Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Original Article

Risk factors for degenerative aortic valve disease in India: A case control study

Gp Capt D.S. Chadha^{a,*}, Brig S.K. Malani^b, Brig P. Bharadwaj, VSM^c,
G. Karthikeyan^d, Brig P.K. Hasija^e

^a Senior Advisor (Medicine & Cardiology), Command Hospital (Air Force), Bangalore, India

^b Consultant (Medicine & Cardiology), Command Hospital (Central Command), Lucknow, UP, India

^c Consultant (Medicine & Cardiology), Military Hospital (Cardio Thoracic Centre), Pune 411040, India

^d Professor (Cardiology), AIIMS, Delhi, India

^e Brig Med (MG & G Area), Mumbai, India

ARTICLE INFO

Article history:

Received 31 July 2016

Accepted 9 March 2017

Available online 18 April 2017

Keywords:

Aortic valve stenosis

Coronary artery disease

Risk factors

ABSTRACT

Background: Degenerative aortic valve disease often co-exists with coronary artery disease (CAD) and studies done in western populations have shown that it shares the same risk factors which cause CAD. However little is known in this context among Asian Indians. The current study looks into the risk factors of degenerative aortic valve disease in Asian Indian population.

Methods: Ninety-one consecutive patients with severe aortic stenosis (AS) reporting for left heart catheterization prior to valve replacement surgery at a tertiary care centre were recruited for the study. They were compared with age and sex matched controls selected from a database of 3200 patients referred for elective diagnostic left heart catheterization for suspected CAD. Following traditional cardiovascular risk factors were assessed in all patients: age, gender, family history of CAD, smoking history, presence of diabetes, hypertension and dyslipidemia.

Results: The mean age of the study population was 57.8 ± 8.2 years (range, 40–80 years). Smoking, family history of CAD and hypercholesterolemia were significantly more prevalent in patients with degenerative AS compared to those with normal valves. No significant difference was noted in the presence of diabetes mellitus. On multivariate logistic regression, family history of premature CAD (OR 3.68; CI 1.38–9.78) smoking history (OR, 2.56; CI, 1.21–5.39), and raised LDL levels (OR, 5.55; CI, 2.63–11.69) were independently associated with the aortic stenosis patient cohort.

Conclusions: The study showed a significant association of cardiovascular risk factors with aortic stenosis independent of age and gender in Asian Indian patients.

© 2017 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

* Corresponding author.

E-mail address: agiamu@gmail.com (D.S. Chadha).

<http://dx.doi.org/10.1016/j.mjafi.2017.03.004>

0377-1237/© 2017 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

Introduction

Degenerative aortic valve disease (DAVD) leading to aortic stenosis (AS) is commonly noted in elderly population. It is associated with an increased risk of death due to cardiovascular causes.¹ With increasing longevity, the occurrence of DAVD in India is increasing.² Coronary artery disease (CAD) often co-exists with DAVD and shares the same risk factors which are responsible for coronary artery disease.^{1,3–6} It is now hypothesized that this disease may be due to an active inflammatory process like atherosclerosis unlike previously held thought of age being the only risk factor responsible for it.^{2–6}

However, despite there being evidence linking DAVD and atherosclerosis, these disease processes are not synonymous for only about 50% of patients with DAVD have significant CAD.¹ On the other hand, most patients with CAD do not have DAVD. A lot of work has been done in developed countries in patients with DAVD because of its high prevalence; however, no study is available from India in this group of patients. Hence there is a need to examine the relationship between cardiovascular risk factors and DAVD. In the current study we look at cardiovascular risk factors in age and sex matched patients with and without DAVD with severe aortic stenosis.

Materials and methods

Ninety-one consecutive patients of DAVD with severe aortic stenosis (AS) and a similar number of age and sex matched patients undergoing elective diagnostic coronary angiography for suspected CAD at a tertiary care hospital were included in the study.

