Biventricular Pulsus Alternans in a Dog with Pulmonic Stenosis and Sepsis

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INTRODUCTION

Pulsus alternans is characterized by beat-to-beat variability in cardiac contractile strength despite a regular cardiac rhythm. It occurs uncommonly, usually in association with severe left ventricular (LV) failure, although a high afterload state or marked hypovolemia can also provoke it. Right ventricular (RV) or, most likely, biventricular pulsus alternans is rarely reported. We describe the transient occurrence of biventricular pulsus alternans in an adult dog with congenital pulmonic stenosis (PS) that developed sepsis following a traumatic injury.

CASE PRESENTATION

A 9-year-old, 4.1 kg, spayed female miniature Pinscher dog was presented to the Emergency Service at the Veterinary Medical Center of the Iowa State University College of Veterinary Medicine because of a painful right forelimb lameness of at least 2 days' duration, progressive anorexia, and lethargy. Another dog in the household was suspected to have attacked this one while the owners were away for a few days. The dog also was known to have had a systolic heart murmur from a young age, although its cause was undefined.

On physical examination, the dog was depressed but responsive and non–weight bearing on the right forelimb. The area over the right shoulder was painful and irregularly swollen, with palpable subcutaneous emphysema and a small puncture wound draining a bloody, purulent material. Several superficial skin abrasions were also present on the right side. The heart rate was 140 beats/minute with a regular rhythm, body temperature was 102.1° F (within normal), and body condition was quite thin (body condition score, 2/9). The dog was estimated to be 5%-7% dehydrated. A loud systolic murmur prompted a subsequent request for cardiac consultation. Exudate from the puncture wound was collected for bacterial culture, and intravenous fluid, antibiotic (amoxicillin/clavulanic acid and enrofloxacin), and analgesic therapy were then instituted.

Radiographs revealed multiple fractures of the right scapula, adjacent soft tissue swelling with gas lucencies, and two fractured dorsal spinous processes. Clinical laboratory abnormalities included leukocytosis (26.1×10^3/uL; reference range, 6-17 $\times 10^3$/uL) with many toxic and band neutrophils, lymphopenia, nonregenerative anemia (hematocrit, 21.5%; reference, 37%-55%), mild acidosis, mildly decreased serum electrolytes (Na^+, 134 mEq/L, reference, 141-151 mEq/L; K^+, 3.4 mEq/L, reference, 3.9-5.3 mEq/L; Cl^-, 110 mEq/L, reference, 112-121 mEq/L; Ca^{++}, 8.2 mg/dL, reference, 9.7-11.3 mg/dL), and hypoalbuminemia (1.9 mg/dL; reference, 2.7-4.0 mg/dL). Cardiac troponin I (cTnI) concentration, obtained following cardiac consultation, was elevated at 0.2 ng/mL (reference, 0.01-0.07 ng/mL). By day 2, serum K^+ was 3.9 mEq/L, while other electrolyte concentrations remained mildly decreased. The final microbiology report indicated a heavy growth of *Streptococcus equisimilis*.

Findings at initial cardiology examination included a regular heart rate of 140 beats/minute, pink membranes, and a grade 5/6 systolic murmur, with the palpable thrill localized to the left cardiac base. Subtle beat-to-beat alteration in murmur intensity, as well as arterial pulse strength, was suspected. No jugular venous distension or pulsation was observed. Lung sounds were normal.

Echocardiography showed mild septal flattening with a normal to slightly small left ventricle and severe RV hypertrophy with moderate chamber dilation. The right atrium was moderately dilated, with mural hypertrophy evident; the left atrium was normal in size. The pulmonary valve leaflets were thickened and fused, with systolic doming; there was poststenotic dilation of the pulmonary trunk. These findings are typical for congenital PS. The tricuspid valve appeared mildly thickened. Mitral and aortic valves were structurally normal. Color Doppler revealed high-velocity pulmonary outflow turbulence, mild pulmonary and tricuspid valve regurgitation, and trivial mitral regurgitation. Continuous-wave Doppler revealed dramatic beat-to-beat alteration in pulmonary outflow velocity that was not ascribable to translational motion or arrhythmia (Figure 1); the simultaneous electrocardiogram (ECG) documented sinus tachycardia (heart rate, 180 beats/minute).

