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Fatal acute lung injury after balloon valvuloplasty in a dog with pulmonic stenosis

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A one-year-old, 8.7 kg, female, French Bulldog was referred to the Department of Cardiology of the Istituto Veterinario di Novara for the management of a severe form of pulmonic stenosis (PS). The dog had a history of exercise intolerance and right-sided congestive heart failure (ascites). At presentation, the dog was already receiving atenolol 0.8 mg/kg PO q12h, furosemide 0.3 mg/kg PO q12h, benazepril 0.3 mg/kg PO q24h and spironolactone 2.3 mg/kg PO q24h. On physical examination the dog was alert and bright, with pink mucous membranes, normal capillary refill time, a heart rate of 110 beats per minute with regular cardiac rhythm, and a respiratory rate of 24 breaths per minute. Jugular venous distension was evident. Cardiac auscultation revealed a left basilar, pansystolic, 4/6 grade murmur. A mild abdominal distention was evident. The rest of the physical examination was unremarkable.

Transthoracic echocardiography showed a thickened pulmonic valve, with systolic “doming” of the pulmonic valve leaflets and marked post-stenotic dilatation. The aorta-to-pulmonary artery ratio was 1,07. Right ventricular concentric hypertrophy and dilation, with flattening of the interventricular septum, and severe right atrial enlargement was evident (Figure 1, Figure 2, Video 1, Video 2). Doppler examination revealed severe tricuspid regurgitation, and high velocity, turbulent pulmonic systolic flow (pulmonary pressure gradient: 158 mmHg). The left heart had normal dimensions, with a mitral inflow pattern of impaired relaxation (E wave velocity 0.39 m/s; A wave velocity 0.45 m/s; E/A ratio 0.86; isovolumetric relaxation time 59 msec). Mild pericardial effusion was evident. Abdominal ultrasound showed hepatomegaly, dilated caudal vena cava and mild abdominal effusion.

Standard 6-lead electrocardiography showed sinus rhythm with right-shift of the QRS mean electrical axis.

All the clinical and echocardiographic findings were indicative of a severe type A valvular pulmonic stenosis with signs of systemic venous congestion and right-sided congestive heart failure.

A complete blood count and serum biochemical analysis were performed. A mild non-regenerative anemia was revealed (hematocrit 36.6%; reference range: 37.3 – 61.7 %). The biochemical analysis only showed a mild increase in blood urea nitrogen (36 mg/dl; reference range: 7-27 mg/dl). The other serum biochemical parameters were within reference intervals. In the coagulation profile PT was normal, aPTT was mild increased (21.1 sec, upper reference limit 20.0 sec), fibrinogen was mild decreased (101 mg/dL; lower reference 125 mg/dL), Antithrombin III, D-dimers and fibrinogen degradation products were normal.

ECG-gated computer tomography confirmed the presence of PS with post-stenotic dilation and severe right cardiac enlargement. No evidence of coronary artery abnormalities was seen.

A pulmonary balloon valvuloplasty (PBV) was performed. Before general anesthesia, the patient received a premedication with fentanyl (3 mcg/kg IV) and midazolam (0.2 mg/kg IV). Anesthesia was induced with propofol (3.4 mg/kg IV) and maintained with isoflurane (1.5%) with an inspired fraction of oxygen of 0.70. During the procedure cefazoline (20 mg/kg IV) and unfractionated heparin (75 UI/kg IV) were administered. Continuous monitoring included clinical evaluation, inspiratory, and expiratory fractions of CO2, O2, and isoflurane, spirometry, electrocardiographic monitoring, pulse oximetry and non-invasive blood pressure.