The diagnosis of DAVD was performed on the basis of clinical criteria (absence of history of any acquired or congenital valvular heart disease) and on the echocardiographic findings of morphological changes suggestive of AS (thickened aortic cusps with reduced systolic opening). Severe AS was defined as the aortic valve area $<0.75 \text{ cm}^2$ calculated using continuity equation.⁷ Peak and mean gradients of $>64 \text{ mmHg}$ and $>50 \text{ mmHg}$ respectively were also used to define severe AS. Patients with moderate AS, severe aortic regurgitation and other valvular lesion were excluded from the study. Cases were pair matched for age and gender with those without aortic valve disease out of a pool of patients referred for elective diagnostic coronary angiogram for suspected CAD. Written consent was taken from all the patients for participating in the study.

Coronary angiography

Coronary angiography was performed in all the patients in order to define the extent and severity of disease. At least 70% reduction in the diameter of major epicardial coronary arteries [left anterior descending (LAD) or left circumflex (LCx) or right coronary artery (RCA)] and their branches was used as definition of significant coronary artery disease. In the case of left main coronary artery (LMCA) the definition was revised to include cases which had 50% reduction of the luminal

diameter. Depending on coronary angiogram patients were classified into those with or without significant CAD. In those with obstructive coronary lesions the extent of disease was further classified into single vessel, double vessel or triple vessel disease based on the number of coronary arteries affected.

Patient characteristics

The medical records of cases and controls were reviewed for the cardiovascular risk factors which included age, gender, family history of premature CAD, smoking history, presence of diabetes mellitus and hypertension. A complete lipid profile was done to record total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL) and high-density lipoproteins (HDL) prior to the coronary angiogram. American college of cardiology criteria was used to diagnose dyslipidemia.⁸ Diagnosis of diabetes mellitus (DM) was made if the fasting glucose was $>126 \text{ mg/dL}$, or if the patient was already on treatment for same. Patients with either systolic pressure $>140 \text{ mmHg}$ and/or diastolic pressure $>90 \text{ mmHg}$ were classified as hypertensive while history of smoking was defined as >10 pack-years of smoking. Body mass index (BMI) was computed for all patients and obesity was defined as BMI $>30 \text{ kg/m}^2$. Family history of premature CAD was defined as disease first degree male relative of <55 years and first degree female relative of <65 years of age.

Statistical analysis

Demographic and clinical characteristics are presented as mean $\pm$ standard deviation (SD) or as proportions as appropriate. An independent t-test was used for continuous variables and Chi-square test for categorical variables. Conditional logistic regression adjusted for matching variables (age, gender) were used to calculate the odds ratios (OR) along with their 95% confidence intervals (CI). Multivariable logistic regression was performed to identify independent predictors of DAVD. A p value of <0.05 was considered significant. SAS software package version 9.2, SAS Institute, Cary was used for analysis.

Results

The study population consisted of 91 patients of DAVD with severe AS; the mean age of study population was 57.7 ± 8.3 years (range, 40–80 years). The traditional coronary risk factors of the study population are as given in Table 1. Majority of the study population was male (71.4%). Significant CAD was diagnosed in 24.2% of patients with DAVD.

In patients with DAVD dyslipidemia, (elevated cholesterol, elevated LDL and low HDL levels) history of smoking, and family history of premature CAD were significantly more prevalent than controls ($p < 0.01$). No significant difference was noted in the presence of diabetes and the levels of triglycerides. Hypertension was significantly higher in the controls compared to the cases ($p = 0.06$).

When limiting the analysis to patients with DAVD with normal coronaries, dyslipidemia (elevated cholesterol,

Table 1 – Traditional cardiovascular risk factors in patients with degenerative aortic valve disease (DAVD) compared with control.

Variables	DAVD ^a (n = 91)	Control ^a (n = 91)	p value	OR (95% CI) ^b
Age (years)	57.7 ± 8.3	57.9 ± 8.2		
Males	71.4	71.4		
CAD	24.2	24.2		
Body mass index	23.2 ± 2.1	22.9 ± 1.9	0.60	1.23 (0.72, 1.28)
Smoking	46.2	26.4	<0.01	2.52 (1.33, 4.85)
Diabetes mellitus	33.0	29.7	0.64	1.16 (0.62, 2.18)
Hypertension	37.4	54.9	0.02	0.49 (0.27, 0.89)
Family history of premature coronary artery disease	27.5	9.9	<0.01	3.56 (1.54, 8.20)
Cholesterol in mg/dL (per SD increase)	216.1 ± 34.2	172 ± 37.3	<0.001	4.18 (2.67, 6.56)
Low density lipoprotein in mg/dL (per SD increase)	134.6 ± 30.7	109.6 ± 31.4	<0.001	2.57 (1.75, 3.78)
High density lipoprotein in md/dL (per SD increase)	38.7 ± 3.6	41.0 ± 4.5	<0.001	0.52 (0.36, 0.75))
Triglycerides in md/dL (per SD increase)	147.4 ± 42.7	142.8 ± 48.9	0.50	1.11 (0.82, 1.48)

