

Histopathological and morphometric analysis of surgically resected thoracic aortic aneurysm due to bicuspid aortic valve disease (BAVD)

A. Sathish Selvakumar¹, Sudheer Arava^{2,*}, Ruma Ray³, S.K. Choudhary⁴

¹Assistant Professor, ²Associate Professor, ^{3,4}Professor, ¹⁻³Dept. of Pathology, ⁴Dept. of CTVS, ¹ESIC Medical College and PGIMSR, Chennai, Tamil Nadu, ²⁻⁴All India Institute of Medical Sciences, New Delhi, India

***Corresponding Author: Sudheer Arava**

Email: aravaaiims@gmail.com

Received: 11th August, 2018

Accepted: 30th August, 2018

Abstract

Objectives: Bicuspid Aortic Valve Disease (BAVD) is a rare entity associated with ascending aortic aneurysm. We present the histopathological and morphometric data of BAVD cases who had thoracic aortic aneurysms requiring surgical intervention.

Materials and Methods: Thirteen cases of BAVD from 298 cases of ascending thoracic aortic aneurysms requiring surgical intervention between 1995 to 2009 were included. Controls were obtained from autopsy cases with normal aortic valve. Tunica intima was examined for fibrosis (FIB-1), and inflammation (INFL1). Tunica media was examined for lamellar count (LC) and inflammation (INFL 2) whereas elastic fragmentation (EF), cystic medial degeneration (CMD), medionecrosis (MN), smooth muscle disarray (SMD) and fibrosis (FIB-2) were graded by semi-quantitative grading system. CMD was subjected to morphometric area measurement. Tunica adventitia was examined for fibrosis (FIB 3) and inflammation (INFL 3).

Results: In media EF (P<.001), SMD (P=.002), FIB-2 (P=.002) and MN (P=.02) were significantly greater in cases than controls. More BAVD cases had CMD (low grade =76.92%, moderate grade = 7.69% and high grade = 15.38%), when compared to only 6 controls (46.15%) having low grade CMD, although statistically not significant. Mean LC was greater in controls than cases (P= <0.001) and CMD area by morphometry using image analysis software was lesser (P=0.041) in controls than cases. The intima and adventitia did not show any significant findings.

Conclusion: Patients with BAVD have significant degenerative medial changes of ascending thoracic aorta causing aneurysmal dilatation. They require surveillance, risk factor assessment and clinical disease management of aneurysmal complication.

Keywords: Bicuspid aortic valve, Aortic aneurysm, Tunica media, Disease management.

Introduction

Bicuspid aortic valve (BAV) is one of the most prevalent congenital cardiac malformations along with atrial septal defects.¹ BAV is associated with high occurrence of aortic valvular stenoses, regurgitation, endocarditis, aortic vessel aneurysms (10 to 35% of the cases) and dissection (4% of the cases).¹⁻⁴ It is a sporadic heterogenous disorder with an autosomal dominant (AD) inheritance pathway due to a complex pathogenesis involving genetic defects at the level of the aortic valve and vessel wall leading to the increased diameter of aortic root.⁴⁻⁶ Abbott was the first author to suggest an association between BAVD and ascending aortic aneurysms.⁷ Many explanations have been given for the increased association of BAV with aortic aneurysms and McKusick et al showed the association of bicuspid aortic valve with cystic medial degeneration of the aorta.^{6,8} Authors have also reported that the aortic wall changes in BAV could occur because of the physiologic shear and stress of the blood flow, while others have claimed it to occur in the absence of valve stenosis or incompetence and has led to the suggestion of a common developmental error responsible for the aortic wall changes.⁹⁻¹¹ Surgical intervention has been recommended for patients with BAV in view of the potential development of aortic aneurysm and dissection.^{2,12} Data on the histological and morphometric analysis of the ascending aortic wall tissue in BAV patients with thoracic aortic aneurysms are relatively less in the available literature.⁴ The

purpose of this study is to present a detailed histopathological and morphometric evaluation of 13 cases of BAV who presented with ascending thoracic aortic aneurysms and underwent surgical repair and to compare the findings with age and sex matched otherwise normal thoracic aortic tissue obtained from autopsy cases.

