Right atrial appendage aneurysms in veal calves and beef cattle: anatomopathological investigations and aetiopathogenetic hypotheses

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Abstract

Objectives: Right atrial aneurysms have been reported in bovine species, but a clear aetiopathogenesis has never been elucidated.

Animals: 1079 veal calves (6-9 months old) and 313 beef cattle (10-24 months old) housed in intensive livestock farming systems and regularly slaughtered were included in the present study.

Methods: Hearts were externally examined and the identified right atrial aneurysms were submitted for gross and histopathological investigations.

Results: Right atrial aneurysms, which involved the right auricle, were detected in both veal calves (4.63%) and beef cattle (8.63%). Two types of aneurysms were observed: one type showing communications with the atrial lumen, the other one having no connections with it. Aneurysms communicating with the atrial lumen were characterized by endocardial fibrosis, whereas the other ones showed arterial characteristics (intimal fibromuscular hyperplasia and medial elastic fiber and fibrous tissue deposition).

Conclusions: Considering the similarities with the right atrial aneurysms reported in people, the aneurysms communicating with the atrial lumen were considered to be caused by an inherent atrial weakness (so called "*loci minoris resistentiae*" areas). On the contrary, the aneurysms with no communications with the atrial lumen, whose localization suggested an origin from the intramural coronary arteries of the pectinate muscles, may be subsequent to systemic hypertension due to intensive livestock farming conditions.

Keywords

Aneurysm;

Atrium;

Bovine;

Heart.

Introduction

Aneurysms or diverticula are persistent and circumscribed dilations of cardiac walls, valves or vessels [1,2].

In human medicine, right atrial aneurysms or right atrial appendage aneurysms are described as saccular outpouchings from an otherwise normal right atrium [3,4] that communicate with the atrial lumen via a broad neck [3]. They are rare congenital or acquired anomalies [4,5] identified with equal sex distribution [3,4]. Congenital aneurysms are thought to arise due to dysplasia of muscular wall of right atrium [6] or congenital absence of myoblasts in this region due to embryonic viral infection or other insults [7]. Acquired aneurysms could be subsequent to long-standing elevated right atrial pressure and increased right atrial volume due to a variety of disease processes including pulmonary hypertension, congenital cardiac defects and heart failure [4]. Endocardial fibrosis is a common histopathological finding [4], accompanied in some cases by lymphocytic infiltration [8] or lipomatous degeneration [9].

In veterinary medicine, right atrial aneurysms have been reported in several animal species, such as swine, horses, and cattle [10]. Right atrial aneurysms are frequently observed in young swine (reported prevalence of 0.82) and usually involve the atrial wall (considered a *locus minoris resistentiae*, a place of less resistance), with wall weakening and thinning subsequent to increased atrial pressure. Hovewer, a genetic predisposition is also considered [11]. In horses, right atrial aneurysms are tipically acquired and their frequency increases with age [12]. In bovine species, right atrial aneurysms are infrequently detected at the slaughterhouse in veal calves and beef cattle [13,14]. They can also involve the left atrium in a lower percentage of cases [13].

Given their low prevalence, a clear aetiopathogenesis of right atrial aneurysms in cattle has not been elucidated. The present study aims to describe systematically the right atrial aneurysms observed in regularly slaughtered veal calves and beef cattle and provide hypotheses regarding their aetiopathogenesis.

Animals, Materials and Methods

1079 veal calves (6-9 months old) and 313 beef cattle (10-24 months old) from different herds of Northern Italy were regularly slaughtered between January 2013 and June 2014 and included in the present study. Veal calves were all male and belonged to mixed (93%, 1004/1079), Charolaise (3%, 38/1079), Holstein Friesian (2%, 19/1079) and Piedmontese (2%, 18/1079) breeds. Beef cattle were all male too and belonged to Blonde d'Aquitaine (43%, 136/313), Charolaise (27%, 83/313), Piedmontese (13%, 42/313), Croisè (7%, 21/313), mixed (7%, 21/313) and Limousine (3%, 10/313) breeds. Veal calves were reared in individual stalls or group pens (6-10 animals/pen) with a traditional diet of milk replacer and solid feed, while beef cattle were housed in tie-stalls with a concentrated diet of corn silage, corn, hay and a commercial protein supplement. After slaughter, all hearts were submitted to the Department of Veterinary Sciences of University of Turin for anatomopathological investigations.