^a Characteristics expressed as means (SD) or percentage.

^b Each model was adjusted for the matching age, gender and presence of angiographic CAD, and thus odds ratio for these variables holds no meaning.

Standard deviation (SD) for cholesterol (41.82 mg/dL), LDL (33.41 mg/dL), and HDL (4.23 mg/dL) in the overall study sample were used to estimate odds ratio.

Table 2 – Traditional cardiovascular risk factors in patients with degenerative aortic valve disease (DAVD) and controls with normal coronaries.

Variables	DAVD (n = 71) ^a	Control (n = 71) ^a	p value	OR (95% CI)
Age (years)	56.2 ± 7.1	56.4 ± 7.3	0.87	
Sex (males) (%)	71.8	71.8		
CAD (%)	0.0	0.0		
Smoking (%)	45.1	28.2	0.03	2.25 (1.08, 4.70)
DM (%)	36.6	26.8	0.20	1.58 (0.77, 3.3)
Hypertension (%)	36.6	52.1	0.06	0.52 (0.26, 1.04)
Family history of premature CAD (%)	26.8	12.7	0.04	2.58 (1.07, 6.23)
Triglycerides in mg/dL (mean ± SD)	147.3 ± 46.3	142.7 ± 51	0.58	1.09 (0.80, 1.49)
Cholesterol in mg/dL (mean ± SD)	219.4 ± 30.1	172.2 ± 38.9	<0.001	6.26(3.38, 11.61)
LDL in mg/dL (mean ± SD)	137.5 ± 30.6	108.5 ± 30.7	<0.001	3.21 (1.98, 5.22)
HDL in mg/dL (mean ± SD)	38.3 ± 3.4	40.7 ± 4.6	0.001	0.53 (0.33, 0.76)

^a Characteristics expressed as means (SD) or percentage, adjusted for age and gender.

elevated LDL and low HDL levels), history of smoking, and family history of premature CAD were significantly more prevalent in this sub group compared to controls (patients with normal valves and normal coronaries) ($p < 0.05$). No significant difference noted in the presence of diabetes and hypertension (Table 2).

On multivariate logistic regression, family history of premature CAD (OR 3.68; CI 1.38–9.78) smoking history (OR, 2.56; CI, 1.21–5.39), and raised LDL levels (OR, 5.55; CI, 2.63–11.69) were independently associated with the DAVD patient cohort (Table 3).

Discussion

Association between the development of DAVD with severe AS and traditional coronary risk factors has been well documented.^{1,3–5,9} The result of the present case control study shows a strong association of cardiovascular risk factors with the

presence of severe AS in Asian Indian patients. This is the first such study to demonstrate this association in an Asian Indian population.

The incidence of obstructive CAD noted in the patients with DAVD in the present study was 24.2% this is similar to that reported from a study done by Manjunath et al. in patients with DAVD from South India.²

Atherosclerosis and DAVD increase in prevalence with increasing age but neither is a consequence of ageing. Both conditions share many common risk factors. The pathogenesis of both disorders is a multistage process which involves endothelial damage, lipid deposition, inflammation and osteoblastic transformation.^{10–12} In the early stages there is valvular endothelial damage which leads to accumulation of lipids. The lipids so accumulated undergo oxidative modification. The oxidized lipid products are cytotoxic and capable of inducing inflammatory response. The inflammatory response leads to accumulation of the inflammatory cells which along with the cytokines so released lead to fibrosis and thickening

Table 3 – Multivariable logistic regression for the presence of degenerative aortic stenosis.