The peak pulmonary velocity of the stronger beats was approximately 5.2 m/sec (estimated peak pressure gradient 108 mm Hg). Peak aortic outflow velocity (1.12 m/sec) showed similar, but less dramatic, variation (Figure 2).

An M-mode recording at the ventricular level also showed subtle beat-to-beat alteration in ventricular free wall motion (Figure 3).

Tricuspid annular plane systolic excursion (TAPSE) was lower than reported for normal dogs at 6 mm (95% prediction interval for a normal 4 kg dog = 7.2-11.5 mm).[1] The TAPSE:aorta ratio was 0.46 (>0.65 reported for normal dogs),[2] although similar to dogs with severe pulmonary hypertension (canine values associated with PS are not available). Left ventricular systolic function appeared normal (fractional shortening 39%, calculated from M mode; ejection fraction 57%, calculated from two-dimensional right parasternal long-axis images using Simpson's method of discs). A resting six-lead ECG documented regular sinus rhythm, right axis deviation, normal waveform durations, and no discernable electrical alternans.

The dog showed clinical improvement by the following morning. In addition to fluid, antibiotic, and analgesic therapy, low-dose atenolol (0.25 mg/kg every 12 hours) was added to reduce myocardial oxygen

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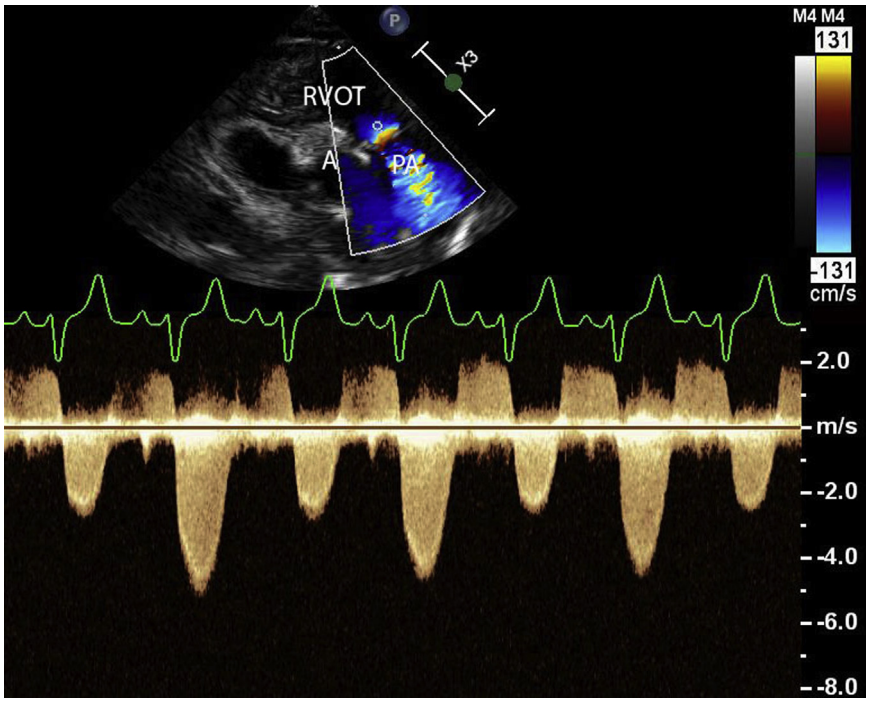

Figure 1 Duplex continuous-wave and color Doppler echocardiogram, from left cranial short-axis view. There is marked beat-to-beat alternation in pulmonary outflow velocity despite a regular sinus rhythm (lead II ECG in middle of image; heart rate, 180 beats/minute), indicating RV pulsus alternans. Peak velocity of the stronger beats is approximately 5.2 m/sec (estimated peak pressure gradient 108 mm Hg) in this dog with severe congenital PS. Mild pulmonary regurgitation is also present. *A*, Aorta; *PA*, pulmonary artery; *RVOT*, RV outflow tract.

