Cardiovascular Pathology 80 (2026) 107781

Contents lists available at ScienceDirect

Cardiovascular Pathology

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

Aortic regurgitation as a cause of sudden cardiac death with aortic and left ventricular remodelling - the role of the bicuspid valve

Lauren Moran *, Joseph Westaby, Mary N. Sheppard

Cardiovascular and Genomics Research Institute, City St George's University of London, Cranmer Terrace, Tooting SW17 0RE, London, UK

ARTICLE INFO

Keywords:
Aortic valve
Sudden cardiac death
Bicuspid aortic valve

ABSTRACT

Background and objective: Aortic regurgitation (AR) results in blood flow from the aorta back into the left ventricle, which leads to left ventricular hypertrophy and dilation which, in a clinical setting, leads to heart failure and death. However, it is not a well-recognised cause of sudden cardiac death (SCD).
Methods: We identified 10 cases of AR with no other cause of death from our database of 8,551 cases of SCD. All these cases had a full autopsy with negative toxicology. Diagnosis of AR was based upon the presence of prominent ridges on the edge of the aortic valve (AV) cusps with aortic root dilatation, and no significant calcification within the cusps. We measured heart weight, circumference of aortic annulus and ascending aorta, diameter of left ventricle, and circumferential left ventricle wall thickness prospectively. Cases were age and sex matched 2:1 to individuals with morphologically normal hearts with normal aortic valves.
Results: Age was 43±14 years, with 7 males and 3 females in the AR group, and 14 males and 6 females in the control group. Heart weight was significantly higher in individuals with AR compared to controls (642±200g vs 370±75g, $p<0.001$). All cases showed thick regurgitant ridges on the edges of all valvular leaflets macroscopically. The aortic annulus circumference (73±14mm vs 54±7mm, $p<0.001$) and the circumference of the ascending aorta (85±27mm vs 56±7mm, $p<0.001$) were significantly dilated in AR. The left ventricular cavity diameter was significantly larger in AR (52±15mm vs 30±8mm, $p<0.001$). There was no significant difference seen in maximal wall thickness of the left ventricle (16±6mm vs 14±2mm, $p=0.068$). 7 out of 10 AR cases had bicuspid aortic valves (70%) while two were rheumatic and one just had a dilated aorta. Microscopically, left ventricular fibrosis was seen in 7 of the AR cases (70%).
Discussion: AR is a rare cause of SCD, most commonly associated with bicuspid aortic valve. It can be recognised by prominent ridges on the AV cusps and/or thickening of the cusp free margin with aortic annular dilatation. It is only considered significant as a cause of death when found with increased heart weight, left ventricular dilatation, and/or ventricular fibrosis in the absence of other cardiac pathology. We demonstrate that there is a strong association between BAV, AR and SCD. As BAV is a congenital condition, clinical or surgical intervention could potentially prevent subsequent cardiac enlargement and fibrosis, thereby preventing SCD.

1. Introduction

Aortic regurgitation is a valvular abnormality in which there is inadequate closure of the aortic valve during diastole leading to reverse aortic blood flow into the left ventricle, causing ventricular volume overload. This leads to cardiac hypertrophy and dilatation of the left ventricle [1].

AR can result from primary disease of the valve cusps, or secondary to disease of the aortic root. Rheumatic disease is worldwide the most common cause, in which retraction of the AV cusps occurs as a result of fibrous thickening. The most common causes of AR in Europe are degenerative AR (secondary to annuloaortic ectasia), calcific AV disease (often in conjunction with aortic stenosis), infective endocarditis, and congenital bicuspid AV [1]. AR can also be functional, secondary to aortic dilatation and aortic dissection. Annuloaortic ectasia is the most common cause of AR with dilatation of the aortic annulus, prolapse of valve cusps, and dilatation of the sinotubular junction. The AR is associated with a spectrum of aorta phenotypes: 1) AR with root aneurysm; 2) AR with normal root size, but aneurysm of ascending aorta; 3) isolated AR, where both the aortic root and ascending aorta are within