Variables	Odds ratio	95% confidence interval	p value
Smoking	2.56	1.21–5.39	0.01
Diabetes	1.55	0.73–3.30	0.25
Hypertension	0.31	0.15–0.63	<0.01
Family history	3.68	1.38–9.78	<0.01
Low density lipoprotein (>130 mg/dL)	5.55	2.63–11.69	<0.0001
High density lipoprotein (<40 mg/dL)	0.98	0.44–2.20	0.96

of the valve. The above changes are noted in early stages of aortic valve involvement resulting in AV thickening described as aortic valve sclerosis.^{10–12} Mineralization is the dominant feature of aortic stenosis; this occurs during late stages of disease when there is progressive mineralization of the valve along with osteoblastic activity which results in progressive calcification of the valve. These later changes are quite distinct from the pathogenesis of atherosclerosis where the lipid deposition leads to plaque rupture and subsequent vascular thrombosis.¹¹ Smooth muscle-cell proliferation and lipid-laden macrophages a hallmark in atherosclerosis is not noted in patients with aortic stenosis.¹² It is for this reason that lipid lowering with statins has not been found to effective in preventing the progression of aortic stenosis. Nevertheless, a small reduction in the progression of the disease cannot be ruled out. Aortic valve sclerosis is also noted in patients with CAD hence presence of a sclerotic aortic valve may indicate underlying coronary artery disease.¹³ In patients with aortic sclerosis over the age of 65 years with no coronary artery disease at study entry, increased risk of cardiovascular mortality was noted over a follow up of 5.5 years.¹⁴ But despite this both the disease processes are not identical as only 25–50% of patients with severe aortic stenosis have significant coronary artery disease.

Even though atherosclerosis and DAVD share same risk factors most patients with CAD do not develop aortic valve disease.^{1,5} In this study we tried to analyze the strength of association of some of the traditional risk factors of atherosclerosis with DAVD. Dyslipidemia has been strongly associated with the development of aortic stenosis; similar association was noted in our study.^{1,3–5,9–15} Sprecher et al. reported that AS occurs at an early age with faster rate of progression in patients of homozygous hypercholesterolemia where it is noted along with premature coronary artery disease.¹⁶ In a study conducted by Kamath et al. AS progression was found to be twice as high in the patient population with a serum cholesterol level greater than 5.0 mmol/L.¹⁷ In our study also there was strong and independent association of dyslipidemia (raised cholesterol and low density lipoprotein) with DAVD.¹⁸ High density lipoprotein by virtue of its antioxidative and anti-inflammatory properties has been noted to prevent the progression of atherosclerosis. The same has been recorded in the patients of DAVD where an inverse relationship with rate of progression of aortic stenosis has been recorded against the level of serum high density lipoprotein.¹⁸

Many studies have consistently shown a significant relationship of smoking with development and progression of DAVD.^{1,3–5} In some of the studies the rate of progression of calcific aortic stenosis has been rapid in smokers.^{4,5} In the

present study smoking was noted to be associated with aortic valve stenosis. However, whether cessation of smoking assists in preventing the progression of aortic stenosis is yet to be proven. Amongst other risk factors obesity has also been noted to be a risk factor for the DAVD but the same was not noted in the present study.

Hypertension was noted more in the controls as compared to patients with DAVD. One explanation of this could be that patients with hypertension (both with and without CAD/DAVD) are likely to present simply because of left ventricular diastolic dysfunction prompting work up for CAD/DAVD. Because hypertension is very common in the general population and CAD and DAVD are much less common, the majority of patients with hypertension who are evaluated for either of these conditions are likely not to have them. Therefore, more hypertensives are likely to be in the “control” arm of subjects presenting to hospital. This however does not imply that hypertension has protective effect towards development of DAVD.

On progression to its most severe form, DAVD with severe AS becomes debilitating and devastating requiring surgical intervention. However, this form of severe aortic stenosis is noted in only 2% of individuals less than 60 years.^{1,2} In the current study DAVD with severe AS was noted to occur at least a decade earlier than that seen in Europeans or Americans.^{1,7,19} We noted a higher prevalence of family history of premature CAD in patients with DAVD than controls. It is likely that this played a role in the premature occurrence of disease in the Asian Indian subjects but the same cannot be substantiated.