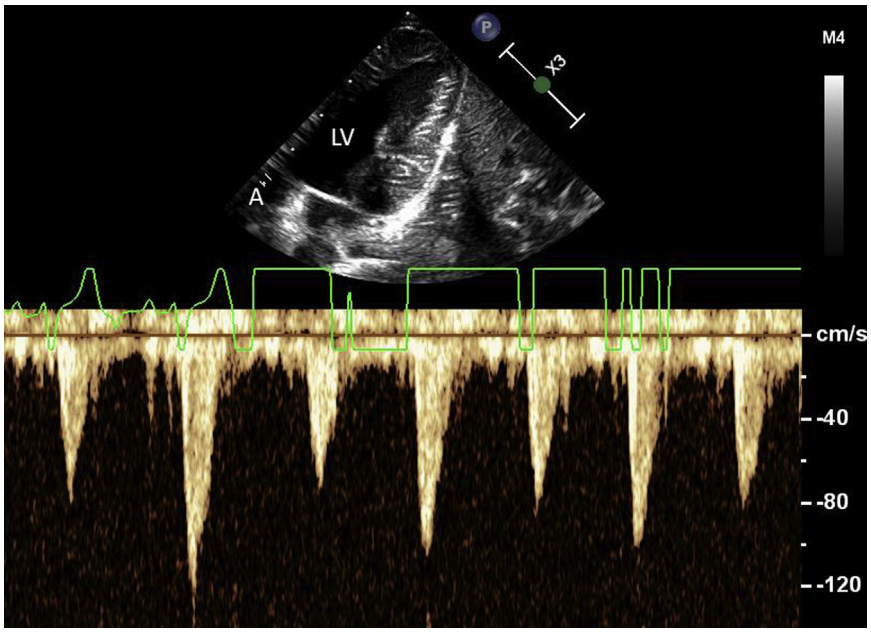

Figure 2 Continuous-wave Doppler image of LV outflow, recorded from a left apical position. The alternation in peak velocity here is evidence for concurrent LV pulsus alternans in this dog, even though LV structure and systolic function measures appeared normal. Sinus rhythm is clearly evident in the first two cardiac cycles, although ECG artifact obscures the trace in the remainder of this frame. At all other times during the study, no premature complexes or other rhythm disturbances were observed. *A*, Aorta; *LV*, left ventricle.

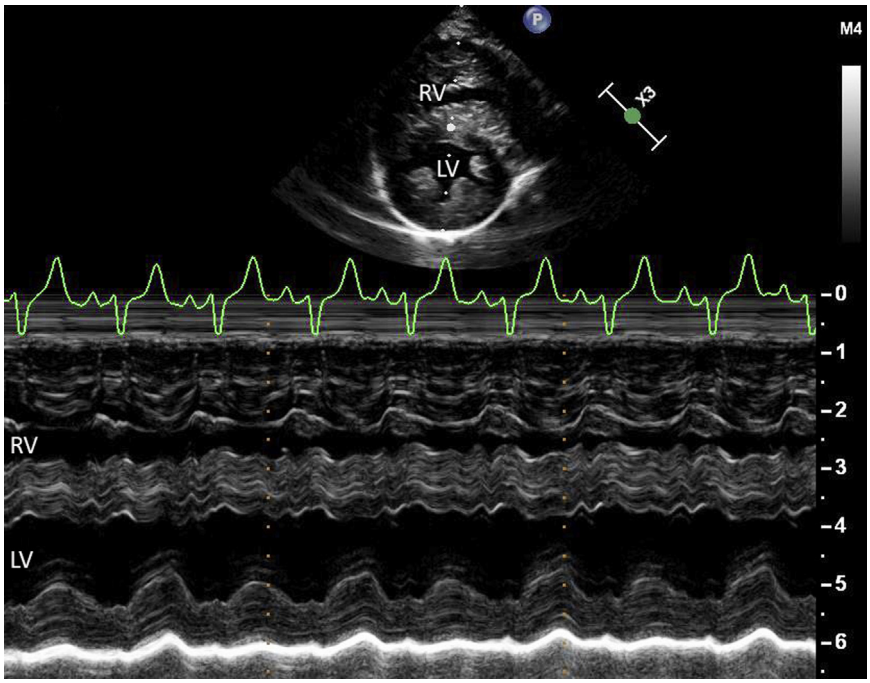

Figure 3 M-mode echocardiogram at the ventricular level, obtained from the right parasternal short-axis view. Alternating (every-other-beat) variation in the systolic excursion of both LV and RV walls is present. This is most evident in the LV posterior wall. Heart rate, 180 beats/minute. *LV*, Left ventricle; *RV*, right ventricle.

demand. Brief cardiac reevaluation later in the day showed an alert patient with a heart rate of 120 beats/minute and sinus rhythm. Mild jugular venous pulsation, without distension, was observed on this exam. The systolic murmur was slightly softer (graded 4/6). No beat-to-beat variation in murmur or arterial pulse intensity was apparent. Doppler interrogation now showed uniform pulmonary (4.5 m/sec) as well as aortic (0.91 m/sec) peak outflow velocity (Figure 4).