The patient was placed in left lateral recumbency, the lateral aspect of the neck was aseptically prepared, and the right external jugular vein was isolated in which an 8 French introducer has been inserted. Right ventriculography was performed using a

5.2 French pigtail catheter, and the pulmonary valve stenosis was shown. The pulmonary artery was catheterized with a 4 French Berenstein catheter, through which an extra-Stiff guide wire (260 cm) was passed. A 12 mm x 4 cm balloon was used. The balloon to pulmonary ratio was 1.36. At this point the balloon was inflated three times at the level of the pulmonic valve stenosis until the waist caused by the impression of the stenotic valve on the balloon disappeared.

Post-operative echocardiography performed one hour later showed a significant reduction of right atrial size (right atrial minor dimension: from 55 to 39 mm) and right ventricular size (right ventricular end-diastolic diameter: from 28 to 20 mm) from the right parasternal long-axis view [Boon 1998; Serres 2009; Chetboul 2018]. The opening and mobility of the pulmonary valve leaflets significantly improved. In addition, the pulmonary pressure gradient decreases from 158 mmHg pre-operative to 40 mmHg post-operative, corresponding to a 75% reduction.

The dog recovered well from the anesthesia and was transferred into the intensive care unit for the normal post-operative management where all the clinical parameters and lung ultrasound were normal. Two hours later, the dog suddenly showed severe respiratory distress. Lung ultrasound showed diffuse numerous-to-confluent B lines bilaterally, compatible with pulmonary edema. Focus cardiac ultrasound showed significant increase in left cardiac size in comparison to pre-operative echocardiography (left atrial-to-aortic root ratio: from 1.48 to 2.17; normalized left ventricular internal dimension in diastole: from 1.25 to 1.78). In addition, echocardiographic signs of increased left ventricular filling pressure were present (E wave peak velocity 1.28 m/s, A wave velocity 0.3 m/s, E/A ratio 4.3; isovolumetric relaxation time 31 msec).

A bolus of furosemide at the dose of 2 mg/kg IV was administered and then a constant rate infusion at 1 mg/kg/hr was started. The patient was also treated with oxygen therapy using a continuous positive airway pressure (CPAP) helmet. Two hours later, no clinical improvement was observed and lung ultrasound showed a worsening in the pulmonary edema. Thus, mechanic ventilation was started under general anesthesia using a total intravenous anesthesia of propofol (0.2 mg/kg/min) and midazolam (0.5 mg/kg/hr). The respiratory condition continued to worsen, and the patient spontaneously died. The owners requested necropsy.

The heart and lungs joined by vascular connections were stored in formalin 4% and sent to the Department of Veterinary Sciences of the University of Turin. The external examination of the heart showed severe dilatation of the right atrial and the first portion of the pulmonary trunk, and severe enlargement of the right ventricle (**Fig. X1**). At the transverse cut section of the heart, performed at the level of the third middle of the left ventricle, concentric hypertrophy of the right ventricle has been observed, with a thickness of 1 cm at the level of the free wall. Concentric hypertrophy of the left ventricle wall (thickness of the interventricular septum: 2 cm; thickness of the free wall: 1.5 cm) has also been observed. The outflow tract of the right ventricle presented an appreciable thickness (1.3 cm) of the infundibulum wall. Moreover a severe increase of the volume of the supraventricular crest was associated. The pulmonary valve observed from the arterial aspect showed thickened and irregular leaflets with the free edge adhering to the endothelial surface of the sino-tubular junction **(Fig X2**). The longitudinal cutting section conducted at the level of the outflow tract of the right ventricle and including the right and intermediate flaps of the pulmonary valve, so between the right and left side of the heart, demonstrated the severe increase in thickness of the valve flaps that showed

irregular, whitish and compact portions in the peripheral area and gelatinous material in the center with reddish streaks. Also from this point of view was clearly visible the solid fusion of the free margin of the flaps with the endothelial surface of the sino-tubular junction (**Fig. X3A and B**). In addition the lungs appeared brownish, with increased of consistency due to abundant edema.