* Corresponding author.
E-mail address: laurenmoran99@gmail.com (L. Moran).

https://doi.org/10.1016/j.carpath.2025.107781
Received 12 March 2025; Received in revised form 11 September 2025; Accepted 17 September 2025
Available online 18 September 2025

normal size limits. In all 3 phenotypes, even in isolated AR, there is invariably dilatation of the aortic annulus to > 25mm diameter. This dilatation of the root can be found in both tricuspid and bicuspid aortic valves and is aggravated with increasing age and hypertension [2]. Rarer causes include connective tissue syndromes such as Marfan's, or inflammatory disorders such as arthritis, ulcerative colitis, and giant cell arteritis [1]

AR can be categorised as acute or chronic. Acute AR is classified as an abrupt increase in the end-diastolic volume of the left ventricle; infective endocarditis, aortic dissection and trauma are the most common causes of acute AR. Chronic AR is prolonged which leads to dilation and hypertrophy of the left ventricle over time. The most common causes of chronic AR are degenerative annuloaortic dilatation associated with hypertension, age, and hyperlipidaemia, and a bicuspid aortic valve (BAV) [3].

In a clinical setting, AR can lead to heart failure and death. Clinical progression to cardiac failure in patients with non-inflammatory aortic root disease is slower than in patients with infective disease but faster than in those with rheumatic cusp disease [4].

At present it is not a well-recognised cause of sudden cardiac death and cases in the literature are difficult to find. Pathologists find AR difficult to diagnose at autopsy, with no established guidelines. This is the first study to provide a guideline for the pathological identification of AR as a cause of SCD.

2. Methods

All cases were extracted from a database of hearts referred to the CRY cardiovascular pathology unit between 2014 and 2023. The extraction was filtered to produce cases in which the final diagnosis was sudden cardiac death due to aortic regurgitation. Sudden cardiac death was defined as death occurring within one hour of the development of symptoms or within 24 hours of last being seen alive and well if unwitnessed, and (Figs. 1-3) the diagnosis of AR was based on the presence of prominent ridges or thickening at the edges of the aortic valve cusps, with no significant calcification in conjunction with aortic dilatation.

Macroscopic and microscopic examination was performed in accordance with the published guidelines [5]. The heart weight, circumference of aortic annulus and ascending aorta, diameter of left ventricle, and left ventricular wall thickness were measured prospectively. The aortic annulus was measured at the sinotubular junction at the level of the commissures, across the superior cusp edges, and the ascending aorta measurement was taken 2cm distal to this. Measurements of the left ventricle were taken at the mid-ventricular level. Myocardial fibrosis was identified using routine histological analysis of formalin-fixed paraffin embedded (FFPE) blocks containing myocardial sections taken during macroscopic analysis. The sections were stained with haematoxylin and eosin (H&E), and fibrosis was confirmed using picrosirius red (PSR) stain.

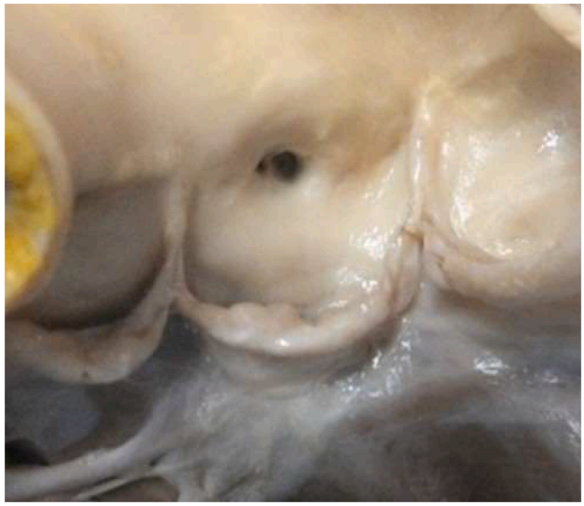


Fig. 1. A regurgitant tricuspid aortic valve.