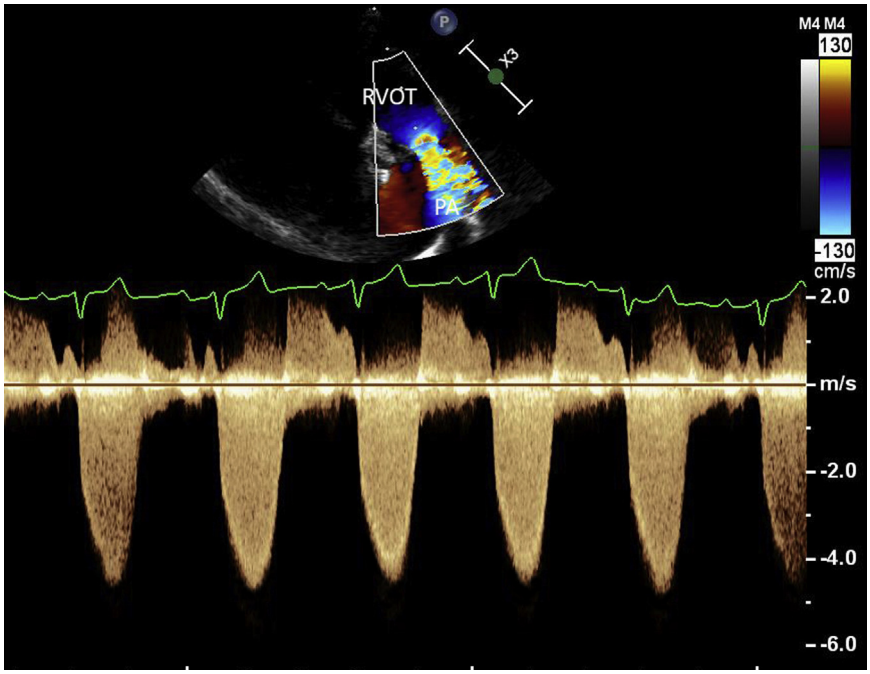

Figure 4 Doppler recording of pulmonary outflow from the same orientation as in Figure 1 and obtained the following day. Pulsus alternans has resolved (peak pulmonary outflow velocity is now 4.5 m/sec; peak pressure gradient, 81 mm Hg). The sinus rhythm is now at a slower rate (120 beats/minute) than the previous day. *PA*, Pulmonary artery; *RVOT*, RV outflow tract.

The recommendation was made for pulmonary balloon valvuloplasty after the infection and orthopedic issues were resolved. The dog was discharged from hospital that evening with instructions to continue medications (oral antibiotic, analgesic, atenolol), restrict activity, and schedule an initial reevaluation with the referring veterinarian within the week. Unfortunately, the dog was lost to follow-up.

DISCUSSION

Pulsus alternans is an uncommon phenomenon of successively alternating strong and weak ventricular contractions despite a regular cardiac rhythm. Left ventricular pulsus alternans is described most often. In some cases, the peak ventricular pressure generated during "weak" beats is too poor to open the aortic valve, producing a pulse rate that is half of the direct heart rate. In other cases, subtle beat-to-beat variation in arterial pulse strength might be noticed during physical examination. Severe LV systolic dysfunction, as from dilated cardiomyopathy or coronary artery disease, usually underlies pulsus alternans.[3,4] In people, LV pulsus alternans also has been reported with severe aortic stenosis, hypertrophic obstructive cardiomyopathy, mitral stenosis, prosthetic valve dysfunction, systemic hypertension, and dobutamine infusion.[3-6] Tachycardia, hypovolemia, or vasodilator administration sometimes induces pulsus alternans, especially in patients with underlying myocardial disease or heart failure.[3,7-9]