Materials and Methods

All tissues of thoracic aortic aneurysm vessel wall after surgical intervention were sent for pathologic assessment. The study is a cross sectional comparative study of 13 bicuspid aortic valvular disease (BAVD) from 298 cases of thoracic aortic aneurysms which required surgical intervention between 1995 to 2009 and an equal number of ascending thoracic aortic tissue samples from age and sex matched autopsy cases with normal trileaflet aortic valve who died of non-cardiovascular illness which were procured after appropriate informed consent. Other cases due to varied etiologies were excluded. All tissues of thoracic aortic aneurysm vessel wall after surgical intervention were sent for pathologic assessment. Tissue samples obtained approximately 1.0 cm distal to the sinotubular junction in the ascending aorta were received in closed labelled container containing 10% buffered formalin solution. Four to five-micron sections were cut from the paraffin embedded tissues for light microscopy. They were stained by, Haematoxylin and Eosin (H&E), Verhoeff's Van Gieson (VVG), Masson's Trichrome (MT) and Alcian blue –

Periodic Acid Schiff (AB-PAS). Both cases and controls were subjected to histopathological and morphometric evaluation by two observers and consensus was obtained, and in cases of discrepancies after re-evaluation. The data were subjected to appropriate statistical analysis. Ethical clearance was obtained.

Histopathological Evaluation: All the 13 BAVD and equal number of control cases were examined for the following variables in the intima, media and adventitia respectively. The tunica intima was evaluated for fibrosis (FIB 1-increase in collagen content), inflammation (INFL 1-granulomatous/ non-granulomatous). The tunica media was evaluated for lamellar count (LC- manual counting of lamellar units and a lamellar unit is comprised of elastic lamellae, smooth muscle cells and interlamellar connective tissue matrix), elastic fragmentation (EF- fragmentation of elastic fibre network), cystic medial degeneration (CMD-accumulation of mucoid substances causing formation of cyst like spaces in media and is also known as myxoid extracellular matrix accumulation), smooth muscle disarray (SMD-alteration in the normal concentric parallel orientation of smooth muscle cells), fibrosis (FIB 2-increase in collagen content), medionecrosis (MN- loss of medial smooth muscle cell nuclei) and inflammation (INFL 2- granulomatous/non-granulomatous).^{9,14} The tunica adventitia was evaluated for fibrosis (FIB 3- increase in the collagen content) and inflammation (INFL 3-granulomatous/non-granulomatous). The above parameters were subjected to qualitative assessment (QLA), semi-quantitative assessment (SQTA) and quantitative assessment (QTA). In the QLA the presence or absence of the parameters were noted down. A value of 1(YES) was given if present and 0 (NO) if absent. All the parameters of intima, inflammation of media and all parameters of adventitia were assessed qualitatively. In SQTA each variable was graded from 0 to 3 according to the severity (0 and 1- low grade, 2- moderate grade and 3- high grade) as per the criteria given in the semiquantitative grading system suggested by Mauro de Sa et al.^{9,14} The grading of EF, CMD, SMD, FIB 2 and MN was done using the same microscopic settings at 200X magnification (NIKON, Microscope systems, Japan). The QTA had manual counting of the lamellar units [Lamellar Count (LC)] at 100X magnification from intimal aspect towards adventitia in two worst affected areas and mean was taken along with the morphometric assessment of CMD area. Morphometric analysis was done by computerised image analysis system using Image pro-plus analysis software 4.1 (Media

Cybernetics Corporation, USA). All the images of the representative areas were captured with a 12-bit digital camera using 200X magnification with the same microscopic settings. Slides with CMD in AB-PAS stain were chosen from each case and the best representative area was identified for area measurement (in μm^2). Appropriate statistical analysis was performed for the individual parameters between the study and the control groups using Statistical Package for Social Sciences (SPSS) version 21.

