

The relationship of bicuspid aortic valve phenotype and pattern of aortopathy: a meta-analysis



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Background - Aortopathy in patients with bicuspid aortic valve (BAV) is increasingly recognized to be a heterogeneous disease entity. Likewise, many studies suggest that the bicuspid valve morphology influences aortic dilatation, but the association of the two is controversial. We therefore, compared, in a metaanalysis, the effect of right-left coronary cusp fusion (RL) and right-non coronary cusp fusion (RN) on the pattern of aortic dilatation.

	3	tatistics for			Difference in						
Difference in means	Standard error	Variance			Z-Value	p-Value		means and 95% CI			
3.000	0.413	0.170	2.191	3.809	7.265	0.000			{		
1.100	0.275	0.076	0.561	1.639	3.997	0.000					
5 1.500	0.636	0.405	0.253	2.747	2.358	0.018			-	-	
5.000	1.073	1.152	2.896	7.104	4.658	0.000				+	-
-0.500	0.501	0.251	-1.481	0.481	-0.999	0.318					
1.848	0.708	0.501	0.460	3.236	2.610	0.009					
							-8.00	-4 .00	0.00	4.00	8.0
	in means 3.000 1.100 5 1.500 5.000 -0.500	in means error 3.000 0.413 1.100 0.275 5 1.500 0.636 5.000 1.073 -0.500 0.501	in means error Variance 3.000 0.413 0.170 1.100 0.275 0.076 5 1.500 0.636 0.405 5.000 1.073 1.152 -0.500 0.501 0.251	in means error Variance limit 3.000 0.413 0.170 2.191 1.100 0.275 0.076 0.561 5 1.500 0.636 0.405 0.253 5.000 1.073 1.152 2.896 -0.500 0.501 0.251 -1.481	in means error Variance limit limit 3.000 0.413 0.170 2.191 3.809 1.100 0.275 0.076 0.561 1.639 5 1.500 0.636 0.405 0.253 2.747 5.000 1.073 1.152 2.896 7.104 -0.500 0.501 0.251 -1.481 0.481	in means error Variance limit limit Z-Value 3.000 0.413 0.170 2.191 3.809 7.265 1.100 0.275 0.076 0.561 1.639 3.997 5 1.500 0.636 0.405 0.253 2.747 2.358 5.000 1.073 1.152 2.896 7.104 4.658 -0.500 0.501 0.251 -1.481 0.481 -0.999	in means error Variance limit limit Z-Value p-Value 3.000 0.413 0.170 2.191 3.809 7.265 0.000 1.100 0.275 0.076 0.561 1.639 3.997 0.000 5 1.500 0.636 0.405 0.253 2.747 2.358 0.018 5.000 1.073 1.152 2.896 7.104 4.658 0.000 -0.500 0.501 0.251 -1.481 0.481 -0.999 0.318	in means error Variance limit limit Z-Value p-Value 3.000 0.413 0.170 2.191 3.809 7.265 0.000 1.100 0.275 0.076 0.561 1.639 3.997 0.000 5 1.500 0.636 0.405 0.253 2.747 2.358 0.018 5.000 1.073 1.152 2.896 7.104 4.658 0.000 -0.500 0.501 0.251 -1.481 0.481 -0.999 0.318 1.848 0.708 0.501 0.460 3.236 2.610 0.009	Standard Lower Upper	Standard Lower Upper	Standard Lower Upper

Figure 1. Difference in means of indexed values of BAV RN versus BAV RL at the level of sinuses of valsalva. Pooled effects showed significant difference between the two groups.

Study name		St	Difference in					
	Difference in means	Standard error	Variance	Lower limit		Z-Value	p-Value	means and 95% CI
Avadhani 2015	-1.200	1.357	1.840	-3.859	1.459	-0.885	0.376	
Della Corte 2013	3.000	0.523	0.274	1.975	4.025	5.735	0.000	
Evangelista 2017	3.200	0.457	0.208	2.305	4.095	7.009	0.000	
Habchi 2017	2.000	0.511	0.261	0.999	3.001	3.917	0.000	
Huang 2014	3.000	1.048	1.098	0.946	5.054	2.862	0.004	
Jassal 2010	5.000	1.053	1.109	2.936	7.064	4.749	0.000	
Kang 2012	-0.600	1.008	1.015	-2.575	1.375	-0.595	0.552	
Khoo 2013	3.200	0.535	0.286	2.152	4.248	5.983	0.000	
Mahadevia 2014	-3.400	1.445	2.087	-6.231	-0.569	-2.354	0.019	
Miskoweiz 2015	4.400	1.323	1.750	1.807	6.993	3.326	0.001	
Roman 2017	4.100	0.977	0.954	2.186	6.014	4.198	0.000	
Russo 2007	12.200	1.305	1.703	9.642	14.758	9.348	0.000	
Sun 2017	3.000	0.461	0.212	2.097	3.903	6.512	0.000	
	2.941	0.606	0.367	1.753	4.128	4.852	0.000	
								-8.00 -4.00 0.00 4.00 8
								Wider in BAV RN Wider in BAV RL

Figure 3. Difference in means of non-indexed values of BAV RN versus BAV RL at the level of sinuses of valsalva. Pooled effects showed significant difference between the two groups.

