Review Article

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Aortic valve fenestrations: a review

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Abstract

Background: Aortic valve fenestrations (AVFs) seem to be relatively common; however, their impact in human heart disease is not entirely clear.

Methods: A review was carried out to assess all scientific literature on human patients related to AVFs, as described in the published literature. The search was conducted on 2 different databases, Medline (PubMed), and ISI Web of Knowledge.

Results: Fifty-five reports were under analysis. Autopsy studies showed AVFs to be present in 55.9% of individuals studied in such studies. They occur more frequently in men and, in general, their frequency increases with age. Although common, fenestrations rarely cause regurgitation; however, they may play an important role in the pathophysiology of some cases of severe aortic regurgitation. AVFs have been described in patients with Down syndrome and Marfan syndrome, in patients with bicuspid or quadricuspid valves, and in patients with myxomatous valvular degeneration. Echocardiographic assessment of aortic regurgitation seems to have limitations in the diagnosis of valvular fenestrations.

Conclusions: Fenestrations of the aortic valve are very common and are associated with certain clinical conditions. It is unknown if AVFs play any role in the current epidemic of aortic valve disease. Future studies should aim to better define the role of AVFs in aortic valve disease, to further understand its etiology and to develop diagnostic criteria.

Keywords: aortic insufficiency, aortic regurgitation, aortic valve fenestrations, review

Introduction

Aortic valve (AV) disease is increasingly prevalent and has a varied etiology. AV fenestrations (AVFs) have been recognized as a cause of AV disease for more than a century.[1–3] Although they are not a rare finding, AVFs are currently seen as a relatively infrequent cause of valve disease, namely of AV regurgitation (AR).

Early data[4] points in the direction that AVFs are seen in more than half of examined hearts. The most frequent site of the fenestrations is adjacent to the attachment of the free edge of the cusp to the aortic intima. Fenestrations are usually ovoid apertures, with the long axis parallel to the free edge of the valve. Their frequency increases with age up to the fourth decade of life, they are more common in men and multiple fenestrations could be seen in the same patient.[4]

Fenestrations have been seen in AVs that exhibit features of myxomatous degeneration[5–14]; however, congenital fenestrations can also occur.[4,6,7,15–20]

We conducted a review to assess all scientific literature on human patients related to AVFs, as described in the published literature.

Methods

We conducted a review according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Search strategy

A comprehensive review of the literature was performed to identify all reported articles on AVFs. The search was conducted on 2 different databases, Medline (PubMed) and ISI Web of Knowledge, in July 2019. The search queries in both databases were as follows: “aortic valve fenestration”; “aortic valve fenestrations”. No restrictions concerning date of publication were imposed. The lists of references of studies included in the final analysis were also manually searched.

Inclusion criteria

The review considered all human studies reporting on AVFs. Both prospective and retrospective human studies were included.

Exclusion criteria

We excluded articles that were not available in English or Spanish, as well as reports regarding animals (nonhuman) and publications with no original data.

Study eligibility assessment

Study eligibility was individually assessed by 2 investigators. No formal quality assessment was carried out, since a significant number of articles were case reports.

CZ and SCT contributed equally for this manuscript.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Full text of 7 articles were unavailable, one[21] of which was not included in Table 1 for that reason, while the remaining six[22–27] were considered, since they appeared to contain relevant information. The data of four[24–27] was obtained from the respective abstracts and two[22,23] from other cited reports (Fig. 1).[8,28]

Study selection and data extraction

The investigators individually assessed if studies addressed the topic under study, and if all inclusion/exclusion criteria prespecified for the review (as described above) were met. This was done initially through title and abstract analysis, and then (if abstracts complied to specifications) through full-text assessment. Any discrepancies were resolved by consensus between the authors. Data extraction was performed independently by 2 authors using a predesigned extraction form. The following items were extracted from each study by 2 authors (C.Z. and S.T.) independently and presented in the Table 1: author, year, number of patients, sex, age, AV description, and main findings.

Results

We selected 29 articles with the first query and 75 articles with the second query on the PubMed database, and 81 articles with the first query and another 81 articles with the second query on ISI Web of Knowledge. Twelve additional records were identified through other sources. Of the 278 records screened, 222 were excluded after title and abstract review as not meeting the inclusion criteria. A total of 55 articles were included in our study, according to the selection criteria. In Table 1 we present the data for 54 of these articles, for which we were able to obtain data. As shown in Figure 2, only 1 study was published in the 1920s,[4] 1 from the decade of 1930,[29] 5 from the decade of 1950,[5–7,20,30] 4 from the decade of 1960,[31–34] 6 from the decade of 1970,[22,35–39] 5 from the decade of 1980,[19,21,23,40,41] 6 from the decade of 1990,[8,9,18,28,42–44] 8 from the decade of 2000,[10,11,16,17,45–48] and 19 from the decade of 2010.[12–15,24–27,49–59]

With regard to study design, 39 (70.9%) were case reports, 3 (5.5%) were small case series, 7 (12.7%) studies were cross-sectional, 5 (9.1%) were cohort studies (including 1 prospective cohort study and 4 retrospective cohort studies), while 1 (1.8%) study was a cross-sectional study which included also case reports.

Prevalence of aortic valve fenestrations in autopsy studies

We identified 4 larger series of patients, corresponding to autopsy studies.[4,7,24,57] The prevalence of fenestrations in AV in these 4 reports is summarized in Table 2. Out of a total number of 919 examined hearts, 545 hearts exhibited AVFs. Therefore, we estimate that the prevalence of fenestrations in AVs is 55.9%.

Foxe[4] described a series of 188 (62.7%) cases of AVFs, out of 300 cases studied. According to this author, the most frequent site of the fenestrations was adjacent to the attachment of the free edge of the cusp to the aortic intima, and the fenestrations were usually ovoid apertures, with the long axis parallel to the free edge of the valve.[4] Further major findings are presented in Table 1. Friedman and Hathaway[7] examined 342 hearts, of which 72% had semilunar valve fenestrations; 2 cases had clinical disease. Fenestrations in the AV were seen in 190 cases (55.6% of the total number of hearts).

Losenno et al[24] studied 67 cadaveric human hearts, of which 26 (38.8%) had fenestrations in the AV. The results showed that fenestrations occurred most frequently in the left coronary cusp (LCC) (50%), followed by the right coronary cusp (RCC) (33.3%) and least frequently in the noncoronary cusp (NCC) (16.7%). The authors studied the dimensions of the AV cusps with and without fenestrations and concluded that cusps with fenestrations are generally larger than nonfenestrated cusps. In addition, the NCC and RCC tend to be larger than the LCC in AVs with fenestrations, but not in valves without fenestrations. The authors conjectured that the fenestrations could develop as a result of unequal shear stress on the cusps of eccentric AVs.