Results

The characteristics of the study and control population shows that they are comparable as indicated by the statistically non-significant p values by Chi square test of significance (Table 1). Table 2 shows the comparison of the various intimal, medial and the adventitial parameters between the BAVD cases and controls by Chi square test of significance. The tunica intimal and adventitial parameters did not have any statistically significant changes between the two groups. However, the severity of EF ($P < 0.001$), SMD ($P = 0.002$), FIB 2 ($P = 0.002$) and MN ($P = 0.020$) were significant in BAVD cases than the controls (Table 2). More number of cases had CMD (low grade = 76.92%, moderate grade = 7.69% and high grade = 15.38%), when compared to only 6 controls (46.15%) having low grade CMD, although the semi quantitative analysis was statistically not significant ($P = 0.109$) (Table 2). The comparison of mean lamellar units manual count and CMD area measurement by morphometry between the cases and controls as performed by Student's t test (independent sample) showed that the mean lamellar count is greater among the controls and the CMD area (in μm^2) by morphometry is lesser among them (Table 3). The box and whisker plot show the comparison of mean lamellar counts between cases and controls and it is seen that the controls have a greater lamellar count when compared to the cases and the box and whiskers are non-overlapping. (Fig. 1). The box and whisker plot of the CMD area morphometry between the cases and controls depicts that the CMD morphometry is greater among the cases. (Fig. 2) and there are also several outliers seen in the distribution. The difference between the cases and controls is minimal, but non-overlapping. Table 4 shows all the results of the various intimal, medial and adventitial parameters assessed by the qualitative #, semi quantitative \$ and quantitative assessment * (LC and morphometric area measurement) methods.

Table 1: Characteristics of the study population

Characteristic	Categories	Cases	Control (p value non-significant by Chi square test of significance)
Age	10 – 20 years	4	2
	21 – 30 years	2	5
	31 – 40 years	2	3
	>40 years	5	3
Sex	Male	3	3
	Female	10	10

Table 2: Pathological features of the aorta among cases and controls

Pathological Features	Cases	Control	P value
Intimal FIB1	2	0	0.240
Medial EF			<0.001
1	7	1	
2	4	0	
3	1	0	
Medial CMD			0.109
1	8	6	
2	1	0	
3	2	0	
Medial SMD			0.002
1	8	1	
2	2	0	
Medial (FIB2)	9	1	0.002
Medial MN	5	0	0.020
Adventitial (FIB3)	3	1	0.297
Adventitial (INFL 3)	2	1	0.5

Table 3: Comparison of lamellar count and CMD morphometry

S. No	Characteristic	Cases (mean ± SD)	Control (mean ± SD)	p value
1.	Lamellar Count	28.08 ± 9.56	45.62 ± 5.18	<0.001
2.	Cystic Medial Degeneration Morphometry	4976.77 ± 7548.8	436.31 ± 504.22	0.041

Table 4: Findings of the qualitative #, semiquantitative \$ and quantitative assessment * (LC and morphometric area measurement) methods of the various intimal, medial and adventitial parameters. [Yes (Y)= 1, No (N)= 0, Grade 0 and Grade 1 together = Low Grade (LG), Grade 2= Moderate Grade (MG), Grade 3= High Grade (HG)]

S. No	CA and CO	Age	Sex	Intima		Media						Adventitia		CMD *	
				FIB (1) #	INFL (1) #	INF L (2)	EF\$	CMD\$	SM D\$	FIB (2) \$	MN \$	LC*	FIB (3) #		INFL (3) #
1.	CA1	18	M	0	0	0	1	1	1	1	0	36	0	0	2839
	CO1	21	M	0	0	0	1	1	1	1	0	36	0	0	1236
2.	CA2	18	M	0	0	0	1	1	1	1	1	26	0	0	2142
	CO2	21	M	0	0	0	0	0	0	0	0	48	0	0	0
3.	CA3	11	M	0	0	0	0	0	0	0	0	28	0	0	0
	CO3	19	M	0	0	0	0	0	0	0	0	50	0	0	0
4.	CA4	31	F	0	0	0	2	1	1	1	1	32	0	0	1725
	CO4	30	F	0	0	0	0	0	0	0	0	47	0	0	0
5.	CA5	36	M	0	0	0	1	0	1	1	0	28	0	0	0
	CO5	35	M	0	0	0	0	1	0	0	0	45	0	0	798
6.	CA6	22	M	1	0	0	1	1	1	1	0	30	1	0	935
	CO6	23	M	0	0	0	0	0	0	0	0	46	0	0	0
7.	CA7	41	M	0	0	0	1	1	1	1	1	28	1	1	1682
	CO7	40	M	0	0	0	0	0	0	0	0	55	0	0	0
8.	CA8	46	M	1	0	0	1	1	1	1	0	34	0	0	1598
	CO8	45	M	0	0	0	0	1	0	0	0	42	0	0	837
9.	CA9	49	M	0	0	0	2	3	2	0	0	18	0	0	24844
	CO9	40	M	0	0	0	0	0	0	0	0	49	1	0	0
10.	CA10	14	M	0	0	0	3	3	2	1	1	5	0	1	17425
	CO10	20	M	0	0	0	0	1	0	0	0	48	0	1	762
11.	CA11	25	F	0	0	0	2	2	1	1	1	24	1	0	7385
	CO11	26	F	0	0	0	0	0	0	0	0	48	0	0	0
12.	CA12	42	F	0	0	0	2	1	0	0	0	46	0	0	1945
	CO12	43	F	0	0	0	0	1	0	0	0	41	0	0	1043
13.	CA13	58	M	0	0	0	1	1	0	0	0	30	0	0	2178
	CO13	51	M	0	0	0	0	1	0	0	0	38	0	0	996

