Holodiastolic Retrograde Flow in the Ascending Aorta in a Dog with Severe Aortic Regurgitation, Aortic Mineralization, and Systemic Hypertension

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INTRODUCTION

Holodiastolic retrograde flow within the ascending aorta has been variably reported in humans with cardiovascular conditions involving marked aortic regurgitation or increased aortic stiffness. In this report, we present a case of holodiastolic retrograde flow within the ascending aorta in a dog with concurrent aortic stenosis, aortic regurgitation, and degenerative valve disease involving the mitral, tricuspid, and aortic valves as assessed using transthoracic echocardiography (TTE) and gross pathologic evaluation. This case report of a dog exhibiting holodiastolic retrograde flow within the ascending aorta on echocardiography illustrates a rare combination of clinical conditions (increased aortic stiffness, severe aortic regurgitation, and systemic hypertension) that have been shown to produce this phenomenon in humans.

CASE PRESENTATION

A 12-year-old, castrated male Pomeranian was presented for evaluation of a chronic, recently progressive cough and mild lethargy. The dog had a history of chronic cough attributable to suspected tracheobronchomalacia, a heart murmur, and protein-losing nephropathy. On physical examination, a body weight of 5.4 kg, a heart rate of 100 beats/min, and intermittent panting, interrupted by a honking cough, were noted. Cardiac auscultation revealed a grade 4/6 left apical systolic murmur and a grade 3/6 right and left basilar diastolic murmur. Femoral pulses were strong, synchronous, and symmetric. Mildly increased bronchovesicular sounds bilaterally, without crackles or wheezes, were also appreciated on auscultation. Oscillometric blood pressure assessment was performed, and an average of eight measurements reflected a systolic blood pressure of 159 mm Hg. Diastolic and mean blood pressures were not recorded. Thoracic radiography was performed and revealed a vertebral heart score of 11.5 (normal range, $\leq$11.2),[1] a vertebral left atrial size of 2.75 (normal range, $<$2.5),[2] and evidence of moderate left atrial and left ventricular (LV) enlargement. Pulmonary vessels were normal in size, and a diffuse bronchial to bronchointerstitial pattern was noted in the caudodorsal lung fields, with no evidence of cardiogenic pulmonary edema. Focal dorsal deviation and narrowing of the trachea at the thoracic inlet were noted. Electrocardiography was consistent with a sinus arrhythmia and a wandering pacemaker (heart rate 100 beats/min). The animal underwent TTE, which revealed severe myxomatous thickening of the mitral valve leaflets with severe prolapse, resulting in moderate to severe holosystolic mitral regurgitation, moderate left atrial enlargement, and moderate LV eccentric hypertrophy (Videos 1 and 2). The aortic valve was also noted to be severely thickened, with reduced excursion, which was suspected to represent a combination of congenital aortic stenosis and myxomatous degeneration (Video 3), due primarily to the severity of stenosis. Severe aortic regurgitation was present, with an average pressure half-time of 168 msec and a peak pressure gradient of 100 mm Hg (Video 4). The aortic peak systolic velocity was markedly increased at 7.25 m/sec (pressure gradient 210 mm Hg; Figure 1A).

Mild concentric hypertrophy of the left ventricle was present, with a focal region of hyperechoic myocardium along the free wall, suggestive of ischemic injury. LV systolic function was hyperdynamic (fractional shortening 45% [normal range, 28%-45%], ejection fraction 65% [normal range, 50%-60%]), and the diastolic filling pattern was consistent with impaired relaxation. LV internal diameter in diastole was increased at 33 mm (normal range, 20-27 mm) and upper limit of normal in systole at 18 mm (normal range, 12-19 mm). On color flow Doppler interrogation, holodiastolic retrograde flow was appreciated within the ascending aorta in all right-sided, left-sided, and subcostal imaging planes and confirmed with spectral Doppler (maximum velocity 4.76 m/sec, pressure gradient 90.78 mm Hg; Figures 1B and 2; Videos 5 and 6). Ideally, extra echocardiographic views to interrogate the descending aorta would have been pursued, but because of the instability of the dog, these views could not be obtained.

The remainder of the echocardiographic findings were unremarkable, with the exception of mild tricuspid regurgitation secondary to myxomatous tricuspid valve disease. The dog was humanely euthanized several days later because of a refractory cough, cyanosis, and poor quality of life.