Ashalatha and Hannah Noone[57] reported on AVs from 210 random autopsy cases. Tricuspid AVs (TAVs) existed in 208 cases. Fenestrations were seen in 110 valves (52.4%). The authors described variations in size and shape of the fenestrations. There were 2 cusps affected in 22% of cases, and 1 cusp in 19% of cases. When 1 cusp alone showed fenestrations, the LCC was the most commonly affected and NCC was the least affected.

Pomerance[33] described a series of 805 hearts studied at autopsy. Fenestrations of the AV were present in 12% of patients younger than 45 years, with an increase in prevalence in the next decade in males. Precise figures on the overall prevalence of fenestrations were not given by the author.

Case reports and small case series

Of the 39 case reports and 3 small case series, there were a total of 63 patients with AVFs. Four (6.3%) patients had bicuspid AVs (BAVs), 45 (71.4%) patients had TAVs, 10 (15.9%) patients had quadricuspid AVs (QAVs) and in 4 (6.3%) patients the number of AV cusps was not specified. The RCC had at least 1 fenestration in at the minimum 38 patients, the LCC was affected in at least 23 patients, the NCC was affected in at least 24 patients, the conjoined in BAVs was affected in 2 patients, and the supernumerary cusp in QAVs was affected in at least 4 patients. Taking into consideration the 45 patients with TAVs, 11 (24.4%) had fenestrations in all cusps. Concerning the 10 patients with QAVs, at least 4 (40%) had fenestrations in all cusps.

At the minimum, 28 patients had ruptured fenestrations in the AV, 21 were reported to have arterial hypertension (of which 19 had chronic arterial hypertension), 18 had no arterial hypertension, and in 24 this topic was not specified.

Fenestration-related aortic regurgitation or stenosis

AVFs were seen in a large research study of patients with AR conducted by Yang et al.[59] The authors noted that of the 382 patients undergoing surgery for moderately severe and severe aortic insufficiency, 12 (3.1%) had fenestration-related AR (2 with BAV and 10 with TAV), but only 1 (0.26%) exhibited AVFs as an isolated mechanism of AR. Out of these 12 cases, 8 (86.7%) had ruptured fenestrations, 9 (75.0%) had cusp prolapse and all had eccentric jets. The authors also recognized that fenestrations with/without rupture as an AR etiology in TAV were underdiagnosed by transesophageal echocardiography because of its limitations in detection of small perforations and free-edge/paracommissural fenestrations.

Cheruvu et al[51] described a series of 1133 patients who had AV surgery, of which 42 had valve fenestrations, and 26 of those had surgery primarily for AR.

One case of AV stenosis[54] and 1 case of supravalvular aortic stenosis were described in association with valve fenestrations[9] (Table 1).

Table 1

List of published reports on aortic valve fenestrations

Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
Foxe (1929)	188 Patients with AV fenestrations out of 300 patients	Age groups from fetus to the eighth decade	The most frequent site of the fenestrations was adjacent to the attachment of the free edge of the cusp to the aortic intima. The fenestrations were usually ovoid apertures, with the long axis parallel to the free edge of the valve.	The frequency of fenestrations increased with age from the fetus to the fourth decade. From the fifth to the eighth decade, there was a slight decrease in prevalence, but an increase in frequency of sclerotic changes which obliterate small defects. In females, the valve leaflets were less frequently involved (36% vs 45%). In 1 case, a man aged 25, the AV had 36 fenestrations. The suggested etiology was persistent strain of blood current against the valve leaflets (presented as the most frequent cause), endocarditis (1 case) and bullet wound (1 case).
2. Cook and Millman (1933)	2	Case 1: male, 3 years and 4 months Case 2: male, 3 years and 5 months	Case 1: autopsy: the right and left coronary cusps were fused. The line of fusion showed considerable thickening. Each half component of the fused cusp presented a fenestration. Case 2: autopsy: the AV consisted of 2 cusps of almost equal size. No line of fusion was visible.	In addition to the presence of bicuspid AVs, both cases presented mental and physical abnormalities of development, case 1 showing cerebral anomalies and congenital cataract, and case 2 Down syndrome. Fenestrations were present in the AV in case 1 and in the pulmonary valve in case 2. There was no clinical evidence of other cardiac abnormalities. Case 2 died from bronchopneumonia. The cause of death in case 1 remains unknown. In the absence of any other apparent cause of death, it seemed probable that the rupture of aortic fenestration was the responsible agent.
3. Castleman and Towne (1951)	1	Male, 50	Autopsy: extensive fenestration involving all of the 3 aortic cusps extending below the line of closure. Histopathology: extensive mucinous degeneration of the cusps between the 2 layers of endothelium.	Marked fenestration of aortic cusps leading to AR, cardiac hypertrophy and dilation (heart weighted 950 gm). The patient presented congestive heart failure symptoms presumably due to severe AR and died in 3 years from a cardiac standstill during an anesthetic induction.
4. Matthews and Darvill (1956)	1	Male, 67	Autopsy: fenestrations measuring 0.4 by 1.1 cm, in both NCC and RCC near their common commissure, extending down into the body of the cusps below the line of valve closure; fusion and mucinous degeneration of the thickened AV cusps, large sinuses of Valsalva; thin strands of tissue lateral to the main fenestration in the RCC, running in a vertical direction from the free margin to become attached to the aortic intima. Histopathology: mucinous degeneration of the AV.	Fenestrations of the AV causes clinical AR, left ventricular hypertrophy, and congestive heart failure. Rupture of the RCC accounted for the sudden appearance of a new murmur and for the rapid worsening of congestive failure.