Gross and histopathological examination

At gross examination, the right atrial aneurysms were described on the basis of their location, distribution and dimensions. The right atrium was successively isolated, and toluidine blue solution was poured into it in order to investigate the presence of communications between the aneurysms and the atrial lumen (Fig. 1). After right atrium removal, the heart was sectioned across the median longitudinal plane in

126 order to evaluate all the cardiac structures. The entire right atrium and multiple
127 myocardial samples of the left and right ventricular free walls and the interventricular
128 septum were collected and fixed in 10% buffered formalin solution. After fixation,
129 transverse sections were performed at 5 mm intervals across the right atrium to
130 evaluate the entire atrial surface and assess for necks connecting the aneurysms
131 with the atrial lumen. Representative aneurysms and myocardial samples were
132 processed by routine methods, embedded in paraffin wax blocks, sectioned at 5 μm
133 thickness, mounted on glass slides and stained with Haematoxylin & Eosin (HE).
134 Selected sections of aneurysms were also stained with Weigert Van Gieson (WVG)
135 and Masson's Trichrome (MT). Tissue sections were finally examined by light
136 microscopy independently by three observers. The discordant cases were reviewed
137 at a multi-head microscope until a consensus was reached.
138
139 **Results**
140 Right atrial aneurysms were detected in 5.53% (77/1392) of the animals included in
141 the present study. In particular, 4.63% (50/1079) of the veal calves and 8.63%
142 (27/313) of the beef cattle were affected.
143 At gross examination, aneurysms involving the atrial appendage appeared as
144 multiple, saccular and round structures with a thin and transparent wall that were
145 either empty or filled with blood. Fourteen of 77 aneurysms (18.18%) were isolated
146 (Fig. 2A), 19 (24.68%) multifocal (Fig. 2B), 10 (12.98%) organized in small clusters
147 (Fig. 2C) and the remaining 34 (44.15%) disseminated (Fig. 2D). The toluidine blue
148 solution allowed the differentiation between two types of aneurysms. The first type
149 (19.48%, 15/77) had a diameter of 0.5-0.6 cm, involved both dorsal and ventral
150 surfaces of the right atrial appendage and were connected with the atrial lumen by a

neck (Fig. 3A). The second type (42.86%, 33/77) had a diameter of 0.1-0.2 cm, were localized within the subepicardial fat of the free margin of the right atrial appendage and showed no communications with the atrial lumen (Fig. 3B). Twenty-nine of 77 aneurysms (37.66%) showed a mixture of the two types. Apart from the right atrial aneurysms, no other cardiac alterations were observed.

At histopathological examination, the aneurysms with atrial connection showed a thin wall with severe and diffuse endocardial fibrosis (Fig. 3C). On the contrary, the aneurysms without any communication with the atrial lumen had a thicker wall and were analogous to a remodeled artery. Indeed, they were characterized by mild and diffuse fibromuscular hyperplasia of the tunica intima and severe and diffuse elastic fiber and fibrous tissue deposition in the tunica media (Fig. 3D). Aneurysms were frequently accompanied by severe and multifocal chronic and proliferative epicarditis, characterized by papillary proliferations of fibrous/fibrovascular tissue infiltrated by mononuclear inflammatory cells (Fig. 3E-3F). Mild and multifocal lymphoplasmacytic inflammation with or without myocardial replacement fibrosis was also observed in the adjacent myocardium. Myocardial samples of the left and the right ventricular free walls and the interventricular septum showed no significant alterations.

Discussion

The results obtained in the present study suggest the existence of two different types of right atrial aneurysms involving the atrial appendage in bovine species: one type directly communicating with the atrial lumen, the other showing arterial characteristics and having no communications with the atrial lumen.

Anatomopathological features of the right atrial aneurysms involving the appendage wall are similar to those reported in humans [4,5,8]. In the present study only young

animals were considered and multiple aneurysms were observed, analogous to the reported occurrence of multiple aneurysms in younger people [5]. Histopathological findings of endocardial fibrosis with or without inflammation were also similar [4,8]. In humans, right atrial appendage aneurysms can be congenital or acquired. In the present study, the more frequent observation of right atrial aneurysms in beef cattle than veal calves suggests these lesions are acquired rather than congenital. Acquired aneurysms in people are thought to result from long-standing elevated right atrial pressure and volume subsequent to pulmonary hypertension, congenital cardiac defects and heart failure [4]. Considering how the animals of the present study did not show gross or histopathologic evidence of any of these disorders or their identifiable consequences, this hypothesis is considered less likely. Nonseptal right atrial aneurysms have been reported in people and often involve the portion of the right atrium classically referred to as the subeustachian sinus, which may be an intrinsic area of weakness in the atrial wall [5]. In animals, the myocardium of the right atrial pectinate muscles may also be absent [15], potentially explaining the "*loci minoris resistentiae*" hypothesized in swine [10]. Therefore, an inherent weakness in the right atrial wall similar to the "*loci minoris resistentiae*" reported in humans [5] and other animal species [10,15] is considered a more likely hypothesis for the atrial aneurysms observed in cattle in this study.