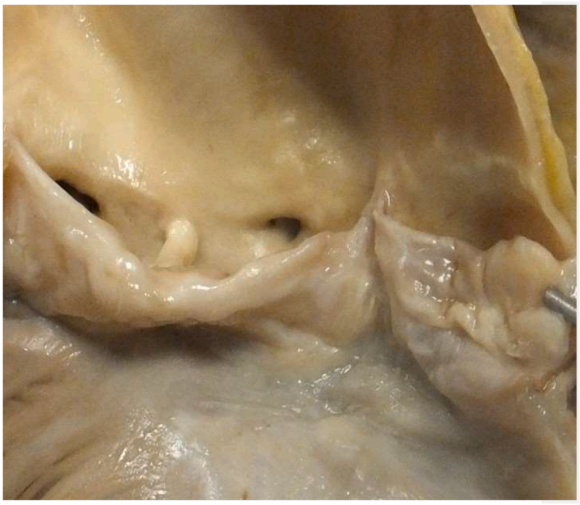


Fig. 2. A regurgitant bicuspid aortic valve with commissural fusion of the left and right coronary cusps.

Dilation of the aortic annulus and ascending aorta was defined as a circumference measuring over 60mm, as outlined in the published literature [5].

For controls, cases were age and sex matched 2:1 with individuals with morphologically normal hearts. This ratio was utilised to improve the power of this review. Statistical analyses were performed using SPSS version 29.

3. Results

Ten cases referred to the CRY cardiovascular pathology laboratory, in which the cause of SCD was due to aortic regurgitation. These cases were extracted from a database of 8,551 cases referred to the lab between 2014 and 2023, where aortic regurgitation was given as a cause of death. Of this cohort, n=7 was male and n=3 female, with a mean age at death of 43±14 from a range of 24-74 years.

Of the ten cases presented, only two had cardiac symptoms prior to their sudden death. None of this cohort were diagnosed with aortic regurgitation in life.

Tables 1-3 When compared to the control cases, the hearts with AR were significantly heavier than the morphologically normal hearts, weighing 642±200g compared to 352±55g. Within the cohort of morphologically normal hearts, the mean circumference of the aortic annulus was 54±6mm, and the ascending aorta was 56±8mm. In cases of aortic regurgitation, the mean circumference of the aortic annulus was 73±14mm, and the ascending aorta was 85±27mm. This confirms a significant difference between the control cases and aortic regurgitation, with the latter showing enlargement of the heart, as well as significant circumferential dilation of both the aortic annulus and the ascending aorta.

Of the ten cases, left ventricular hypertrophy was seen macroscopically in seven cases. Dilatation of the left ventricle was seen in six of the cases, with a mean diameter of 53±15mm compared to 30±6mm in the control group.

Fig. 2 Bicuspid aortic valves were identified in 7 of the 10 cases. Two had rheumatic disease with commissural fusion and retraction of the cusps and one had a tricuspid valve with dilated aortic root in an athlete. Microscopic fibrosis was seen in the free wall and septum in 70% of the AR cases.