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
5. Proudfit and McCormack (1956)	1	Male, 56	Autopsy: rupture of the fenestration in LCC; small fenestration in RCC. Histopathology: increased cellularity and thickening (with fibrin deposition) of the right and left cusp margins.	Rupture of AV resulting in progressive congestive heart failure and death. Autopsy revealed cardiomegaly with massive left ventricular preponderance, rupture of LCC with resultant AR and jet lesion, produced by an abnormal stream of blood striking the endocardium. The patient had suffered thoracic trauma 2 years before.
6. Friedman and Hathaway (1958)	In the 342 hearts examined, 190 (55%) showed AV fenestrations; 2 cases with clinical disease	Case 1: male, 75 Case 2: male, 57	Case 1: autopsy: The LCC and NCC showed large fenestrations measuring 1 by 1.5 cm in each cusp. The defect involved part of the commissure so that complete closure was impaired. There were no inflammatory changes. Case 2: autopsy: all 3 aortic cusps showed fenestrations at the free overlapping margins adjacent to the commissures.	Fenestrated AVs were found in 55% of 342 hearts examined. The LCC showed the highest incidence of fenestration. There was an increase in the severity and frequency of fenestration along with the widening of the aortic ring. This observation suggested a possible common factor underlying both the valvular and large vessel lesions. Increased vascular tension may play some part as evidenced by the slightly greater involvement of the aortic leaflets in systemic hypertension. There was no histologic evidence of inflammation. The findings were reviewed with respect to age, sex, leaflets involved, and in relation to cardiac hypertrophy, intravascular pressure, and dilatation of the outlet, and the presence of diastolic murmurs. The authors hypothesized that fenestrations could be a form of atrophy, which may begin in early childhood or fetus, and that aging, dilatation of the ring and increased intravascular pressure are contributing and modifying factors. Two cases with fenestrated aortic leaflets in hypertensive patients were associated with diastolic murmurs and congestive heart failure.
7. Bailey et al (1959)	1	Male, 29	Perioperative: A large central fenestration in the LCC; the commissural portion of the valve between the LCC and RCC was thickened and calcific; the margin of the RCC was thickened and retracted, and tended to become prolapsed; the NCC was normal.	A case of significant AR due to valvular fenestration, who was submitted to successful surgical AV repair. The defect was repaired with a patch of formalinized polyvinyl sponge (Ivalon) plus the surgical creation of bicuspid AV (LCC and RCC). Bacterial endocarditis engrafted upon a congenital defect (fenestration) was believed to be an important contributing factor to the AR in the present case.

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
8. Marcus et al (1963)	1	Female, 62	Autopsy: RCC and LCC were fenestrated. The valvular endocardium which formed the superior rim of one of the fenestrations of the LCC was disrupted 0.1 cm from the commissure; the endocardial tags that remained were thin, smooth, glistening, and grey.	AR secondary to spontaneous rupture of a fenestrated leaflet in an elderly woman is described. In addition to the ruptured leaflet, autopsy also revealed cardiomegaly (800 g), endocardial sclerosis and congestive heart failure signs.
9. Payan (1966)	1	Male, 76	Autopsy findings: a fenestration between the RCC and LCC which connected the 2 aortic sinuses; an embolus engaged in the fenestration occluded the right coronary artery; fibrosis, thickening and calcification of AV.	Unusual type of fenestration of the AV complicated by engagement of an embolus causing occlusion of the right coronary artery ostium and death.
10. Pomerance (1967)	805 Hearts	414 Males 391 Females	Autopsy findings: fenestrations of the AV present in 12% of patients younger than 45 years of age. Slight increase in prevalence in the next decade in males.	Fenestration largely predominant in the male sex.
11. Symbas et al (1969)	2	Case 1: male, 41 Case 2: male, 15	Case 1: intraoperative: 7–8 mm diameter fenestration of the LCC, adjacent to the commissure between the LCC and NCC, close to the free margin of the leaflet. The edges of the leaflets were thickened but no vegetations were seen. Histopathology: moderate AV thickening and fibrosis with no evidence of an old or recent infection. Case 2: intraoperative: large fenestration of the NCC close to the free margin and adjacent to the commissure between the NCC and the LCC; a small VSD was located beneath the RCC, but none of the coronary cusps were prolapsed.	Two cases of severe AR due to fenestration of the aortic cusps that required AV replacement are described. Both cases presented possible modifying factors: in the first case, systemic hypertension with aortic root dilatation; in the second case, the patient had marked dilation of the sinuses of Valsalva and the ascending aorta, possible due to a connective tissue abnormality. The latter also had a small VSD which was closed by direct suture.
12. Carter et al (1971)	2	Case 1: male, 59 Case 2: male, 49	Case 1: autopsy: a fenestration was present beneath the strand which attached the center of the conjoined cusp of a bicuspid AV to the aortic wall; rupture of the strand allowed the conjoined cusp to prolapse. Case 2: autopsy: laceration of the ascending aorta with resultant upward displacement of the commissure between the NCC and LCC. The NCC was stretched and attenuated and showed fenestrations. The LCC was ruptured.	Case 1: sudden death due to spontaneous isolated rupture of an unusual type of congenital bicuspid AV in which the center of the conjoined cusp was attached to the aorta by a strand of tissue lying above a fenestration. Case 2: patient with cystic medial necrosis of the aorta (who was a brother of the case 1 patient) had a laceration of ascending aorta without dissecting aneurysm, which led to distortion of one commissure and secondary rupture of one and fenestration of the other of the 2 related aortic cusps.
13. Westlake (1973)*	2	Case 1: male, 48 Case 2: male, 63		Case 1: spontaneous rupture of a fibrous strand in the AV. It was not stated which aortic cusp had ruptured. Acute AR was attributed to infective endocarditis. AV replacement was

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
				performed. Case 2: acute AR due to spontaneous rupture of RCC. AV replacement was performed.
14. Becker and Düren (1977)	1	Male, 45	Intraoperative: bicuspid AV with 2 cusps of unequal size. Large cusp with attenuated, blind-ending fibrous cord, which inserted at free edge of valve. At operation, this cord appeared to be disconnected from the inner wall of aorta, while its cusp had prolapsed, thus accounting for aggravated AR. Fenestrations were shown in Figure 1 of the paper.	Sudden worsening of AR due to spontaneous rupture of a fibrous strand which previously had anchored the conjoined cusp of a bicuspid AV to the aorta.
15. Sylvester (1974)	23 Patients with Down syndrome and 56 "mentally subnormal" patients	Down syndrome patients: 11–70 years Controls: 20–84 years	Individual description of cases provided in text.	Necropsy examinations were undertaken on 23 hearts of patients with Down syndrome and 56 mentally subnormal patients used as controls, from 1964 to 1974. The results showed that fenestration of heart valves was significantly commoner in Down syndrome patients than in "mentally subnormal" controls (>50% vs 4%, $P=.001$), occurred at a younger age and showed a pronounced tendency to rise in incidence with increasing age. There was no appreciable difference in sex incidence. AVs were involved more commonly than pulmonary valves. Pathological changes were more severe in Down syndrome patients than in controls.
16. Móran et al (1977)	1	Male, 31	Intraoperative: the commissure between the RCC and NCC had become completely detached from the aortic wall and prolapsed into the left ventricle. Both leaflets had a large fenestration located adjacent to their insertion into the valvular annulus.	The authors describe the first case of spontaneous rupture of a fenestrated AV successfully managed by surgical valvuloplasty.
17. Pérez et al (1978)	1	Male, 29	Intraoperative: fenestration of the NCC.	A case of severe AR due to fenestration of the NCC submitted to AV repair is described. The patient also had aortic root dilatation.
18. Davies (1980)[†]	1	Male, 49		AR due to a rupture of a fibrous strand in the AV. AV replacement was performed.
19. Hurle et al (1985)	36 (14 with fenestrations)		Scanning electron microscopy: fenestrations were frequently observed in the lunular region of the leaflets.	Fenestrations were present in the lunules of 14 specimens, with a higher incidence in specimens from subjects who were middle-aged or older. Observations with SEM suggest that fenestrations