Regarding the right atrial appendage aneurysms showing arterial characteristics, whose localization suggests an origin from the intramural coronary arteries of the pectinate muscles, the etiopathogenesis is more difficult to hypothesize. A genetic predisposition is considered less likely as the animals in the present study came from different geographic areas and belonged to several breeds and mixed-breeds. A possible etiopathogenesis hypothesis may be found in the intensive livestock farming

of the animals. A hyperalimentation with concomitant absence of exercise, cohabitation in restricted spaces and psychosocial stressor factors could lead to an increased metabolic rate, followed by increased cardiac output and consequently systemic hypertension development. Furthermore, hypertension has been reported as a possible subclinical pathological change in stress-related situations [16]. Blood pressure measurements were not available in the present study, so this hypothesis cannot be confirmed. Blood flow to the heart also occurs mainly during diastole, because intramuscular blood vessels are compressed and twisted by the contracting heart muscle during the systolic phase [17]. Therefore, diastolic hypertension should be mainly involved. However, coronary remodeling has been recently reported in systemic hypertension of both spontaneously hypertensive rat [18] and aortic coarctation mini-pig [19] models. Hypertensive rats also showed an “outward remodeling” phenotype, in which an increase in medial thickness is associated with arteriolar enlargement with little or no reduction in lumen diameter [18]. This phenotype is typical of systemic hypertension, as previously observed in renal hypertension in rats [20]. The aneurysms with arterial characteristics observed in the present study seemed to show the “outward remodeling” phenotype, thus supporting the hypothesis of systemic hypertension. Another critical point of this hypothesis could be represented by the presence of elastic fibers in the tunica media of the aneurysms, which is not characteristic of the intramural coronary arteries. However, a relationship between elastic fiber organization and/or deposition in resistance arteries and hypertension has been recently observed in spontaneously hypertensive rats models [21,22]. Firstly, the initial increase in mechanical stress imposed on vascular smooth muscle cells by high blood pressure could trigger the abnormal deposition of elastin [23]. On the other hand, the significant increase in the elastin content [22] and

the aberrant organization of elastic membranes [21] in arteries may be associated with the compromised mechanical performance of these arteries, leading to increased stiffness and inward remodeling [22]. Although elastic fibers organization/deposition and hypertension could be cause and effect of each other, this relationship could support the hypothesis of systemic hypertension.

Conclusions

In conclusion, the present study identifies two types of right atrial appendage aneurysms in bovine species and proposes two different etiopathogenetic hypotheses for them. The right atrial appendage aneurysms communicating with the atrial lumen are probably caused by an inherent atrial weakness, whereas those originating from the intramural coronary arteries of the pectinate muscles may be subsequent to systemic hypertension due to intensive livestock farming conditions. Further investigations are necessary to confirm these hypotheses.

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Figure captions

Figure 1. Isolated right atrium after toluidine blue solution application. Epicardial surface. Aneurysms that communicate with the atrial lumen appear blue (*), while the remaining arterial-type aneurysms lack blue-staining.

Figure 2. Gross characteristics of the right atrial aneurysms identified in the present study. A) Isolated aneurysms (*) within the subepicardial fat of the free margin of the right auricle. B) Multifocal aneurysms (arrow) involving the dorsal surface of the right auricle. C) Multiple aneurysms organized in small clusters (arrowhead) within the dorsal surface of the right auricle. D) Multiple aneurysms disseminated through the entire dorsal surface of the right auricle.

Figure 3. Gross and histopathological features of the two types of right atrial aneurysms observed in the present study. A) Focal aneurysm connected with the atrial lumen by a neck (arrow). B) Multifocal aneurysms with no connections with the atrial lumen (arrowhead). C) Aneurysms with atrial communication show a thin wall with severe and diffuse endocardial fibrosis (Masson's Trichrome stain, 10x magnification, bar = 100μm). D) Aneurysms not communicating with the atrial lumen show arterial characteristics. Mild and diffuse fibromuscular hyperplasia of the tunica intima (*) and severe and diffuse elastic fiber (arrow) and fibrous tissue (arrowhead) deposition in the tunica media are evident (Weigert Van Gieson stain, 10x magnification, bar = 100μm. Picture in the lower right: Weigert Van Gieson stain, 20x magnification, bar = 100μm). E) Multifocal aneurysms accompanied by mild and focal epicarditis. Epicardium appears reddish and thickened (*). F) Chronic and

proliferative epicarditis with papillary proliferations of fibrous/fibrovascular tissue infiltrated by mononuclear inflammatory cells (Haematoxylin & Eosin stain, 10x magnification, bar = 100µm).

Masson's Trichrome stain = collagen stains blue, while cytoplasm and muscle fiber stain red.

Weigert Van Gieson stain = elastic fiber stains black, collagen stains red and cytoplasm and muscle fiber stain yellow.