Multiple samples were examined for histological investigation, in particular samples of the lung were analyzed using standard stain with Hematoxylin and Eosin (HE), and the special stains Phosphotungstic Acid-Hematoxylin (PTAH) to demonstrate the presence of fibrin, and Weigert Van Gieson to simultaneously highlight elastic fibers and connective tissue. Multiple samples of the right ventricle stained with HE and with Masson's trichrome to highlight fibrosis were examined. The pulmonary valve and the infundibulum of the right ventricle were analyzed using HE, Weigert Van Gieson and Masson trichrome staining in order to demonstrate fibrous tissue and elastic fibers. Finally portions of the free wall of the left ventricle with the parietal flap of the mitral valve stained with HE were investigated.

For the lung the main histological findings are represented by diffuse and severe broncho-alveolar edema associated to mixed leukocyte infiltrate. Multifocal and alveolar deposition of eosinophilic fibrillar material positive to PTAH was identified as fibrin associated with red blood cells and mixed leukocyte infiltrate (**Fig. X4A-B**). Diffuse and severe congestion and multifocal alveolar hemorrhages have also been observed. A focal venous thrombosis and multifocal, moderate to severe lymphoplasmacytic interalveolar infiltration have been demonstrated. The free wall of the right ventricle showed diffuse and significant hypertrophy of myocardiocytes associated with multifocal and moderate to severe myocardial interstitial fibrosis positive to Masson’s trichrome stain. The flaps of the pulmonary valve have shown

189 severe thickening due to the deposition of a severe fibrosis in the peripheral areas
190 and myxomatous tissue in the most central portions (**Fig. X5**), associated with
191 necrosis probably consequence of the mechanical action of the PBV. The fusion of
192 the free margin with the endothelium of the sino-tubular junction appears to consist of
193 dense fibrous tissue associated with proliferation of elastic fibers as demonstrated by
194 the Weigert Van Gieson and Masson's special stains.
195 Finally, the free wall of the left ventricle showed moderate and widespread
196 hypertrophy of myocardiocytes.
197 On the basis of anamnestic information, clinical and anatomopathological data, a
198 diagnosis of pulmonary stenosis type A and acute respiratory distress syndrome
199 (ARDS) after balloon valvuloplasty was made.
200

201 **Discussion**

202 In the present case, PBV resulted in a significant reduction in the pulmonary valve
203 pressure gradient (75%). PBV for pulmonary stenosis is considered successful when
204 it is obtained a reduction of the pressure gradient across the pulmonary valve by at
205 least 50% [Thomas 1995]. However, a fatal ARDS occurred soon post-operatively.
206 The most serious complications of this procedure reported in the veterinary literature
207 include life-threatening arrhythmias, cardiac or vascular perforation, valve damage,
208 intramyocardial contrast injection during ventriculography, pneumothorax, pulmonary
209 thromboembolism and pulmonary edema [Bairn, 1996; Claretti 2019]. Pulmonary
210 edema can be the consequence of sudden increase in pulmonary blood flow after the
211 dilation of a long-standing stenosis, with sudden increase in right ventricular output
212 and volume overload of the left heart. The subsequent increases in left atrial
213 pressure and pulmonary venous pressure may cause pulmonary edema [Walk 2001].

The incidence of pulmonary edema after PBV is reported in up to 15-22% of cases in humans, and the severity of symptoms varies from severe to self-limited condition [Yacuby 2014]. In human medicine, fatal ARDS after PBV was first described in a case report in 2001. Similar to our case, the patient suffered from a severe PS whit right-sided congestive heart failure that was treated with BPV, the interventional procedure was successful with a reduction of the pulmonary pressure gradient of 78%. However, after few hours the patient developed a severe respiratory distress. Like in our case, non-invasive oxygen therapy did not lead to improvement of the systemic oxygenation. The mechanic ventilation was necessary, however the patient died after three days. The mechanism underlying the acute lung injury in this case was reported as a possible consequence of pulmonary reperfusion-ischemia injury associated with an increased hydrostatic pressure due to a non-compliant left ventricle [Ostovan 2015]. To the authors' knowledge, the present case is the first report that describes an ARDS after PBV in a dog.