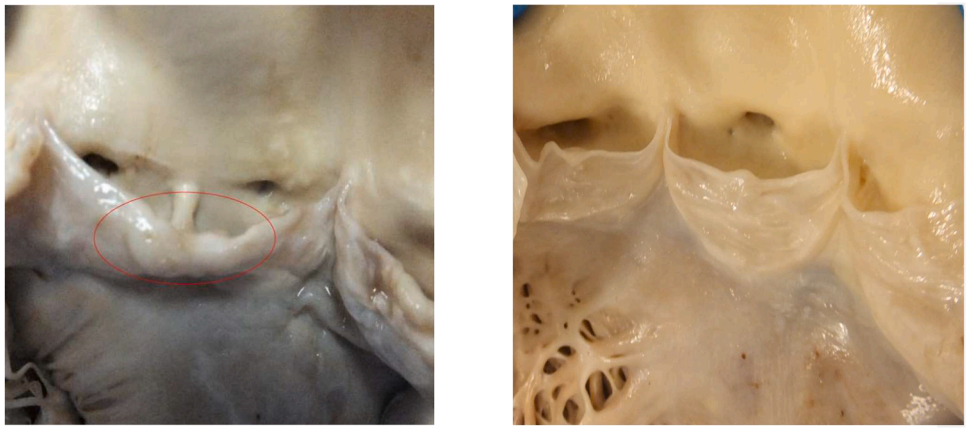


Fig. 3. Regurgitant ridges visible on valve cusps in AR in comparison with a normal, non-regurgitant aortic valve.

Table 1
Parameters measured in AR cohort.

	1	2	3	4	5	6	7	8	9	10
Sex	M	M	F	M	M	M	F	M	M	F
Age	48	33	43	30	43	74	42	47	24	45
BMI	28	39	26	-	26	-	28	33	-	-
Heart Weight (g)	685	727	510	420	789	520	575	1,110	584	496
Aortic Annulus Circumference (mm)	70	70	50	80	90	95	85	70	60	60
Ascending Aorta Circumference (mm)	93	65	75	110	120	130	80	60	55	60
LV diameter (mm)	75	50	45	50	55	35	75	35	60	40
LV wall thickness (mm)	18	18	10	11	16	15	13	30	14	17
Bicuspid AV (Y/N)	Y	Y	Y	Y	N	Y	N	N	Y	Y

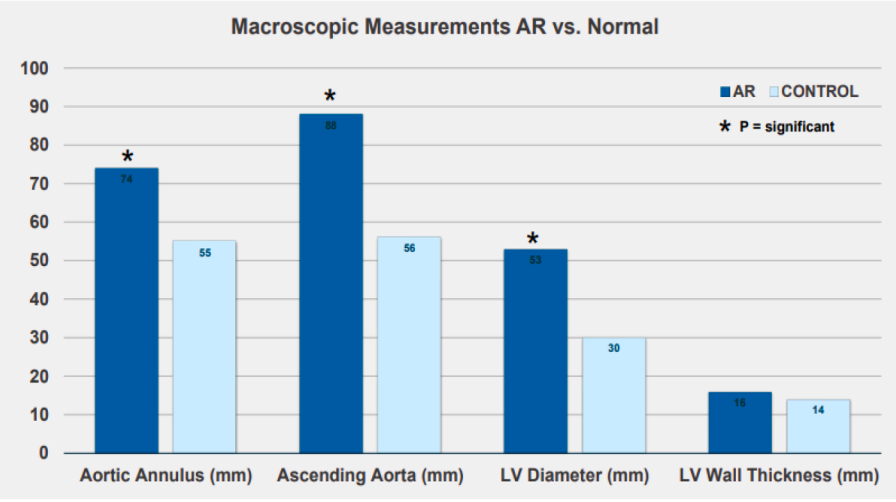
Table 2
Results of statistical analysis.

	AR	Control	P-Value
Heart Weight (g)	642±200	352±55	0.0003
Aortic Annulus Circumference (mm)	73±14	54±6	0.0001
Ascending Aorta Circumference (mm)	85±27	56±8	0.004
LV Diameter (mm)	52±15	30±6	0.003
LV Wall Thickness (mm)	16±6	12±1	0.06

4. Discussion

Aortic regurgitation is a valvular abnormality in which there is inadequate closure of the aortic valve during diastole. This leads to reverse aortic blood flow into the left ventricle, causing ventricular volume overload with dilation and hypertrophy [6]. The combination of dilation and hypertrophy means that the overall function of the LV is compensated, but a decline in systolic function and ejection fraction will occur over time as the wall thickening is outpaced by the haemodynamic load. Our findings correlate with the published literature in that all our

Table 3
Bar chart depicting the difference in morphometric measurements between the AR and control groups. Those indicated with an asterisk show a statistically significant difference.



cases of AR associated with SCD had an increased heart weight and the majority (70%) displayed left ventricular hypertrophy and dilation.