CA-cases, CO-control, Age in years, M-Male, F-Female, Lamellar count- Manual count, CMD- Morphometric measurement (μm^2)

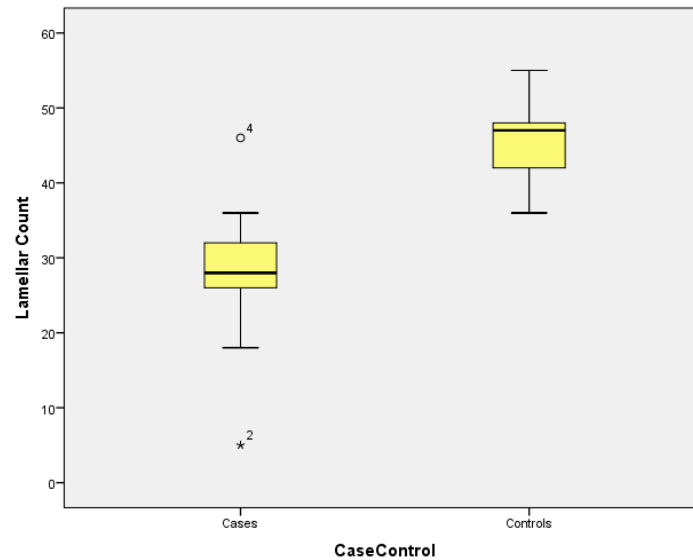


Fig. 1: Boxplot of lamellar count comparing cases and controls

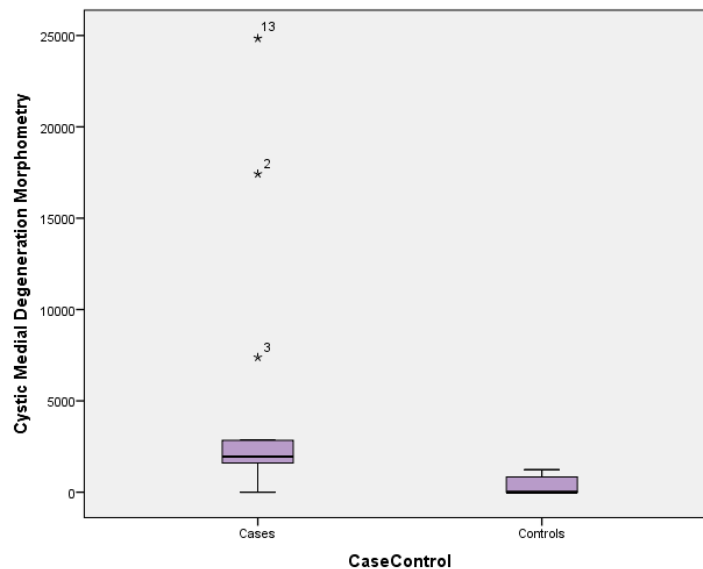


Fig. 2: Boxplot of cystic medial degeneration morphometry comparing cases and controls

Discussion

Bicuspid aortic valvular disease (BAVD) is a clinically heterogeneous entity with patients presenting from infancy to late adulthood comprising complications involving aortic valve to aortic vessel wall.⁷ The age of our cases ranged from 11 to 58 years. It has a prevalence of 1% to 2% in the general population with a 2:1 to 4:1 predilection for males: females and our study had a 3:1 male predominance.^{2,7} Dilatation of aortic root and ascending aorta is more common and has an incidence of 30 to 70% in BAVD patients.⁷ The tunica intima and tunica adventitia were examined for the presence of inflammation and fibrosis but did not reveal any statistically significant findings when compared with the control group. As the degenerative

changes of tunica media is at the crux of aortic dilatation, we discuss on the various degenerative parameters observed in the tunica media.