ARDS is a pathological condition characterized by pulmonary increased capillary permeability, edema and inflammation [3]. ARDS is not a disease, but a clinical condition defined by acute respiratory failure that arises following an insult of the lung or that involves secondary the lungs [4]. There are several pathophysiologic derangements that are central to the development of ARDS, including dysregulated inflammation and increased lung endothelial and epithelial permeability. It is also important to note that environmental and genetic factors contribute to the susceptibility and severity of ARDS [6]. The mechanism by which a relief of high transvalvular gradient produces acute lung injury is a source of debate. Some authors reported the theory of inflammation mediated reperfusion-ischemia injury as in lung transplantation, while others propose increase in end-diastolic volume of a

noncompliant left ventricle [7]. Another mechanism can be the acute increase in pulmonary blood flow after stenosis resolution that cause ARDS consequently to the inability of the microvasculature to restrict blood flow and the subsequent increase in hydrostatic pressure [8]. Whereas the increase in hydrostatic pressure seems to be the most prevalent mechanism by which ARDS happens, the difference of severity of the presentation let think that inflammatory mediated reperfusion ischemic injury might play a role [5]. In the present case the histological examination of the lung showed severe, acute findings such as edema and sterile alveolar inflammatory reaction, overlap with the damage observed in humans in case of pulmonary graft complicated by ischemia-reperfusion injury. In particular, it has been demonstrated in this case the production of reactive oxygen species (ROS) that induces the activation of the innate immune system and a rapid and complex inflammatory reaction with endothelial and epithelial dysfunction and release of cytokine (12).

XXX

The prevention and management of this condition is also not clear. However, in human medicine, it is suggested to reduce the balloon dimension and perform consequent PBV to gradually dilate the pulmonic stenosis. Using this method, it is possible to reduce the risk of sudden increase of hydrostatic pressure [9]. Consider the condition in which left heart could not be able to adapt an acute increase in preload after the dilation, it could be reasonable to think that standard therapy for congestive heart failure may prevent the edema [5].

Conflicts of interest statement

The authors do not have any conflicts of interest to disclose.

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Figure captions

Fig. X1 Heart, left side (auricular surface). Severe dilatation of the right atrium and enlargement of the right ventricle. The pulmonary artery and aorta were cut near their origin. 1: left auricle. 2: origin of the pulmonary artery. 3: origin of the ascending aorta. 4: right atrium. 5: infundibulum of the right ventricle. Arrow: haemorrhage close to origin of pulmonary artery and ascending aorta.

Fig. X2 Arterial aspect of the pulmonary valve. The flaps are thickened, irregular, brownish in colour and with the free margin fully attached to the endothelium of the sino-tubular junction (arrow).

Fig. X3A. Right outflow tract, longitudinal cutting section including the right and intermediate flaps of the pulmonary valve. Severe thickness of the infundibulum and

313 the supraventricularis crest secondary to severe thickening of the pulmonary valve
314 cusps.
315 Fig. X3B. Detail of the previous image. Notice thickening of pulmonary cusps and
316 solid fusion with the endothelium of the sine-tubular junction.
317 Fig. X4A. Histological finding of the lung characterized by alveolar deposition of
318 eosinophilic fibrillar material identified as fibrin and associated with red blood cells
319 and mixed leukocyte infiltrate. H&E, 10X.
320 Fig. X4B. Alveolar deposition of eosinophilic fibrillar material positive to PTAH and
321 identified as fibrin. PTAH stain, 10 X.
322 Fig. X5. Pulmonary cusp, severe thickness secondary to the severe in the peripheral
323 areas and myxomatous tissue in the most central portions (arrows). Masson's
324 special stains, 10 X