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
				appear initially as multiple small perforations which then coalesce and form larger apertures. It is also probable that small fragments of valve tissue are detached into the bloodstream during the genesis of fenestrations. In most cases, fenestrations appeared as a large hole occupying most of the lunule. In 2 young people, the fenestrations appeared as several small holes indistinguishable by simple examination.
20. Coltharp et al (1988)	1	Male, 20	Intraoperative: malformed AV with 4 equal-sized cusps, each of which had a single, large, symmetrical, and central fenestration. One of the cusps was flail, allowing incomplete coaptation of the 4 leaflets and producing regurgitation over and above that caused by the central fenestration in each leaflet.	Quadricuspid AV with single, central fenestration in each leaflet, with a possible congenital origin. The authors conjectured that the patient's long-term regurgitation (from 2 years of age) was caused by the central fenestrations and that his worsening symptoms were related to the single leaflet's becoming flail. AV replacement was performed.
21. Matsukawa et al (1988)	1	Male, 75	Intraoperative: Large perforation in the NCC; AV with 4 almost equal-sized cusps with a supernumerary cusp interposed between the RCC and NCC. Small fenestrations at the 4 commissures were visualized.	Quadricuspid AV with a large perforation in the NCC resulting from bacterial endocarditis, submitted to AV replacement. Inspection of the AV also showed small fenestrations at the 4 commissures, which were thought to be congenital.
22. Kaplan et al (1991)	1	Male, 63	Autopsy: each AV cusp was fenestrated at the insertion of the cusp at the commissures. The largest fenestrations were in the LCC and RCC and extended well below the valvular lines of closure. The edges of the fenestrations were smooth and demonstrated no ulceration or inflammation. Regurgitant jet lesions were present on the ventricular septum.	Large AV fenestrations producing chronic AR, in the absence of hypertension or aortic annular dilatation, in an otherwise structurally normal AV. A congenital origin for these large fenestrations was speculated.
23. Aoyagi et al (1992)	1	Male, 62	Intraoperative: the AV consisted of 3 equal-sized and 1 smaller cusp, with the supernumerary cusp located between the RCC and NCC. Three fenestrations were found in the RCC. Histopathology: The resected cusps showed fibrotic thickening with calcification and no sign of previous inflammatory disease.	A case of quadricuspid AV with associated AR, with 3 fenestrations in the RCC, was described. AV replacement was performed.
24. Sun et al (1992)	1	Male, 3 years and 9 months	Autopsy: the AV was dysplastic and stenotic; circumferential narrowing above the sinuses of Valsalva; the posterior cusp was focally fused with its supravalvular ridge; the free margin of the entire RCC was fused completely with the	Sudden death of a child who had supravalvular aortic stenosis with fusion of the RCC to the supravalvular aortic ridge, resulting in a closed sinus of Valsalva except for a few fenestrations in the dysplastic RCC, which provided the only

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
			supravalvular ridge, transforming the right sinus of Valsalva into a blind pouch and isolating the right coronary ostium from the aortic lumen except for a few pinpoint fenestrations in the upper central portion of the RCC.	communication between the aortic lumen and the right sinus of Valsalva.
25. Lee et al (1996)	1	Female, 57	Echocardiography: mild to moderate AR consisting of 2 jets, including a central one and one passing through the LCC. Intraoperative: The LCC had a fenestration in its posterior lunula that was functionally patent, as the commissure next to it had been pulled from its normal position by the mitral sewing ring placement. The fenestration's edges were rolled and fibrotic, apparently in reaction to the blood flow through it.	A case of a fenestrated AV that developed clinically significant AR after mitral valve replacement surgery, as the sewing ring distorted the base of the AV. The AR was due both to compromised central cusp coaptation and to an LCC fenestration that became functionally significant after mitral valve surgery.
26. Akiyama et al (1998)	1	Male, 40	Echocardiography: massive AR with severe prolapse of the RCC; enlarged aortic ring. Intraoperative: there were fenestrations in all 3 cusps; one chordae-like elongated fibrous strand attached to the RCC at the commissure between the RCC and LCC had ruptured and the RCC had prolapsed into the left ventricular cavity. Histopathology: myxomatous AV, no signs of endocarditis.	Acute massive AR due to spontaneous rupture of a fibrous strand in a fenestrated AV of a patient with Marfan syndrome. Emergency surgical AV replacement was performed.
27. Blaszyk et al (1999)	1	Male, 65	Echocardiography: the AV was severely incompetent due to prolapse of the NCC. Autopsy: the AV had 3 cusps of similar size, with minimal calcification and no vegetations or commissural fusion. Two large fenestrations involved the left lunular aspect of the NCC. Rupture of the delicate cord-like remnant above the fenestrations resulted in a flail prolapsing cusp.	Acute AR due to spontaneous rupture of a fenestrated cusp. Surgical intervention was recommended, but the patient died of an acute intracranial hemorrhage 2 weeks later.
28. Yotsumoto et al (2003)	5 Patients with AV fenestration out of 9 patients with congenital quadricuspid AV	5 Males: 49, 57, 59, 61, 70 4 Females: 47, 65, 66, 68	All 9 patients had quadricuspid AVs. Histopathology disclosed fibrous thickening and myxoid degeneration in the AR cases.	Small cusp fenestration was seen in 5 of the AR patients with congenital quadricuspid AV. However, this was probably not the cause of the AR. All patients underwent AV replacement.
29. Vaideeswar and Deshpande (2003)	1	Male, 30	Autopsy: large fenestrations (0.5–0.8 cm) were seen at the commissural aspects of the right and noncoronary cusps, which extended toward their bases. Similar smaller deficiencies were also seen adjoining the commissure between coronary cusps.	Acute aortic dissection in a young male with concomitant AV fenestrations. A congenital developmental anomaly that produced concomitant degenerative changes in the cusps with large fenestrations, and medial degeneration of the aorta with resultant acute dissection, was assumed to exist.

