm, p=0.026; proximal vs. distal, 900±280μm vs. 1,370±460μm, p=0.044), while in valves with uniform collagen distribution there was no difference among the thickness of the three thirds of the leaflet (One-way RM ANOVA, p=0.157) (Fig. 3D).

DISCUSSION

The findings of the present study are similar to the findings of others in regard to the number of leaflets of the truncal valve, although in the present series there were more cases of valves with two or four leaflets than described in the rest of literature[1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. However, a difference of current findings when compared to those from the literature is the fact that an association was found between the presence of four leaflets and the presence of dysplasia, but unlike what had been previously described the presence of two leaflets did not appear to be related to the presence of truncal valve dysplasia.

Dysplasia of the truncal valve seems to be more a rule than an exception, so that the assessment of the degree of dysplasia is critical in the description of the truncal valve and the consequent abnormalities associated with the dysplasia. Although in the present study we described four progressive categories of truncal valve dysplasia, in most comparisons we combined together the cases presenting valves without dysplasia and those with mild dysplasia, against the cases with valves showing moderate or severe dysplasia, due to the limited sample size. Further studies, with a larger number of cases, might make better use of the four categories classification, perhaps reiterating the findings described here for the unified categories.

Besides that, this study brings a new perspective and guide to the surgeon and echocardiographer in regard to the morphology of the valve, the valvar sinuses and position of the coronary ostia. The categorization of the valve should potentially allow correlations between the valvar dysplasia patterns and the surgical indication and outcomes. Also, from now, both the

cardiologist and the cardiac surgeon should be aware of the higher risk of two-leaflet valves also presenting with a single coronary ostium, which will affect the approach to the valve.

Moreover, the present data showed that valvar dysplasia seems to be less related to the amount of collagen than to the anarchic architecture of the extracellular matrices within the valve leaflet. The appearance of dysplastic leaflets under microscopy, showing amorphous masses of unstained material, suggests that dysplasia is more related to the accumulation of other extracellular matrix components than collagen, probably proteoglycans and glycosaminoglycans, particularly hyaluronan, as previously demonstrated in dysplastic aortic and pulmonary valves[28]. New studies towards analyzing the extracellular matrix organization could help to further elucidate the origin of valve dysplasia in the common arterial trunk. Although the primary cause of valvar dysplasia is not related to the presence of collagen, it is possible to observe collagen deposition in the distal margins of the valve, possibly related to the sheer-stress caused by blood flow turbulence on the valvar surface, supporting Becker hypothesis that a "dysplastic appearance" is worsened by factors unrelated to its embryology[29]. Histological analysis has also shown virtually no difference between the proximal zones of the evaluated leaflets, regardless of the presence or degree of dysplasia, which might support Roos hypothesis that the thickening and deformity of truncal valve are due to an interruption in local development[30].

Current embryology knowledge points to a tripartite fashion of development of the outflow tracts of the heart, with distal, intermediate, and proximal components involved in the formation of the mature structures.[31] The initially common lumen of the outflow tract divides

into aortic and pulmonary components by means of an aortopulmonary septum derived from the dorsal walls of the aortic sac, and expansion, spiraling and fusion of the outflow cushions. It is the appearance of the intercalated cushions in the intermediate part of the outflow tract which give rise to the arterial roots and valves. In common arterial trunk, where the ventriculoarterial junctions are in common, it is nowadays believed that there is failure of fusion of the major outflow cushions, instead of lack of formation of the subpulmonary outflow tract as initially proposed.[3] While the presence of four-leaflet valves in common trunk support the mechanism of failure of fusion of the two outflow and intercalated cushions, cases with three-leaflet valves may point to the possibility of inadequate formation of the pulmonary component, possibly related to hypoplasia of one of the cushions.[31]

Considering all that has been discussed, what is normal for the truncal valve remains to be considered. There are two main concepts of normality. One is the concept of statistical normality, which is used to state what is normal for a population. The other concept of normality is normative, belonging to a family of related concepts like health, disease, and proper functioning, and is used to state what is normal for an individual. When analyzing truncal valve within a comparative context with aortic valves of hearts free of congenital heart disease, none of the concepts of normality applies and the valve can be considered abnormal as a whole. However, when considering the truncal valve separately, in the context of hearts with common arterial trunk, we can begin to discuss some normal ranges for this specific population.