The foremost findings in this study are the increased severity of EF (<0.001), CMD (0.109), SMD (0.002), MN (0.020) and FIB2 (0.002) in the tunica media of BAVD cases when compared with the control group who had normal tricuspid aortic leaflets (Table 2, Fig. 3 and Fig. 4). Similar findings have been detailed by Mauro de Sa et al in 1999 who concluded that the patients with BAVD have severe degenerative changes in the media of the ascending aorta and main pulmonary artery than patients with tricuspid aortic valve disease.⁹ A single lamellar unit consists of two parallel elastin fibers, the smooth muscle cells, collagen

fibers and the ground substance present in-between.^{13,14} The average number of lamellar units in the ascending thoracic aorta ranges from 29 to 56 units during the adulthood.^{14,15} The comparison between the mean lamellar units (manual count) of the cases and controls in our study showed statistically significant reduction in the LC of BAVD cases ($p < 0.001$). This can be attributed to the increased EF ($p < 0.001$) which have led to the medial weakening and aneurysmal dilatation of aortic wall.¹⁴⁻¹⁷ McKusick in 1972 pointed out the association of CMD (also now known as myxoid extracellular matrix accumulation), in the ascending aorta of BAVD patients and the same was also described in studies by Lindsay J in 1988 and Mauro de Sa et al in 1999.^{6,9,17,18} In our study although the CMD in BAVD cases was not statistically significant when compared with the control group, but more number of BAVD cases had high grade CMD and only low grade CMD was present in the controls studied. The morphometric analysis showed that the area of CMD measured was significantly high in the cases when compared with the control group and this finding correlate with the various studies suggesting a primary role of CMD in the aortic aneurysmal dilatation.^{9,18-21} This finding of CMD could be due to the combination of arterial tree developmental defects.^{6,17,18} Although, 46% of our controls with four subjects aged ≥ 35 years, had low grade CMD, the change could be explained by age related degenerative changes as suggested by Schlatmann TJM and Becker AE in 1977 and few other studies.^{9,13,14,21,22} No association between the age and degenerative changes was observed in annuloaortic patients or normal subjects by Savunen and Aho in 1985.^{22,23} Our study had both moderate grade and high-grade EF and CMD in both the younger (< 20 years) and older (> 40 years) cases, which suggests that age related changes alone is not enough for the complete expression of CMD in the media of BAVD.

Many studies have described an increased occurrence of changes like smooth muscle disarray (SMD), extracellular matrix disarray, smooth muscle nuclei loss by apoptosis i.e medionecrosis (MN) and asymmetric dilatation of aorta in BAVD patients.^{7,9,23-25} Our study had similar findings of statistically significant SMD (0.002) and MN (0.020) in BAVD cases when compared to the autopsy controls. The lesser differentiation of the vascular smooth muscle cell (VSMC) layer, its apoptosis (MN), disorderedly arrangement (SMD) and its dysfunction in the aortic wall appears to play an important pathogenetic role in BAVD.^{2,7,25-27} These histological changes in BAVD appear to be in between the changes seen in the aortopathy of tricuspid aortic valves and Marfan's patients.⁷ In Marfan syndrome these changes are seen extensively and also there is a higher than normal prevalence of BAVD which could be explained by the abnormality of the microfibrillar protein

found in both the conditions.^{7,9} All our cases had no inflammation which was similar to the observations available in the literature.^{9,18,19} These changes in the media is greatly influential in the reduction of the cohesive and tensile strength and is responsible for the increased occurrence of aortic root dilatation, ascending aorta aneurysms and dissection necessitating an early surgical intervention.^{9,27,28}