Necropsy was performed, which revealed severe segmental tracheal stenosis, mild myxomatous tricuspid valve disease, severe myxomatous mitral valve disease with chordae tendineae rupture, and aortic stenosis (valvular and subvalvular) combined with severe myxomatous degeneration of the aortic valve (Figure 3). Specifically, histopathologic review of the aortic valve leaflets revealed severe expansion of the leaflets by paucicellular basophilic mucinous wispy to fibrillar material with rare embedded spindle-shaped cells, consistent with myxoid degeneration. This change was noted to extend to the dense and firm region corresponding to the grossly

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VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, right parasternal long-axis four-chamber view, demonstrates myxomatous mitral valve disease with severe anterior mitral valve thickening, left atrial enlargement, and LV dilation.

Video 2: Two-dimensional TTE with color flow Doppler from the right parasternal long-axis four-chamber view demonstrates moderate mitral valve regurgitation.

Video 3: Two-dimensional TTE, right parasternal long-axis view of the aorta, demonstrates thickening of the aortic leaflets.

Video 4: Two-dimensional TTE with color flow Doppler from the subcostal view demonstrates severe aortic regurgitation.

Video 5: Two-dimensional TTE with color flow Doppler from the right parasternal long-axis view demonstrates turbulent systolic flow (aortic stenosis) and holodiastolic retrograde flow (aortic regurgitation) in the ascending aorta.

Video 6: Two-dimensional TTE with color flow Doppler from the right parasternal short-axis view demonstrates turbulent systolic flow (aortic stenosis) and holodiastolic retrograde flow (aortic regurgitation) at the level of the aortic valve.

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observed subvalvular endocardial thickening. Fibrous tissue was noted alongside these cellular changes, leading the pathologist to make note that the changes and severity of those changes described could make congenital stenosis indistinguishable from age-related degenerative changes. An important differential diagnosis in this case would include an absence of congenital aortic stenosis in favor of severe myxomatous degeneration of the aortic valve and the subvalvular lesion on gross images representing a jet lesion due to severe, chronic aortic regurgitation. The aortic root exhibited increased fibrous tissue and deposition of amorphous material marked by numerous variably sized foci of osseous and chondroid metaplasia (mineralization). Renal pathologic findings were consistent with marked bilateral renal glomerulonephritis.

Histopathologic diagnosis revealed mild pulmonary edema, lymphoplasmacytic and eosinophilic bronchitis, lymphoplasmacytic tracheitis, and severe chronic aortic fibrosis with osseous and chondroid metaplasia (valve and aortic wall).

DISCUSSION

This report is a description of holodiastolic retrograde flow in the ascending aorta in a dog. Diastolic retrograde flow in the ascending aorta, descending aorta, and aortic arch has been previously reported in humans. Under normal conditions, both antegrade and retrograde blood flow occurs in the ascending aorta during diastole. The retrograde flow is suspected to support coronary arterial perfusion and contribute to closure of the aortic valves with termination of systole.[3,4] Although not often readily appreciated on TTE, a small amount of diastolic retrograde flow has been noted in healthy human adults and pediatric patients and is considered physiologic.[5,6] Diastolic retrograde flow in the healthy human adult is best seen in the descending thoracic aorta and is brief, typically not exceeding the first third of diastole; the remainder of diastole is characterized by antegrade flow.[5] This physiologic diastolic retrograde flow increases with age and decreasing aortic compliance.[4,5]

Holodiastolic retrograde flow is not a normal finding in humans and has been reported with a variety of cardiovascular conditions, particularly those associated with severe aortic regurgitation or increased aortic stiffness, including systemic hypertension and plaque formation along the aorta.[5-7] Holodiastolic retrograde flow velocity and duration also increase with increasing severity of aortic regurgitation, making this finding on echocardiography a reliable criterion for grading the severity of aortic regurgitation in humans.[5,8] Holodiastolic flow reversal in the aorta has also been described in humans with sinus of Valsalva rupture, aortic dissection (involving flow into the false lumen), upper extremity arteriovenous fistulas, and left-to-right shunting patent ductus arteriosus, although most of these reports pertain specifically to flow reversal within the descending aorta rather than the ascending portion.[5,8,9]