Three-leaflet valves with absent or mild dysplasia seems to fill both statistical and normative normality criteria. It is the most prevalent pattern, accounting for 48% of the cases

described in this study and 45.1% in literature, besides being the one with lower clinical prejudice in patients with common arterial trunk. These valves also present greater symmetry within each leaflet and greater similarity between the leaflets. On histological analysis, these valves present more uniformity in the distribution of extracellular matrices and thinner leaflets.

The other presentation of truncal valve that stands out from the statistical point of view is that with four leaflets and severe dysplasia. However, this presentation is the one with the greatest clinical significance[19, 24] and, therefore, cannot be considered normal from the normative criteria. These valves tend to present exactly the contrary to those described above, with asymmetry within the leaflets, differences between them, anarchic distribution of extracellular matrices and thicker leaflets. In a way, this presentation may be considered the regular valve abnormality in hearts with common arterial trunk. Our sample, however, might be biased as it analyzes mainly patients who died in infancy, thus representing a study limitation. In clinical practice, this presentation with four severely dysplastic semilunar leaflets might be less common, since cases with lower-grade dysplasia have better survival and are probably underrepresented in our series. However, if one stands in the surgeon's position, the majority of the patients undergoing truncal valve repair present a four-leaflet valve, as we showed in the review of the retrospective surgical studies. From a surgical perspective, besides the challenges already found in the surgical correction of the common arterial trunk, in cases with severely dysplastic and four-leaflet valves, additional technical difficulty is present and correlates with greater postsurgical morbidity.

CONCLUSION

Although common arterial trunk may present two main patterns of semilunar valves, one with three leaflets and absent or mild dysplasia and the second with four leaflets and severe dysplasia, there is still great variability with regard to thickness, organization of the extracellular matrix and proportions of the semilunar leaflets. These two patterns are statistically more frequent in our postmortem series, with possibly different outcomes in the clinical perspective.

REFERENCES

1 Gelband H, Gersony WM, Vanmeter S. Truncal valve abnormalities in infants with persistent truncus arteriosus - clinicopathologic study. *Circulation* 1972;**45**:397-&.

2 McElhinney DB, Reddy VM, Rajasinghe HA, et al. Trends in the management of truncal valve insufficiency. *Annals of Thoracic Surgery* 1998;**65**:517-24.

3 Van Praagh R, Van Praagh S. The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. *Am J Cardiol* 1965;**16**:406-25.

4 Fuglestad S, Puga F, Danielson G, et al. Surgical pathology of the truncal valve: a study of 12 cases. *Am J Cardiovasc Pathol* 1988;**2**:39-47.

5 Deshpande J, Desai M, Kinare S. Persistent truncus arteriosus--an autopsy study of 16 cases. *Int J Cardiol* 1992;**37**:395-9.

6 Suzuki A, Ho SY, Anderson RH, et al. Coronary arterial and sinusal anatomy in hearts with a common arterial trunk. *Ann Thorac Surg* 1989;**48**:792-7.

7 Butto F, Lucas RJ, Edwards J. Persistent truncus arteriosus: pathologic anatomy in 54 cases. *Pediatr Cardiol* 1986;**7**:95-101.

8 Gerlis L, Wilson N, Dickinson D, et al. Valvar stenosis in truncus arteriosus. *Br Heart J* 1984;**52**:440-5.

9 Ceballos R, Soto B, Kirklin JW, et al. Truncus arteriosus. An anatomical-angiographic study. *Br Heart J* 1983;**49**:589-99.

10 Crupi G, Macartney FJ, Anderson RH. Persistent truncus arteriosus. A study of 66 autopsy cases with special reference to definition and morphogenesis. *Am J Cardiol* 1977;**40**:569-78.

11 Thiene G, Bortolotti U, Gallucci V, et al. Anatomical study of truncus arteriousus communis with embryological and surgical considerations. *Br Heart J* 1976;**38**:1109-23.

12 Calder L, Van Praagh R, Van Praagh S, et al. Truncus arteriosus communis. Clinical, angiocardiographic, and pathologic findings in 100 patients. *Am Heart J* 1976;**92**:23-38.

13 De Leval M, McGoon D, Wallace R, et al. Management of truncal valvular regurgitation. *Ann Surg* 1974;**180**:427-32.

14 Elami A, Laks H, Pearl JM. TRUNCAL VALVE REPAIR - initial experience with infants and children. *Annals of Thoracic Surgery* 1994;**57**:397-402.