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
30. Akiyama et al (2004)	6	6 Males, 42–68 (mean 53.3)	Echocardiography: abnormal fibrous cord attached to the prolapsing cusp was visible in 3 cases with ruptured fenestrated valve; an intact fenestrated fibrous cord at the commissure was seen in 1 case. Intraoperative: Fenestrations were located within every cusp at all 3 commissures in 5 cases, and the other case had fenestrations within only 2 cusps. The RCC was fenestrated in all cases. One fenestrated fibrous cord was torn in 3 cases and 2 fibrous cords of 2 different cusps located at the same commissure were torn in 1 case. The fenestrated fibrous cords were intact in 2 cases. The site of the ruptured fenestrated fibrous cords was on the RCC (4 cases). One of them had the other ruptured fibrous cord on the NCC. Histopathology: the excised AVs showed moderate to severe myxomatous degeneration in all 6 cases. The end of the ruptured fenestrated fibrous cord showed severe myxomatous degeneration.	6 Male patients with massive AR and enlarged fenestrations or ruptured fenestrated fibrous cords were investigated. 4 Cases had family histories of AR. All 6 patients showed moderate to severe AV myxomatous degeneration and enlargement of aortic annulus. 4 Patients had one or 2 ruptured fibrous cords, located at the RCC.
31. Bourgault et al (2007)	1	Male, 72	Echocardiography: Moderate AR and a mobile lesion on the right aortic cusp. Intraoperative: fenestrations were seen to be present on the aortic cusps. One thread-like elongated fibrous strand of 10 mm length attached to the RCC resembled a rupture fenestration. Histopathology: The AV had myxomatous degenerative changes and a wide fenestration on the RCC, which was ruptured on 1 side causing the free edge of the valve to appear as a filiform excrescence.	AV fenestration bridging strand rupture, discovered in the course of coronary artery surgery. Valve replacement was carried out.
32. Reade et al (2009)	1	Male, 67	Intraoperative: AV fenestrations at all 3 commissural connections to the sinus.	Ascending aortic dilatation with consequent tearing of the weaker leaflet tissue below the commissural attachments, causing fenestrations in each of these attached areas. Significant AR was due to inappropriate central coaptation and the peripheral fenestrations. Surgical AV replacement was performed.
33. Kawanishi et al (2008)	1	Male, 56	Echocardiography: quadricuspid AV with an accessory cusp between the RCC and NCC. Intraoperative: AV with 3 cusps of equal size and one small accessory cusp between the RCC and NCC. The valve leaflets were thickened with some calcification and fenestration.	Male with quadricuspid AV and severe regurgitation who underwent surgical AV replacement. The resected cusps showed fibrotic thickening with calcification and fenestration.

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Table 1
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Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
34. Watabe et al (2009)	1	Male, 7 months	Intraoperative: the AV was tricuspid, but the LCC had a large defect with thin tissue. The defect was thought to be the result of spontaneous rupture of the fibrous strand of the fenestrated AV.	Severe AR due to spontaneous rupture of a congenitally fenestrated AV in a 7-month-old male, in whom a Ross procedure was performed.
35. Urbanski (2009)	56 (13 With commissural fenestrations with cusp prolapse)	-		56 Patients underwent tricuspid AV repair due to AR; 13 Patients (23%) revealed commissural fenestrations with cusp prolapse.
36. Schäfers et al (2010)	111 (39 With fenestrations)	85 Males 26 Females 1–85 years; mean age 57 ± 17 years		111 Patients underwent AV reconstruction for regurgitant tricuspid AVs without root dilatation. Cusp prolapse was associated with fenestrations in 39 subjects. Fenestrations are not infrequent in the absence of root dilatation. Fenestrations were observed in the presence of normal configuration of aortic cusps and in pediatric patients with normal AV function. A fenestration was closed most frequently on the RCC (n = 28) and less frequently on the left (n = 4) or NC (n = 9) cusps. Two fenestrations were closed in 2 individuals.
37. Losenno et al (2012)	40 (15 With fenestrations)	–		The AVs from 40 adult cadaveric specimens were harvested and examined for fenestrations. 37.5% of all specimens were found to have AVs with at least one fenestrated cusp. Of those with fenestrations, 73.3% were in the LCC, 53.3% were in the RCC and 33.3% were in the NCC. Preliminary data suggested that cusps with a smaller perimeter are more prone to fenestrations.
38. Losenno et al 2012)	67 (26 With fenestrations)	73.2 ± 16.0		67 Adult cadaveric hearts were harvested and examined: 26 (38.8%) hearts had fenestrations of the AV cusps. Of those valves, 50% had one fenestrated cusp, 38.5% had 2 fenestrated cusps and 11.5% had fenestrations in all 3 cusps. Fenestrations occurred most frequently in the LCC (50%), followed by the RCC (33.3%) and least frequently in the NCC (16.7%). Cusps with fenestrations tend to be larger than non-fenestrated cusps, with significant differences noted in the free-margin length, attached length, perimeter, and area of the NCC.

(*continued*)

Table 1
(continued).

Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
				Furthermore, most dimensions of the NCC and RCC were significantly larger than the LCC in AVs with fenestrations, but not in valves without fenestrations.
39. Ishige et al (2012)	1	Female, 56	Echocardiography: tricuspid AV with border irregularity and partial thickness without calcification, prolapse, and perforation. A mobile fibrous strand (length 7 mm) was detected at the LCC commissure. Intraoperative: the NCC had a giant fenestration (size 17 mm × 3 mm) and the LCC had a fibrous strand rupture, namely, a torn strand of its fenestrated cusp. Histopathology: Rupture of elastic fibers and spindle-cell proliferation with myxoid matrix in the perforated site of the NCC, and degeneration of collagen fibers and lipomatous metaplasia in the basal NCC.	Moderate AR due to fibrous strand rupture of a fenestrated LCC. Surgical AV replacement was performed.
40. Akasaka et al (2012)	1	Female, 56	Echocardiography: severe AR with an abnormal fibrous strand on a prolapsed LCC. Intraoperative: fenestration of the LCC at the commissure between the right and left coronary cusps. Histopathology: myxomatous degeneration of the AV.	Acute severe AR due to fibrous strand rupture in a fenestrated AV. Surgical AV replacement was performed.
41. Yamasaki et al (2012)	1	Male, 74	Echocardiography: sclerotic changes in the right and noncoronary cusps, consisting of an almost bicuspid configuration, with a rudimentary LCC, which had a hole 5 mm in diameter.	Presence of a rudimentary LCC with a 5-mm fenestration, diagnosed by 3D-echocardiography. The rudimentary cusp covered the left coronary ostium but the flow was maintained thanks to the fenestration. AV replacement was performed.
42. Cheruvu et al (2013)	1133	–	42 Cases with fenestrated AV, of which 26 had surgery primarily for AR: 20 tricuspid, 5 bicuspid, and 1 quadricuspid. Leaflet prolapse seen in 11 patients. Three, 2 and 1 leaflets fenestrated seen in 9, 10, 7 patients. 11 Patients with dilated aortic root in isolation or accompanied by a dilated ascending aorta.	All patients underwent surgery for AV insufficiency.
43. Mahara et al (2014)	61 (9 With fenestrations)	–		61 Patients who underwent AV plasty for AR were investigated. 9 patients had AV fenestration that required autologous pericardial patch closure. In 7 of those 9 patients, AR was due to the fenestration, as diagnosed by pre-operative 3D-echocardiography.
44. Ohira et al (2014)	1	Female, 48	Intraoperative: quadricuspid AV with fenestrations in the 2 NCCs.	Quadricuspid AV with severe central AR submitted to repair surgery. Fenestrations in

(*continued*)

Table 1
(continued).

Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
				the 2 noncoronary cusps, near the commissure between them, were detected intraoperatively.
45. Jodati et al (2014)	1	Male, 52	Echocardiography: Thickened and calcified AV (rheumatic disease), with severe regurgitation. Intraoperative: Malformed AV with 3 equal-sized cusps, each of which had a single large central fenestration. Histopathology: AV with degenerative changes with fibrosis, sclerosis, and calcification suggestive of rheumatic involvement.	Rheumatic AV disease submitted to AV replacement surgery. Surgery revealed a malformed AV with large central fenestrations in all 3 aortic cusps.
46. Irisawa et al (2014)	1	Male, 76	Echocardiography: tricuspid AV with fenestrated cusps with fibrous strands in the RCC and NCC. The LCC was prolapsed and had dropped into the left ventricle. A ruptured fibrous strand was attached to the LCC. Intraoperative: fibrous strands were found in all cusps. The right and noncoronary cusps formed fenestrations, and the LCC had a ruptured fibrous strand.	76-Year-old patient with severe acute AR who underwent AV replacement surgery. The valve was tricuspid with fibrous strands in all cusps. The right and noncoronary cusps formed fenestrations, and the left coronary cusp had a ruptured fibrous strand, which caused the acute AR.
47. Algami et al (2015)	1	Male, 80	Echocardiography: severe AV stenosis with a 15 mm × 4 mm mobile mass attached to leading edge of the RCC of the AV. Intraoperative: the AV was tricuspid with severe calcification at the bases of the cusps. A long fenestration was attached to the free margin of the RCC. Histopathology: the excised valve cusp was consistent with a ruptured, large AV fenestration.	Severe aortic stenosis submitted to balloon valvuloplasty. Postprocedure echocardiography identified a new mobile mass attached to leading edge of the RCC of the AV, which was later confirmed to be a ruptured, large AV fenestration.
48. Avayú et al (2016)	9	7 Males: 28, 36, 42, 53, 56, 58 and 58 2 Females: 66, 75	Echocardiography: slight to moderate myxomatous AVs, tricuspid in 8 patients and bicuspid in 1 patient; every patient presented gross protrusion, fenestration or rupture of the AV into the LVOT; involvement of the RCC in 8 patients and LCC in 1 patient.	Report of 9 cases of spontaneous rupture of an aortic cusp. The etiology can be myxomatous degeneration of the cusp and aortic ring and the RCC is most frequently affected. The presence of a wide fenestration of an aortic cusp can cause severe AR due to rupture of that cusp. This noninfectious and nontraumatic rupture is more frequent in males with chronic hypertension.
49. Ganguli et al (2016)	1	Female, 52	Intraoperative: fenestration of the RCC.	Severe AR due to fenestration of the RCC.
50. Ashalatha and Noone (2017)	210 (110 with fenestrations)	2.5–89	Autopsy: 110 Valves (52%) showed fenestrations: in one cusp only (n=39); 2 cusps (n=46); all 3 cusps (n=24); all 4 cusps (n=1).	210 AVs were investigated during random autopsies. Out of 210 valves, 110 showed fenestrations (52%). The size and shape of the fenestrations varied, starting from pinhole size to 0.5 cm. Lowest age in which the valve showed fenestrations was 2½ year. A relation

(*continued*)

Table 1
(continued).

Study (year)	Number of patients	Sex, Age	Aortic valve description	Main findings
				between age and sex with occurrence of fenestrations was not seen in the present study. All the 4 cusps of the quadricuspid AV showed small fenestrations.
51. Matsukuma et al (2018)	1	Male, 60	Echocardiography: commissural detachment between the LCC and NCC of the AV, suspended by an unruptured commissural fibrous strand of a fenestrated cusp.	Very rare case of aortic root dilatation, commissural detachment and commissural fibrous strand. Aortic root reimplantation and valve repair was performed with success.
52. Mahara et al (2017)	1	Male, 56	Echocardiography: tricuspid AV with prolapsed RCC and severe eccentric regurgitation. 3D-echocardiography: a ruptured fibrous strand was attached to the RCC.	The first documented 3D-echocardiography visualization of spontaneous rupture of a fenestrated cusp, successfully treated with AV repair.
53. Roumy et al (2017)	1	Male, 70	Echocardiography: severe acute AR due to leaflet prolapse. Intraoperative: AV showed a strand rupture of the isolated fenestration.	The patient was admitted as an emergency for acute heart failure after coital exertion.
54. Yang et al (2019)	382 (27 Patients with fenestrations)	315 Males 67 Females 54±16		AV fenestrations were present in 27 (7%) AR patients (3% BAV vs 11% TAV) in surgical and pathological assessment, of which 12 had fenestration-related AR: 8 (67%) had ruptured fenestrations, all had eccentric jets, and 9 (75%) had cusp prolapse by echocardiography. Only 1 case of fenestration as an isolated mechanism of AR. Patients with tricuspid AV had more fenestration-related AR, which was not readily identifiable by TEE.

AR = aortic regurgitation, AV = aortic valve, LCC = left coronary cusp, LVOT = left ventricle outflow tract, NCC = noncoronary cusp, RCC = right coronary cusp, SEM = scanning electron microscopy, TEE = transesophageal echocardiography, VSD = ventricular septal defect. For complete references see text.

* Data extracted from Akiyama, K. (1998) and Blaszyk, H. (1999).

† Data extracted from Akiyama, K. (1998) and Blaszyk, H. (1999).