Bicuspid aortic valve (BAV) leads to degenerative changes in the valvular cusps and is associated with dilation of the ascending aorta [7]. With a prevalence of 0.5-2% of the adult population, BAV is considered the most common cardiac congenital defect [8]. BAV is associated with aortopathy resulting from dilation of the aortic root and/or proximal ascending aorta, as well as dilatation and AR [3]. A previous study carried out in our research unit by Chatrath et al. in 2023 focused on the role of a bicuspid aortic valve in sudden cardiac death. Prevalence of BAV was identified in 1.4% of the CRY database, which correlates with that found in the general population. This study reported seven cases of SCD caused by AR among the cohort of individuals with BAV, highlighting that it is a rare but neglected cause of SCD [9]. While aortic stenosis associated with calcification in a tricuspid or bicuspid valve is well established as a cause of sudden death [9], pure aortic regurgitation in absence of significant calcification is less well established. Our study emphasises the strong link to BAV but there is still rheumatic valve disease and dilated ascending aorta also as rarer causes. Bicuspid aortic valve disease is associated with a high rate of cardiac events. Incremental degrees of aortic stenosis and regurgitation, the presence of aortic dilatation and age are predictive of cardiac events [10]. Patients with BAV should be made aware of its possible familial pattern [11].

Our results show significantly larger aortic annuli in AR patients compared to controls (circumference 73±14mm vs 54±6, $p<0.001$), in keeping with the emerging evidence for the importance of annular dilatation in AR. Annuloaortic ectasia, as evidenced by annular dilatation, is now believed to be the leading cause of AR in the Western world, with an annulus > 25mm regarded as dilated [12]. Our average annular circumference of 73mm in the AR group equates to 23mm diameter, with the control group's 54mm circumference equating to 17mm diameter. It is important to note that these are measurements taken in a formalin fixed un-pressurised autopsy specimen. The annulus is an expandable structure, and in vivo experiences diastolic and systolic pressures. Therefore, the 17mm diameter in the control group would correlate with normal pressurised physiological annular diameters of 21-22mm in adult females and 22-23mm in adult males [13]. Therefore, a flaccid 23mm annulus at autopsy would equate to a much larger annulus diameter in vivo, such as 28mm. Our findings may help to support previous surgical recommendations that suggest when the annulus dilates to > 25mm, a reduction annuloplasty should be performed of the regurgitant aortic valve [14].

Current international guidelines on the management of heart valve disease recommend surgery in AR when the patient is either symptomatic or asymptomatic with LV end-systolic diameter > 50mm or > 25mm/m^2 body-surface area or LVEF ≤ 50% (Class 1 Level B evidence). The recommendations also state that surgery may be considered in asymptomatic patients with LV end-systolic diameter > 20mm/m^2 or LVEF ≤ 55% (Class 2B Level C evidence). This study lends support to the surgical correction of AR when morphological changes have begun to occur in the LV and highlights SCD as another factor to consider when managing patients with AR. Furthermore, it raises the question of whether we should wait for LV changes to occur before offering surgery to these patients [15].

Our findings show that AR is a rare cause of SCD, commonly associated with bicuspid aortic valve, which is mediated through cardiac enlargement with increased heart weight and/or fibrosis. It can be recognised at autopsy by looking for prominent ridges on the AV cusps and thickened cusp free margins with aortic annular dilatation but is only considered significant when found with increased heart weight and/or fibrosis. We demonstrate that there is a strong association between BAV, AR and SCD. As BAV is a congenital condition, clinical or surgical intervention could potentially prevent subsequent cardiac enlargement and fibrosis, thereby preventing SCD.

CRediT authorship contribution statement

Lauren Moran: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Joseph Westaby:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Mary N. Sheppard:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

There are no conflicts of interest or relationships with industry to report.

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