Ex vivo flow patterns, distribution of fluid axial velocity, and wall shear stress have been evaluated in the aortic arch of the dog, demonstrating that the systolic flow through the aortic arch appeared as a single helical antegrade flow revolving in a clockwise direction.[10,11] Regions of lower wall shear stress were identified in these studies,

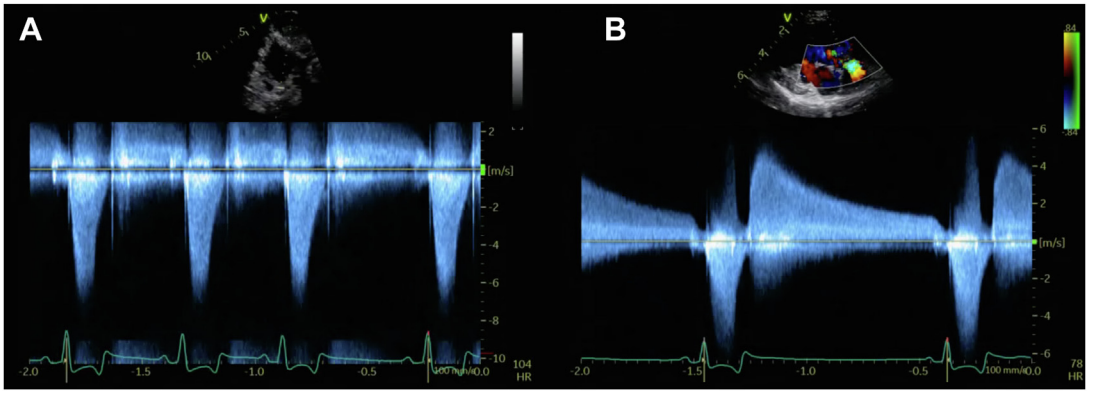

Figure 1 Two-dimensional TTE-guided continuous-wave Doppler spectral display of the aortic valve from the subcostal **(A)** and right parasternal long-axis **(B)** views. Peak aortic systolic velocity was markedly increased at 7.25 m/sec (pressure gradient 210 mm Hg), and peak velocity of the retrograde flow was 4.7 m/sec (91 mm Hg).

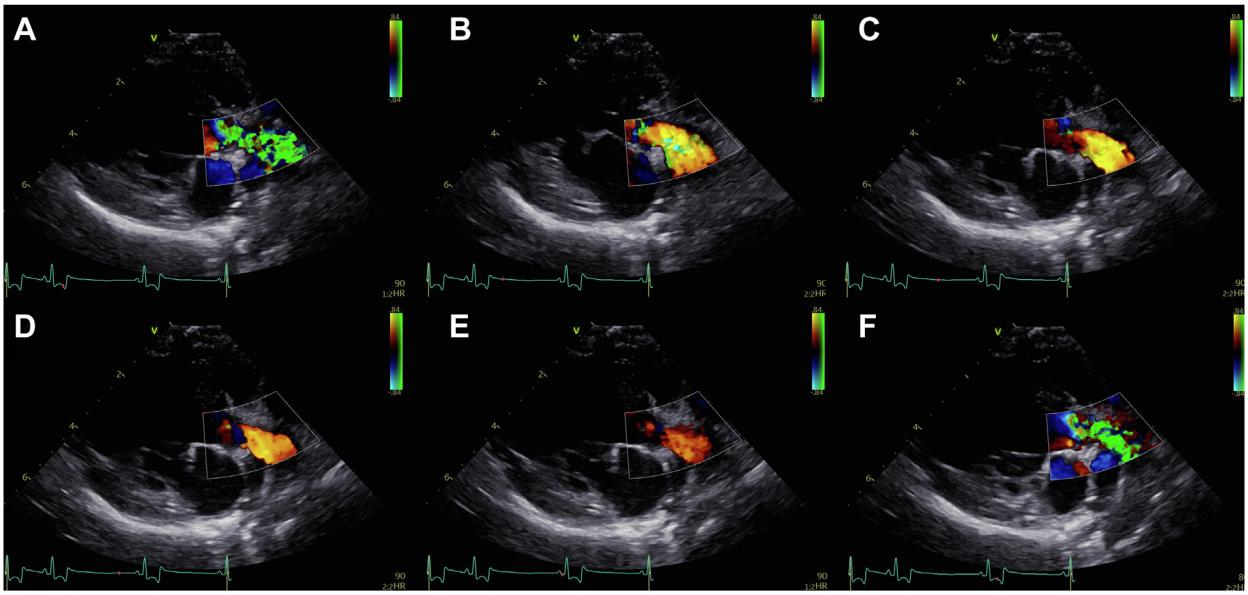

Figure 2 Two-dimensional TTE, right parasternal long-axis view of the aorta with color flow Doppler, demonstrates turbulent flow in the ascending aorta during systole **(A, F)**, consistent with aortic stenosis and retrograde flow in the ascending aorta in early **(B)** and mid **(C, D)** diastole and late diastole **(E)**.