15 Black MD, Adatia I, Freedom RM. Truncal valve repair: Initial experience in neonates. *Annals of Thoracic Surgery* 1998;**65**:1737-40.

16 Imamura M, Drummond-Webb JJ, Sarris GE, et al. Improving early and intermediate results of truncus arteriosus repair: A new technique of truncal valve repair. *Annals of Thoracic Surgery* 1999;**67**:1142-6.

17 Jahangiri M, Zurakowski D, Mayer JE, et al. Repair of the truncal valve and associated interrupted arch in neonates with truncus arteriosus. *Journal of Thoracic and Cardiovascular Surgery* 2000;**119**:508-13.

18 Mavroudis C, Backer CL. Surgical management of severe truncal insufficiency: Experience with truncal valve remodeling techniques. *Annals of Thoracic Surgery* 2001;**72**:396-400.

19 Henaine R, Azarnoush K, Belli E, et al. Fate of the truncal valve in truncus arteriosus. *Annals of Thoracic Surgery* 2008;**85**:172-8.

20 Kaza AK, Burch PT, Pinto N, et al. Durability of truncal valve repair. *Ann Thorac Surg* 2010;**90**:1307-12; discussion 12.

21 Russell HM, Mavroudis CD, Backer CL, et al. Long-term follow-up after truncal valve repair. *Cardiol Young* 2012;**22**:718-23.

22 Russell HM, Pasquali SK, Jacobs JP, et al. Outcomes of repair of common arterial trunk with truncal valve surgery: a review of the society of thoracic surgeons congenital heart surgery database. *Ann Thorac Surg* 2012;**93**:164-9; discussion 9.
23 Perri G, Filippelli S, Polito A, et al. Repair of incompetent truncal valves: early and mid-term results. *Interact Cardiovasc Thorac Surg* 2013;**16**:808-13.
24 Myers PO, Bautista-Hernandez V, del Nido PJ, et al. Surgical repair of truncal valve regurgitation. *Eur J Cardiothorac Surg* 2013;**44**:813-20.
25 Patrick WL, Mainwaring RD, Carrillo SA, et al. Anatomic Factors Associated With Truncal Valve Insufficiency and the Need for Truncal Valve Repair. *World J Pediatr Congenit Heart Surg* 2016;**7**:9-15.
26 Collett R, Edwards J. Persistent truncus arteriosus; a classification according to anatomic types. *Surg Clin North Am* 1949;**29**:1245-70.
27 Russell HM, Jacobs ML, Anderson RH, et al. A simplified categorization for common arterial trunk. *J Thorac Cardiovasc Surg* 2011;**141**:645-53.
28 Stephens EH, Shangkuan J, Kuo JJ, et al. Extracellular matrix remodeling and cell phenotypic changes in dysplastic and hemodynamically altered semilunar human cardiac valves. *Cardiovasc Pathol* 2011;**20**:e157-67.
29 Becker AE, Becker MJ, Edwards JE. Pathology of semilunar valve in persistent truncus arteriosus. *Journal of Thoracic and Cardiovascular Surgery* 1971;**62**:16-&.
30 ROOS A. Persistent truncus arteriosus communis: report of a case with four semilunar cusps and aortic arch on the right side. *Am J Dis Child* 1935;**50**:966-78.
31 Anderson RH, Mori S, Spicer DE, et al. Development and Morphology of the Ventricular Outflow Tracts. *World J Pediatr Congenit Heart Surg* 2016;**7**:561-77.

FIGURES

Figure 1. Graphic representation of three and four-leaflets valves, showing the perimeter percentage occupied by each leaflet within the truncal valve circumference. Closed circle (●) represents the right coronary artery and open circle (○) represents the left coronary artery. Perimeter percentage is expressed as the average and standard deviation. A. Three-leaflet valves with absent or mild dysplasia; B. Three-leaflet valves with moderate or severe dysplasia; C. Four-leaflet valves with absent or mild dysplasia; D. Four-leaflet valves with moderate or severe dysplasia.

Figure 2. Width/height ratio of valvar leaflets according to the degree of dysplasia. One-way ANOVA, p=0.007; *post hoc* Student-Newman-Keuls test: *p=0.046, mild dysplastic vs. severely dysplastic; **p=0.007, non-dysplastic vs. severely dysplastic.

