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1 **Right atrial appendage aneurysms in veal calves and beef cattle:**
2 **anatomopathological investigations and aetiopathogenetic hypotheses.**

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26 **Abstract**

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

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

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

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

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

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51 **Keywords**

52 Aneurysm;

53 Atrium;

54 Bovine;

55 Heart.

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76 **Introduction**

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

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

91 In veterinary medicine, right atrial aneurysms have been reported in several animal
92 species, such as swine, horses, and cattle [10]. Right atrial aneurysms are frequently
93 observed in young swine (reported prevalence of 0.82) and usually involve the atrial
94 wall (considered a *locus minoris resistentiae*, a place of less resistance), with wall
95 weakening and thinning subsequent to increased atrial pressure. However, a genetic
96 predisposition is also considered [11]. In horses, right atrial aneurysms are typically
97 acquired and their frequency increases with age [12]. In bovine species, right atrial
98 aneurysms are infrequently detected at the slaughterhouse in veal calves and beef
99 cattle [13,14]. They can also involve the left atrium in a lower percentage of cases
100 [13].

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

105

106 **Animals, Materials and Methods**

107 1079 veal calves (6-9 months old) and 313 beef cattle (10-24 months old) from
108 different herds of Northern Italy were regularly slaughtered between January 2013
109 and June 2014 and included in the present study. Veal calves were all male and
110 belonged to mixed (93%, 1004/1079), Charolaise (3%, 38/1079), Holstein Friesian
111 (2%, 19/1079) and Piedmontese (2%, 18/1079) breeds. Beef cattle were all male too
112 and belonged to Blonde d'Aquitaine (43%, 136/313), Charolaise (27%, 83/313),
113 Piedmontese (13%, 42/313), Croisè (7%, 21/313), mixed (7%, 21/313) and
114 Limousine (3%, 10/313) breeds. Veal calves were reared in individual stalls or group
115 pens (6-10 animals/pen) with a traditional diet of milk replacer and solid feed, while
116 beef cattle were housed in tie-stalls with a concentrated diet of corn silage, corn, hay
117 and a commercial protein supplement. After slaughter, all hearts were submitted to
118 the Department of Veterinary Sciences of University of Turin for anatomopathological
119 investigations.

120 **Gross and histopathological examination**

121 At gross examination, the right atrial aneurysms were described on the basis of their
122 location, distribution and dimensions. The right atrium was successively isolated, and
123 toluidine blue solution was poured into it in order to investigate the presence of
124 communications between the aneurysms and the atrial lumen (Fig. 1). After right
125 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

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

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

168

169 **Discussion**

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

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

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

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

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

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

231

232 **Conclusions**

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

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324 **Figure captions**

325

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

329

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

336

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

349 proliferative epicarditis with papillary proliferations of fibrous/fibrovascular tissue
350 infiltrated by mononuclear inflammatory cells (Haematoxylin & Eosin stain, 10x
351 magnification, bar = 100µm).
352 Masson's Trichrome stain = collagen stains blue, while cytoplasm and muscle fiber
353 stain red.
354 Weigert Van Gieson stain = elastic fiber stains black, collagen stains red and
355 cytoplasm and muscle fiber stain yellow.