Studies on the ascending aortic medial degenerative changes in annuloaortic ectasia, ascending aortic aneurysms and aortic dissection have all described similar features and all these entities could be associated with BAVD clinically.^{9,22,23,28-30} Larson and Edwards showed that the occurrence of proximal aortic dissection was more in patients with BAV when compared with the necropsy population.¹¹ In a two-dimensional echocardiographic study on 83 individuals with BAV having subgroups with functionally normal, regurgitant or stenotic aortic valves, all subgroups had noticeably increased aortic root size.^{30,31} Since the ascending aorta, aortic arch and semilunar valves are derived from the neural crest, it could be surmised that the BAV and aortic root dilatation reflect a common developmental defect leading to an intrinsic fragility, although the available genetic information is limited at present.^{30,31} The convexity of the ascending aorta and the aortic arch makes it highly susceptible for the medial degenerative changes and therefore the aneurysmal dilatation.⁷ Degenerative changes can also be noted in the aortic root and valve, pulmonary root, ascending aorta and aortic arch because of the common embryologic origin the conotruncus and the anomalous migration of the cells from the neural crest.⁹ However not all the patients with BAV suffer with aortic aneurysms and not all patients with aortic aneurysms have abnormal valve function in BAVD.^{2,7} Consistent with all the above studies we have also found increased severity of the degenerative medial changes in more percentage of BAVD cases than the controls. Periodical radiological assessment becomes essential to monitor the aortic dilatation, assess the risk of aortic rupture and to plan for the surgical intervention as per the available guidelines.^{7,31,32} Familial links in BAVD families suggest an autosomal dominant inheritance with reduced penetrance; however no causative genes have been identified although the role of NOTCH1 has been suspected.⁷ The etiopathogenesis remains still unclear due to the complex roles of congenital, genetic, and/or connective tissue abnormalities making the clinical management very difficult, although few studies have elucidated the genetic defects in hamster aortic valve studies.^{7,32,33}

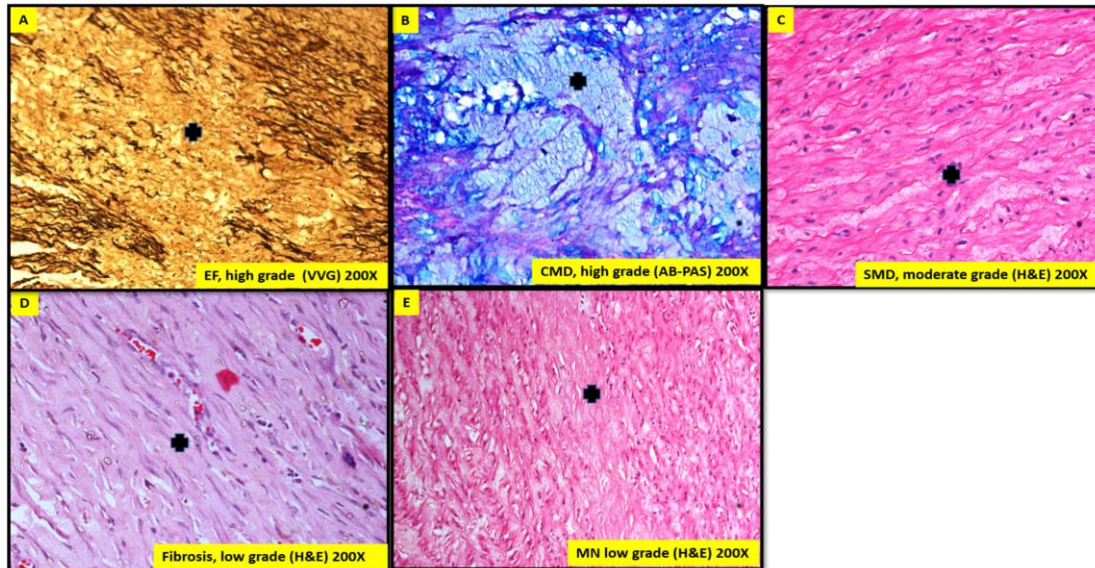


Fig. 3: Histopathological findings in the tunica media of BAVD cases

A) Cross show Grade 3 EF area. B) Cross show Grade 3 CMD. C) Cross show Grade 2 SMD. D) Cross show Grade 1 fibrosis. E) Cross show Grade 1 MN.