Figure 3. Leaflet dimensions according to the degree of valvar dysplasia and collagen distribution. A. Comparison of the leaflet dimensions (proximal, medial and distal thicknesses and area) between valves with absent or mild dysplasia (in blue, with vertical lines) and valves with moderate or severe dysplasia (in red, with horizontal lines). *p=0.006, medial thickness: absent/mild vs. moderate/severe. B. Thickness values (in micrometers) measured in proximal, medial and distal points of each leaflet, according to the degree of dysplasia; valves with absent or mild dysplasia are represented by blues solid lines and valves with moderate or severe dysplasia by red dotted lines. Connected lines represent the variation of measures within the same leaflet. C. Comparison of the leaflet dimensions (proximal, medial and distal thicknesses

and area) between valves with uniform collagen distribution (in green, with vertical lines) and anarchic collagen distribution (in orange, with horizontal lines). *p=0.002, medial thickness: uniform vs. anarchic; **p=0.005, distal thickness: uniform vs. anarchic; ***p=0.005, area: uniform vs. anarchic. D. Thickness values (in micrometers) measured at proximal, medial and distal points of each leaflet according to the collagen distribution; valves with uniform collagen distribution are represented by gree solid lines and valves with anarchic collagen distribution by orange dotted lines. Connected lines represent the variation of measures within the same leaflet.

Figure 4. Histological view of the four categories of truncal valves according to the degree of dysplasia. The pattern of collagen (dark red areas) changes from uniform in the leaflet without dysplasia to anarchic in leaflets with moderate and severe dysplasia. Sirius red stain, objective magnification 1X.