Methods – Up to November 2017, a systematic search was conducted to identify all studies that compared aortic dimensions in patients with BAV. Raw mean differences in millimeters was analyzed using Comprehensive Meta Analysis software (version 3), and data was combined using randomeffect model.

Results - Twenty studies reported aortic dimensions for 3854 patients with RL and 1735 patients with RN BAV (with or without raphe). Indexed and non-indexed values were compared at the level of aortic annulus, sinuses of Valsalva, sinotubular junction and ascending aorta. Using indexed values showed only the sinuses of the Valsalva wider in RL BAV patients (mean difference 1.84 (95% CI: 0.46–3.23), p < 0.009, I2 = 90.4%) (Fig 1). Using non-indexed values showed the annulus (mean difference 1.38 (95% CI: 0.62–2.13), p < 0.000, I2 = 84%), sinuses of Valsalva (mean difference 2.94 (95% CI: 1.75–4.12), p < 0.000, I2 = 88.2%), and sinotubular junction (mean difference 1.28 (95% CI: 0.27-2.29), p < 0.013, I2 = 76.8%) wider in RL BAV patients but similar ascending aorta diameter (mean difference 0.14 (95% CI: -1.16-1.44), p < 0.83, I2 = 87.4%).

Study name		S		Difference in						
	Difference in means	Standard error	Variance	Lower limit		Z-V alue	p-Value		mean	s and 95% CI
Evangelista 2017	0.300	0.271	0.073	-0.230	0.830	1.109	0.268			
Huang 2014	3.000	0.654	0.427	1.719	4.281	4.589	0.000			<u> </u>
lassal 2010	4.000	0.641	0.411	2.744	5.256	6.240	0.000			-
(ang 2012	1.000	0.570	0.324	-0.116	2.116	1.756	0.079			├ ─□ - ┤
(hoo 2013	0.300	0.315	0.099	-0.318	0.918	0.952	0.341			-
/liskowiec 2015	2.000	1.064	1.131	-0.085	4.085	1.880	0.060			├──ф─
Roman 2017	0.600	0.636	0.405	-0.647	1.847	0.943	0.346			+
Sun 2017	1.000	0.230	0.053	0.549	1.451	4.341	0.000			
	1.383	0.385	0.149	0.627	2.138	3.587	0.000			
								-4.00	-2.00	0.00 2.00

Figure 2. Difference in means of non-indexed values of BAV RN versus BAV RL at the level of aortic anulus. Pooled effects showed significant difference between the two groups.

Study name	Statistics for each study								Difference in			
	Difference in means	Standard error	Variance	Lower limit	• •	Z-Value	p-Value	ı	means and 95% CI			
Della Corte 2014	3.000	0.523	0.274	1.975	4.025	5.735	0.000					
Evangelista 2017	1.900	0.523	0.273	0.876	2.924	3.636	0.000					
Huang 2014	0.000	1.001	1.003	-1.963	1.963	0.000	1.000			- \$		
Kang 2012	-1.600	0.905	0.820	-3.375	0.175	-1.767	0.077	-	\dashv	- 		
Khoo 2013	1.300	0.519	0.269	0.283	2.317	2.505	0.012			 - □+		
Miskowiec 2015	3.500	1.539	2.370	0.483	6.517	2.274	0.023					
Sun 2017	1.000	0.422	0.178	0.173	1.827	2.371	0.018			- □-		
	1.280	0.515	0.265	0.271	2.289	2.487	0.013					
								-4.00	-2.00	0.00 2.00 4.0		
								Wider	in BA\	/ RNWider in BAV RL		

Figure 4. Difference in means of non-indexed values of BAV RN versus BAV RL at the level of sinutubular junction. Pooled effects showed significant difference between the two groups.

Conclusions – The meta-analysis found an association between BAV morphology and the pattern of aortic dilatation, suggesting a contributing effect of the transvalvular flow direction and its relationship with the wall. This does not necessarily exclude differences of development style and tissue composition. Thus, categorizing BAV subtypes may serve as a clinical tool for optimum follow-up strategies in order to provide optimum evidence based management.