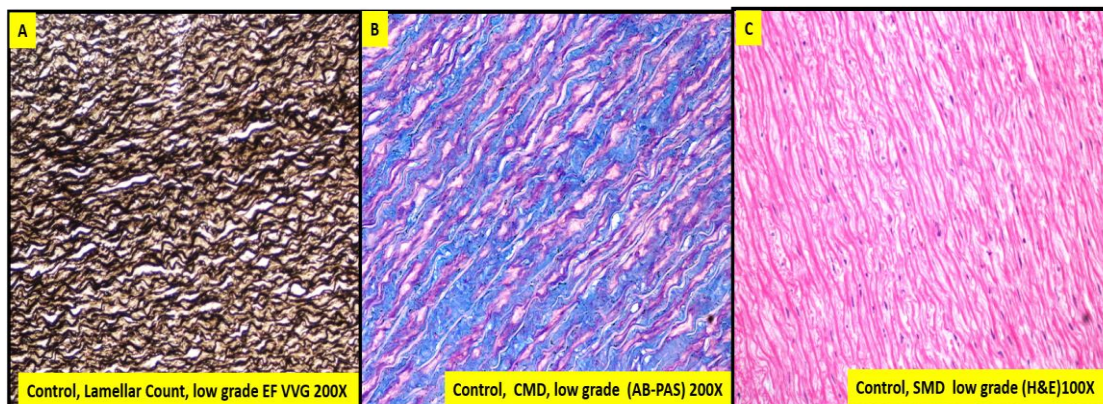


Fig. 4: Histopathological findings in the tunica media of control cases; A, B and C show low grade EF, CMD and SMD in controls examined.

Conclusion

The medial degenerative changes in BAVD patients definitely holds them at increased risk for aortic dilatation, aneurysm formation, and dissection, but all the patients do not behave similarly. Both the medical and the surgical management have to be tailored according to the individual BAVD patients as per the available guidelines. Further research to fill up the knowledge gaps in understanding the pathophysiology and the tissue biology of BAVD will help to optimize the management protocols.

Limitations of the Study

The main limitation of this study is its sample size because of the complex pathogenesis of medial degenerative changes and the rarity of the disease. It therefore requires a higher number of arterial wall samples to determine the extent of the medial changes. The other limitation is the

histological assessment of only a small segment of ascending aorta.

Acknowledgements

Dr. Vijayaprasad Gopichandran, for helping in statistical analysis.

Conflict of Interest: Nil.

References

1. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol* 1997;30(7):1809-1812.
2. Pisanoa C, Maresic E, Balistrerib CR, Candoreb G, Merloa D, Fattoucha K et al. Histological and genetic studies in patients with bicuspid aortic valve and ascending aorta complications. *Interact Cardiovasc Thorac Surg* 2012 Mar;14(3):300-306.