Figure 1

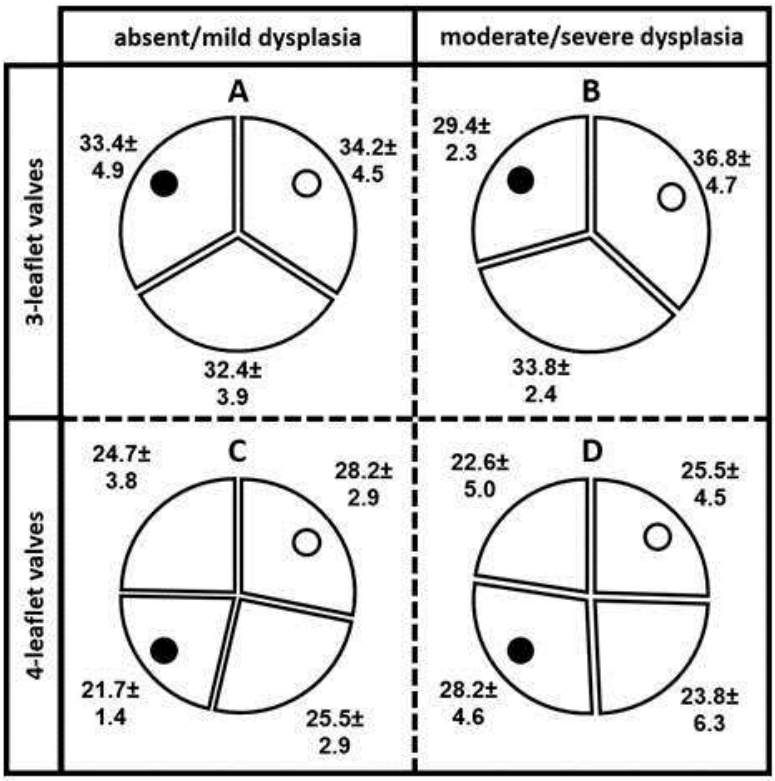


Figure 2

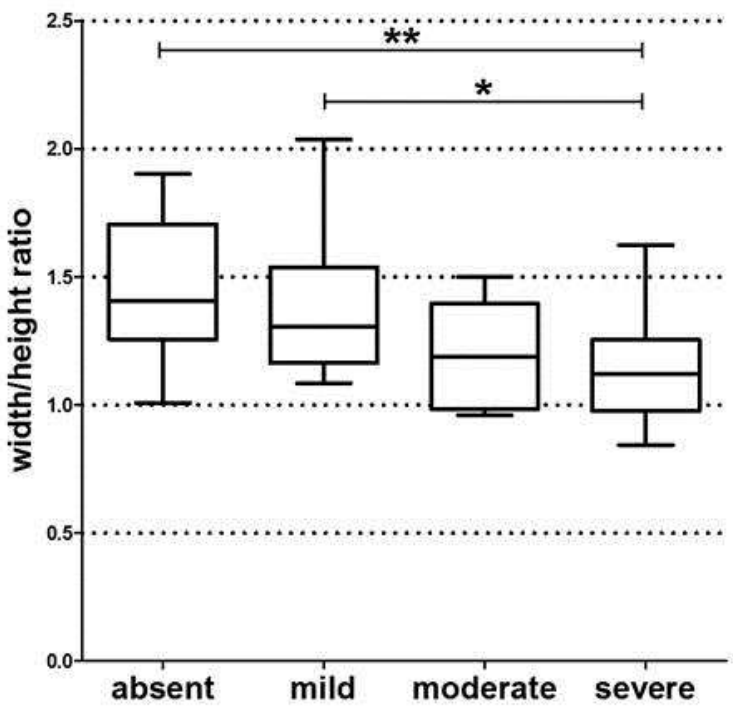


Figure 3

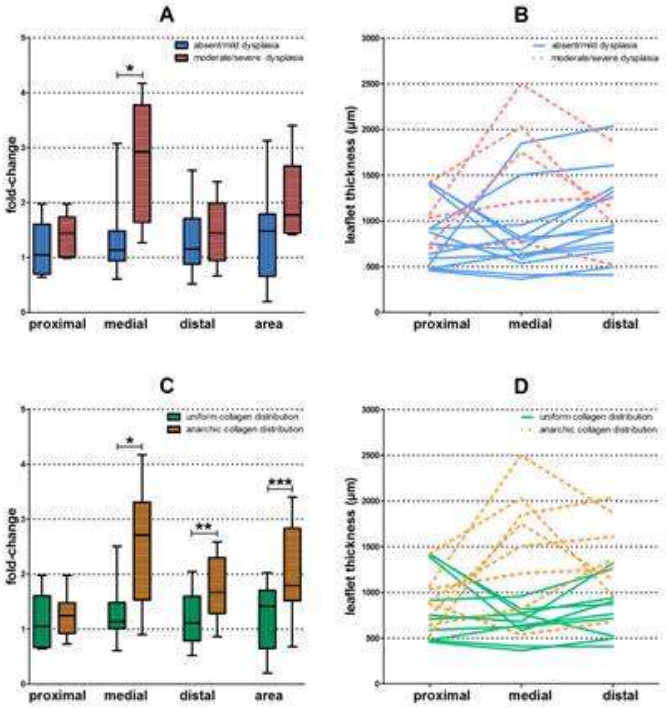


Figure 4

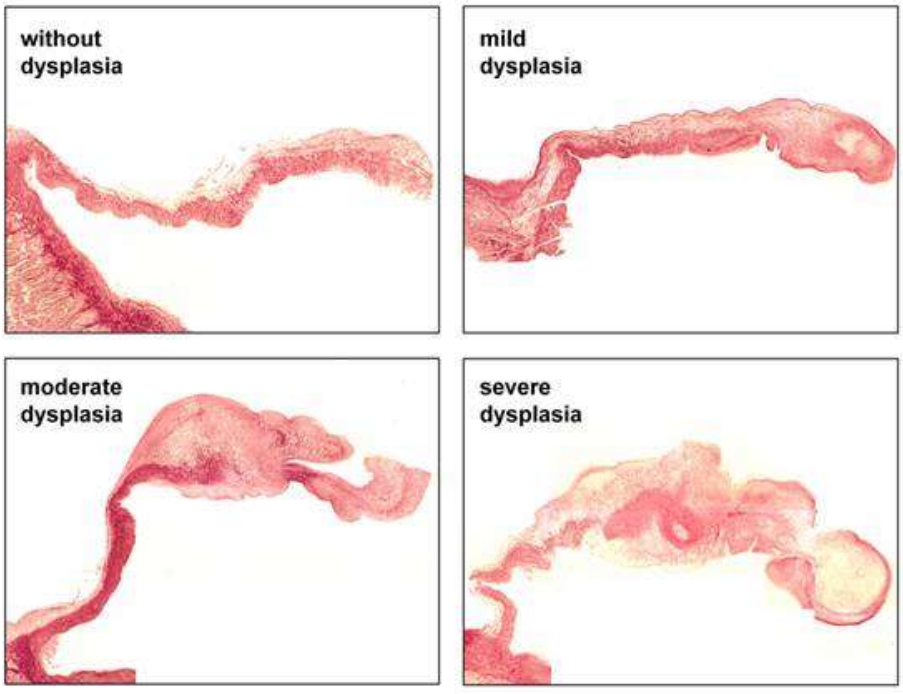
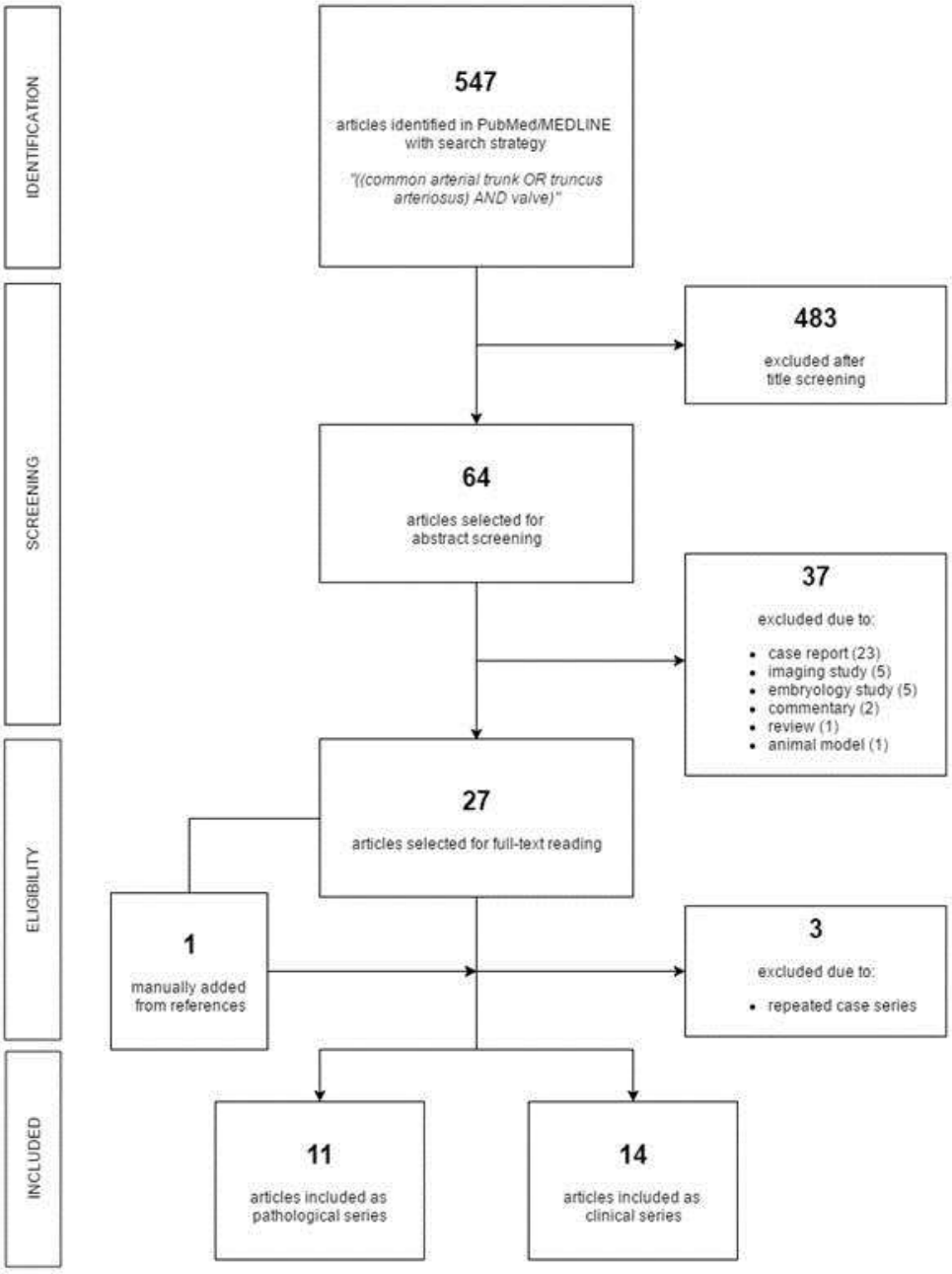


Figure 5


IDENTIFICATION
SCREENING
ELIGIBILITY
INCLUDED
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excluded after title screening
64
articles selected for abstract screening
37
excluded due to:
case report (23)
imaging study (5)
embryology study (5)
commentary (2)
review (1)
animal model (1)
27
articles selected for full-text reading
1
manually added from references
3
excluded due to:
repeated case series
11
articles included as pathological series
14
articles included as clinical series