There are some shortcomings with the present study. The study has small sample size; therefore, it may not be truly representative of Asian Indian population. Small sample size might have contributed to the slightly wide confidence intervals noted in the study. Some of the patients might be those of bicuspid aortic valve disease and not of DAVD as assumed. Trans oesophageal echocardiography or histopathology studies were not done in any of the patients, it is likely that they might have helped in revising the diagnosis in some cases. Sample size of the present study was comparable to the other published international studies, however there are no Indian studies available on the subject.

The present study showed a significant association of cardiovascular risk factors with aortic stenosis independent of age and gender in Asian Indian patients.

Conflicts of interest

The authors have none to declare.

REFERENCES

- Ortlepp JR, Schmitz F, Bozoglu T, Hanrath P, Hoffmann R. Cardiovascular risk factors in patients with aortic stenosis predict prevalence of coronary artery disease but not of aortic stenosis: an angiographic pair matched case control study. *Heart*. 2003;89(9):1019–1022.
- Manjunath CN, Agarwal A, Bhat P, et al. Cardiac surgery for non-coronary lesions in a tertiary care centre. *Indian Heart J*. 2014;66(1):52–56.
- Toro R, Mangas A, Gómez F. Calcified aortic valve disease: association with atherosclerosis. *Med Clin Barc*. 2011;136(13):588–593.
- Sathyamurthy I, Alex S. Calcific aortic valve disease: is it another face of atherosclerosis? *Indian Heart J*. 2015;67(5):503–506.
- Rossi A, Gaibazzi N, Dandale R, et al. Aortic valve sclerosis as a marker of coronary artery atherosclerosis; a multicenter study of a large population with a low prevalence of coronary artery disease. *Int J Cardiol*. 2014;172(2):364–367.
- Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol*. 2012;60(19):1854–1863.
- Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg*. 2014;148(1):e1–e132.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2889–2934.
- Cao J, Steffen BT, Budoff M, et al. Lipoprotein(a) levels are associated with subclinical calcific aortic valve disease in White and Black individuals: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2016;36(5):1003–1009.
- Towler DA. Molecular and cellular aspects of calcific aortic valve disease. *Circ Res*. 2013;113(2):198–208.
- Mathieu P, Boulanger MC. Basic mechanisms of calcific aortic valve disease. *Can J Cardiol*. 2014;30(9):982–993.
- Lerman DA, Prasad S, Alotti N. Calcific aortic valve disease: molecular mechanisms and therapeutic approaches. *Eur Cardiol*. 2015;10(2):108–112.
- Aksoy Y, Yagmur C, Tekin GO, et al. Aortic valve calcification: association with bone mineral density and cardiovascular risk factors. *Coron Artery Dis*. 2005;16:379–383.
- Otto CM, O'Brien KD. Why is there discordance between calcific aortic stenosis and coronary artery disease. *Heart*. 2001;85:601–602.
- Stritzke J, Linsel-Nitschke P, Markus M, et al. Association between degenerative aortic valve disease and long-term exposure to cardiovascular risk factors—results of the longitudinal population based KORA/MONICA Survey. *Eur Heart J*. 2009;30:2044–2053.
- Sprecher DL, Schaefer EJ, Kent KM, et al. Cardiovascular features of homozygous familial hypercholesterolemia: analysis of 16 patients. *Am J Cardiol*. 1984;54:20–30.
- Kamath AR, Pai RG. Risk factors for progression of calcific aortic stenosis and potential therapeutic targets. *Int J Angiol*. 2008;17(2):63–70.
- Hilal OK, Uğur K, Canan D, et al. Role of serum high density lipoprotein levels and functions in calcific aortic valve stenosis progression. *Int J Clin Exp Med*. 2015;8(12):22543–22549.
- Akerström F, Barderas MG, Rodríguez-Padial L. Aortic stenosis: a general overview of clinical, pathophysiological and therapeutic aspects. *Expert Rev Cardiovasc Ther*. 2013;11(2):239–250.