3. Grewal N, Franken R, Mulder BJM, Goumans MJ, Lindeman JHN, Jongbloed MRM et al. Histopathology of aortic complications in bicuspid aortic valve versus Marfan syndrome: relevance for therapy?. *Heart Vessels* 2016;31(5):795–806.
4. Bechtel JFM, Noack F, Sayk F, Erasmi AW, Bartels C, Sievers HH. Histopathological Grading of Ascending Aortic Aneurysm: Comparison of Patients with Bicuspid versus Tricuspid Aortic Valve. *J Heart Valve Dis* 2003;12(1):54–61.
5. Mancuso D, Basso C, Cardaioli P, Thiene G. Clefted bicuspid aortic valve. *Cardiovasc Pathol* 2002;11(4):217–220.
6. McKusick VA. Association of congenital bicuspid aortic valve and Erdheim's cystic medial necrosis. *Lancet* 1972;6(1):1026–1027.
7. Losenno KL, Goodman RL, Chu MWA. Bicuspid Aortic Valve Disease and Ascending Aortic Aneurysms: Gaps in Knowledge. *Cardiol Res Pract* Vol. 2012 Aug; Article ID 145202, page 1-16 pages. <https://doi.org/10.1155/2012/145202>.
8. Guntheroth WG. A critical review of the American College of Cardiology/American Heart Association practice guidelines on bicuspid aortic valve with dilated ascending aorta. *Am J Cardiol* 2008;102(1):107–110.
9. Mauro de Sa, Moshkovitz Y, Butany J, David TE. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the Ross procedure. *J Thorac Cardiovasc Surg* 1999;118(4):588–594.
10. Stebbens WE. Structural and architectural changes during arterial development and the role of hemodynamics. *Acta Anat* 1996;157(4):261–274.
11. Larson EW, Edwards WD. Risk factors for aortic dissection: A necropsy study of 161 cases. *Am J Cardiol* 1984;53 (6):849–855.
12. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circ* 2010;121(13):e266–369.
13. Halushka MK, Angelini A, Bartoloni G, Basso C, Batoroeva L, Bruneval P et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association For European Cardiovascular Pathology: II. Noninflammatory degenerative diseases - nomenclature and diagnostic criteria. *Cardiovasc Pathol* 2016;25(3):247–257.
14. Schlattmann TJ, Becker AE. Histologic changes in the normal aging aorta: Implications for dissecting aortic aneurysm. *Am J Cardiol* 1977;39(1):13–20.
15. Wolinsky H, Glagov S. Comparison of abdominal and thoracic aortic medial structure in mammals. Deviation of man from the usual pattern. *Circ Res* 1969;25(6):677–686.
16. Ruddy JM, Jones JA, Ikonomidis JS. Pathophysiology of Thoracic Aortic Aneurysm (TAA): Is it not one uniform aorta? Role of Embryologic Origin. *Prog Cardiovas Dis* 2013;56(1):68–73.
17. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J Clin Pathol* 2002;55 (7):481–486.
18. Lindsay J. Coarctation of aorta, bicuspid aortic valve and abnormal ascending aortic wall. *Am J Cardiol* 1988;61(1):182–184.
19. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve. Pathophysiology, molecular biology, and clinical implications. *Circ* 2009;119(6):880–890.
20. Bonderman D, Gharehbaghi-Schnell E, Wollenek G, Maurer G, Baumgartner H, Lang IM. Mechanisms underlying aortic dilatation in congenital aortic valve malformation. *Circ* 1999;99(16):2138–2143.
21. Isselbacher EM. Thoracic and abdominal aortic aneurysms. *Circ* 2005;111(6):816–828.
22. Carlson RG, Lillehei CW, Edwards JE. Cystic medial necrosis of the ascending aorta in relation to age and hypertension. *Am J Cardiol* 1970;25(4):411–415.
23. Savunen T, Aho HJ. Annulo-aortic ectasia. Light and electron microscopic changes in aortic media. *Virchow Arch A Pathol Anat Histopathol* 1985;407(3):279–288.
24. Bauer M, Glicch V, Siniawski H, Hetzer R. Configuration of the ascending aorta in patients with bicuspid and tricuspid aortic valve disease undergoing aortic valve replacement with or without reduction aortoplasty. *J Heart Valve Dis* 2006;15(5):594–600.
25. Della Corte A, Quarto C, Bancone C, Castaldo C, Di Meglio F, Nurzynska D et al. Spatiotemporal patterns of smooth muscle cell changes in ascending aortic dilatation with bicuspid and tricuspid aortic valve stenosis: focus on cell-matrix signaling. *J Thorac Cardiovasc Surg* 2008;135(1):8–18.
26. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *Am J Coll Cardiol* 1991;17(3):712–716.
27. Nataatmadja M, West M, West J, Summers K, Walker P, Nagata M, Watanabe T. Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in Marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm. *Circulation*. 2003;108 Suppl 1:II329–34.
28. Hirst AE, Gore I. Is cystic medial necrosis the cause of dissecting aortic aneurysm?. *Circ* 1976;53:915–916.
29. Gore I. Dissecting aneurysms of the aorta in persons under forty years of age. *Arch Pathol* 1953;55:1–13.
30. Klima T, Spjut HJ, Coelho A, Gray AG, Wukasz DC, Reul GJ et al. The morphology of ascending aorta aneurysms. *Hum Pathol* 1983;14(9):810–817.
31. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. Association of aortic dilatation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol* 1992;19(2):283–288.
32. Pachulski RT, Chan KL. Progression of aortic valve dysfunction in 51 adult patients with congenital bicuspid aortic valve: assessment and follow up by Doppler echocardiography. *Br Heart J* 1993;69:237–240.
33. Fernandez B, Duran AC, Fernandez-Gallego T, Fernandez MC, Such M, Argue JM et al. Bicuspid aortic valves with different spatial orientation of the leaflets are distinct etiological entities. *J Am Coll Cardiol* 2009;54(24):2312–2318.

How to cite this article: Selvakumar AS, Arava S, Ray R, Choudhary SK. Histopathological and morphometric analysis of surgically resected thoracic aortic aneurysm due to bicuspid aortic valve disease (BAVD). *Indian J Pathol Oncol* 2019;6(1):9–15.