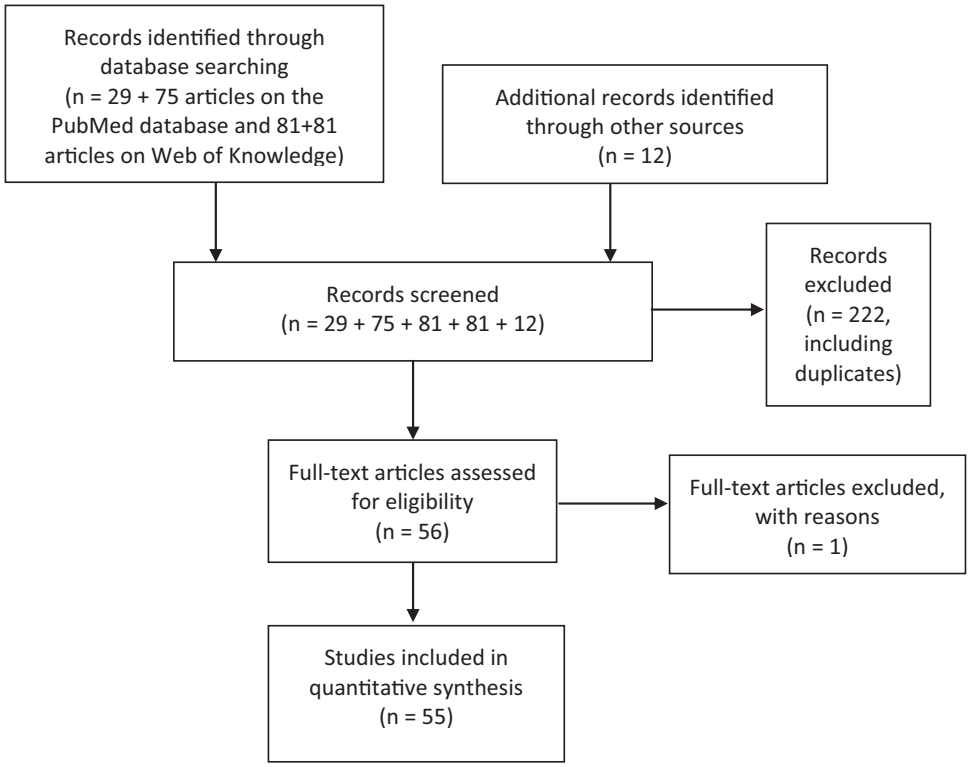

Figure 1. Flowchart showing literature search method. n = number of articles.

Aortic valve fenestrations in Down and Marfan syndromes

AVF was seen in association with Down syndrome. Sylvester[36] conducted an investigation to study the incidence of semilunar valve fenestrations in 23 patients with Down syndrome and in 56 "mentally subnormal" subjects, used as controls. Sylvester identified 10 patients with Down syndrome (43.5%) who exhibited AVFs, whereas in the control group only 2 patients (3.6%) had these features in the valvular leaflets (not specified in which semilunar valve). In addition, the author described that there was a significant increase in frequency with increasing age.

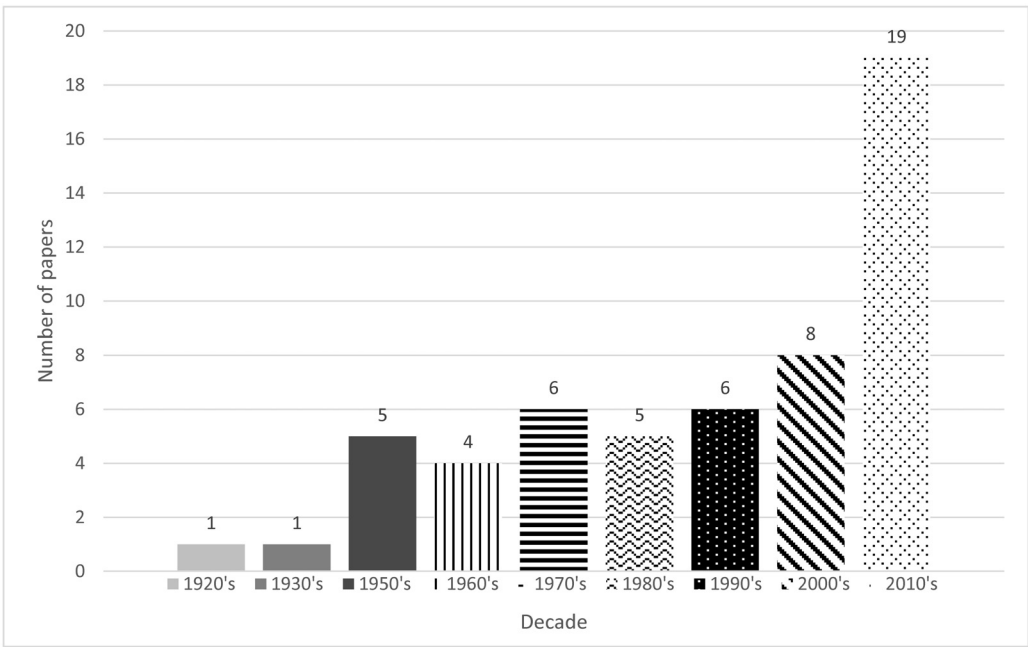

Figure 2. Classification of research papers by year of publication.

Table 2

Prevalence of fenestrations in aortic valves in 4 autopsy studies.

Author(s)	Type of study	Number of hearts examined	Number of hearts with fenestrations	Percentage of hearts with fenestrations
Foxe (1929)	Autopsy	300	188	62.7
Friedman and Hathaway (1958)	Autopsy	342	190	55.6
Losenno et al (2012)	Autopsy	67	26	38.8
Ashalatha and Hannah Noone (2017)	Autopsy	210	110	52.4
Total number		919	514	55.9

A case of AVF was described in association to Marfan syndrome.[8]

Fenestration in bicuspid and quadricuspid aortic valves

As already mentioned above, fenestrations were also seen in association with BAVs. We found 4 case reports[14,29,35,37] and 2 cases in the above mentioned study of Yang et al,[59] in which fenestrations were present in BAVs. All the 6 patients had fenestration-related AR, of which 3[14,35,37] had spontaneous rupture of the fenestrated AV.

Cases of fenestrations in QAVs have also been identified, with at least 10 case reports[19,41,42,46,53] and 1 small case series[10] in the literature. All the cases described patients with AR, but unlike the cases of BAVs, only 1 case[41] had its underlying cause attributed to valvular fenestrations, while in the remaining 9, AR was due to other mechanisms.

Myxomatous degeneration

Many published articles have described myxomatous degeneration in AVs with fenestrations. There are at least 9 case reports and series[5,6,8–14] that found myxomatous changes in the affected cusps. Friedman and Hathaway[7] described in their autopsy study that several aortic leaflets showed myxomatous degeneration in varying degrees; however, it was not possible to make a definite correlation between any of the changes seen in microscopic study and the presence of fenestrations.