which reflect the preferential sites where atherosclerotic lesions occur in humans.[11] Beyond these reports, and other animal model experimental studies, flow patterns within the canine aorta have not been extensively explored, especially with regard to diastolic retrograde flow.

Given the current implications of this finding in human medicine, the presence of holodiastolic retrograde flow within in the ascending aorta of this dog is likely a reflection of the severity of aortic regurgitation along with increased stiffness of the aortic wall secondary to aortic mineralization. The dog's moderate systemic hypertension likely also contributed to the presence of the holodiastolic retrograde flow documented on echocardiography. Aortic mineralization characterized by chondrous and osseous metaplasia affecting the aortic valve leaflets and proximal ascending aorta has been previously reported in dogs as a possible age-related change and may also occur secondary to underlying renal disease, which was present in this patient and confirmed on necropsy.[12] The combination of severe acquired myxomatous degeneration and fibrotic (congenital) aortic stenosis is uncommonly reported in the dog and likely contributed to the severity of the aortic regurgitation documented. Alternatively, if the changes to the aortic valve were secondary to myxomatous degeneration alone, the resulting severity of an acquired stenosis would be a similarly rare finding.

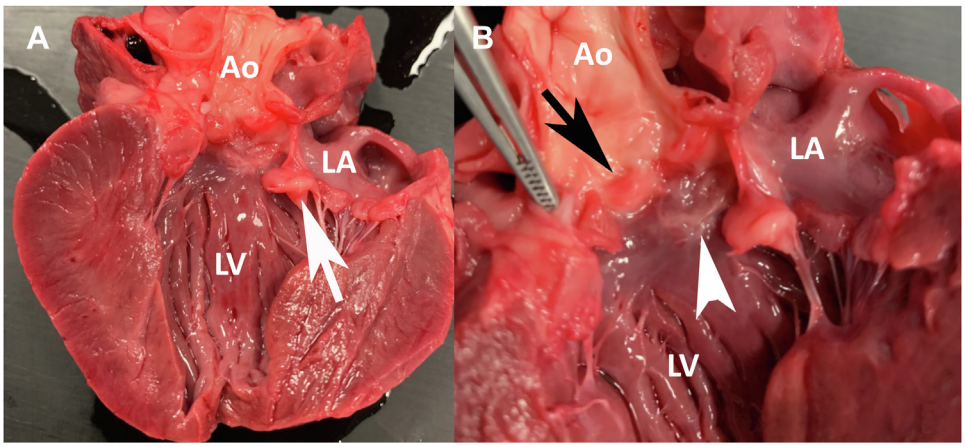

Figure 3 **(A)** Pathologic images postmortem demonstrate the markedly thickened aortic valve leaflets, the subvalvular fibrosis, and myxomatous, severely thickened anterior mitral valve leaflet (*arrow*). **(B)** Closeup view of the aortic valve with mixed degenerative and congenital stenosis (*black arrow*) and the subvalvular fibrous, firm pale ridge of tissue in the left ventricular outflow tract adjacent to the anterior mitral valve leaflet (*arrowhead*). *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle.

CONCLUSION

This case report highlights a rare phenomenon in dogs, and we speculate that this finding could suggest that dogs, like humans, may exhibit characteristic holodiastolic retrograde flow within the ascending aorta in the presence of marked aortic regurgitation, increased aortic stiffness, and elevations in systemic blood pressure. Typically, in the presence of significant aortic regurgitation, the pulse pressure width is greater than normal. In this case, the presence of wide pulse pressure was not determined, as systemic diastolic pressure was not obtained.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with the ARRIVE guidelines and with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Research Council's Guide for the Care and Use of Laboratory Animals.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient (or appropriate parent, guardian, or power of attorney) for the publication of this study and accompanying images.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

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