Discussion

In the present report, we undertook a review concerning AVFs. These fenestrations are commonly located in the commissures, they are considered a frequent condition and their existence is well established for more than a century[1,2]; however, their clinical relevance and possible complications have not been clarified yet.

In our review, we assessed the published articles on this subject, and our results show that an estimate of 55.9% of individuals has fenestrations in aortic leaflets, according to autopsy studies (Table 2). The incidence of fenestrations is considerably higher in men than in women.[7] Its frequency increases with age up to the fourth decade[4,7] and slightly decreases from the fifth decade on, which can be explained by the development of sclerotic lesions that obliterate small defects.[4]

Many authors speculate that the changes caused by myxomatous degeneration in the AV are responsible for the development of the fenestrations; nevertheless, this correlation has not been firmly demonstrated. For instance, Friedman and Hathaway observed similar degenerative alterations in healthy valves without fenestrations. Therefore, the presence of myxomatous degeneration per se is not sufficient to cause these effects, and the contribution of other factors must be considered. In 3[4,7,24] of the 4 biggest patient series, the authors hypothesized that, due to the eccentric anatomic configuration of some AVs,[24] the turbulent shear stress distribution of the blood flow on the leaflets leads to the development of the fenestrations. Moreover, it has been hypothesized that chronic arterial hypertension in some patients might play some role in the etiology of this type of valvular injury, by interacting with the dynamics of the blood stream and creating a tensile stress on the cusps. Nonetheless, it does not explain the existence of fenestrations in valves that are not under such stress, hence chronic hypertension does not seem to be an essential etiologic factor.

On the contrary, Foxe visualized fenestrations in fetal hearts, along with other authors who reported several cases of congenital etiology.[6,7,15–20] Thus, defects during embryonic development may contribute to the adult pattern now described.

Other etiologies such as ulcerative endocarditis,[4,19,20,22] and traumatic origin[4,30] were also identified. However, there is no consensus among the authors as to whether these defects due to secondary causes should be considered as fenestrations. Such a perspective would point to a mechanical etiology for some cases of fenestrations.[4]

In addition, many articles have recognized fenestrations as the space limited by a fibrous strand which anchors the free edge of the cusps to the inner wall of the aorta. In this context, the opening formed in atypical bicuspid AV where a fenestrated raphe joins the valve cusp to the aortic wall is also included in the classification of fenestration.

Currently, the concept of valvular fenestration is not well defined in the literature and is often used as a synonym of perforation, hole, or as an atypical form of bicuspid AV with a fenestrated raphe. Standardized classification criteria for valvular fenestrations in medical terminology are needed to clarify the distinction between this condition and other similar features in future articles.

Although fenestration is a common feature, it rarely causes clinical manifestations or has influence on AV competence. Among the causes of aortic insufficiency, fenestrations account for only 3.1% of AR mechanisms.[59] Nonetheless, regurgitation can occur in cases of large valvular fenestrations,[7,11,15,17,18,20,28,34,38,41,54] particularly in large central ones,[15,20,41] and in spontaneous rupture of fenestrated AVs, causing sudden appearance or worsening of a chronic AR.[6,8,11–14,16,22,23,27–31,35,37,38,45,52,54,56,59] Iatrogenic rupture of a fenestration caused by balloon aortic valvuloplasty was also identified.[54] It has been suggested that the presence of associated modifying factors, such as aortic root dilatation, can trigger fenestration-related AR. Aortic root dilatation, which reduces the height of the subcommissural triangles and the coaptation area of the cusps, leads, as a consequence, to the incorporation of the fenestration into the functional portion of the valve. Incompe-

tence through the fenestration may hence develop, allowing the subsequent presence of a regurgitation jet.[7,31]

Sylvester pointed at an association between Down syndrome and the number of fenestrations in the AV. These were significantly commoner in patients with Down syndrome (43.5%) than in patients with normal karyotype (3.6%), occurred at a younger age and showed a pronounced tendency to rise in incidence with increasing age. The most obvious limitation in this research was the small sample size, which prevented a clear generalized statement about this correlation.

Fenestrations were also seen in association with congenital bicuspid and quadricuspid AVs. Nevertheless, as there are no epidemiological data available concerning the present subject matter and the number of cases reported in the literature is limited, it was not possible to reach conclusive results. Further studies are necessary to assess the incidence of fenestrations in nontricuspid AVs and its possible complications, namely AR.

Concerning diagnostic tests, although AVFs are common features, they are not promptly diagnosed by echocardiography. Because of their anatomic location (coaptation zone or paracommissure), visualization of fenestrations by transesophageal echocardiogram is relatively difficult, meaning that a negative echocardiogram alone cannot exclude their presence. Thus, fenestration-related AR is generally identified during surgical inspection. However, ruptured fenestrations frequently show leaflet prolapse, which could be a clue to their presence.[59] Another suggestive echocardiogram finding is the visualization of a mobile fibrous strand attached to an aortic cusp near its commissure, particularly in a prolapsing leaflet. Although fenestrations rarely cause valvular incompetence, they should be considered in the differential diagnosis of AR, particularly in male patients with chronic AR or acute deterioration of the regurgitation, in the absence of any other plausible cause.

It is unknown whether AVFs play any role in the current epidemic of AV disease, namely if the presence of 1 or more fenestrations changes the incidence of clinical AV disease, either stenosis or regurgitation. Currently, this topic seems to be largely overlooked, not being mentioned in current guidelines.[60] Future research may perhaps establish if the incidence of AV stenosis is changed in association to the previous presence of valve fenestrations.

Limitations

Texts written on non-English or Spanish languages were not considered. We were unable to obtain 7 full texts from the selected reports, one of which[21] was not included in Table 1 for that reason. Four reports were included in Table 1 with the data based on the respective abstracts.[24–27] Concerning the other 2 reports,[22,23] the presented data were obtained from other cited reports.[8,28] Marked differences were seen in the reports under analysis.

Conclusions

Autopsy studies showed AVFs to be relatively common, being present in 55.9% of individuals studied in such studies. They occur more frequently in men and, in general, their frequency increases with age. Fenestrations rarely cause marked regurgitation; however, they may play an important role in the pathophysiology of some cases of severe aortic insufficiency. AVFs have been described in patients with Down syndrome, in patients with bicuspid or with quadricuspid valves, and in patients with myxomatous valvular degeneration.

It is unknown whether AVFs play any role in the current epidemic of AV disease. Future studies should aim to better define the role of AVFs in AV disease, to further understand its etiology and to develop diagnostic criteria.

Acknowledgments

None.

Conflicts of interest

The authors declare no competing interests.

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