Experimentally induced LV pulsus alternans in dogs has been accomplished via rapid pacing and caudal vena caval occlusion or coronary flow reduction.[7] Alternans also has been studied in isolated canine myocardial preparations subject to ischemia, simulated arterial impedance, pressure overload hypertrophy, and other manipulations. Veterinary clinical reports of spontaneous LV pulsus alternans include a dog anesthetized with halothane (an inhalation anesthetic with marked myocardial depressant effect)[10] and a series of English cocker spaniels with dilated cardiomyopathy.[11]

Pulsus alternans affecting the right ventricle appears to be much less common. In people, it has been reported sporadically in cases of severe RV failure, pulmonary hypertension, massive pulmonary embolism, critical PS with RV dysfunction, prosthetic mitral valve thrombosis, mitral stenosis, and diastolic LV dysfunction.[6,12-14] Reports of biventricular alternans are extremely rare in the human literature; associations have included severe LV dysfunction of various causes, anterior wall myocardial infarction, pulmonary embolism, and pulmonary hypertension.[6,13]

We found no previously published reports of RV or biventricular alternans in dogs in the veterinary literature, although anecdotally, concurrent alternans in RV outflow has been observed in dogs with LV alternans and vice versa. Given the interdependence between the right and left ventricles, the development of alternans in one ventricle might reasonably induce the same effect in the other. In the present case, it is unclear which ventricle first developed alternans. Sepsis can negatively affect myocardial contractility; furthermore, decreased preload often is present, whether from dehydration, peripheral vasodilation, or a combination of factors. Both issues can contribute to the development of pulsus alternans. The increase in RV afterload imposed by severe preexisting PS in this case likely exacerbated the effects of sepsis, dehydration, and possibly other factors, contributing to altered RV function and the biventricular pulsus alternans. However, PS alone is unlikely to have caused this phenomenon. The disappearance of pulsus alternans following intravenous fluid administration, anti-infective therapy, and subsequent heart rate reduction supports this assertion. At most, pulsus alternans associated with isolated severe PS would appear quite rare in dogs, even in the presence of RV failure, and it remains unreported. Nevertheless, occasional case reports in people have described pulsus alternans associated with severely increased RV, or LV, afterload.[3,12-14]

The present case showed no clinical evidence for right-sided congestive failure. Yet TAPSE did suggest somewhat reduced RV systolic function. This could reflect decreased inotropy secondary to sepsis and chronically increased RV afterload, the possible influence of decreased preload, or a combination. Left ventricular systolic function appeared to be normal in this dog based on calculated fractional shortening and ejection fraction; nevertheless, the presence of sepsis and volume depletion could have diminished LV function to some degree, compared with the dog's baseline. More advanced methods of ventricular function analysis or additional follow-up echocardiograms might have revealed an impairment; however, these were not performed.

The mechanism of pulsus alternans development has been a subject of study during the past 100 years, although the phenomenon and its association with cardiac disease have been known since at least 1872.[4] On a cellular level, abnormalities of myocardial Ca^{++} handling underlie pulsus alternans.[7-9,15] During pulsus alternans, intracellular Ca^{++} transients become larger then smaller with consecutive beats, which correlates with stronger then weaker contractions, respectively. The development of alternans is thought to represent a relative synchronization of intracellular calcium release events (sparks), which normally occur randomly, yet in proportion to Ca^{++} entry through L-type membrane Ca^{++} channels.[8] Underlying instability in the dynamics of intracellular Ca^{++} concentration could relate to Ca^{++} load within the sarcoplasmic reticulum (SR), slowed Ca^{++} reuptake into the SR, effects of delayed ryanodine receptor recovery on SR Ca^{++} release, or other mechanisms.[9] Besides beat-to-beat changes in inotropy, alternations in ventricular filling (the Frank-Starling effect) or myocardial relaxation, or a combination have also been proposed.[3] The underlying disease process might influence the specific mechanism of pulsus alternans, and additional mechanisms might contribute in some cases.

More broadly, the concept of cardiac alternans encompasses both mechanical and electrical alternans. Besides instability in Ca^{++} cycling, instability in cell membrane potential also can contribute to alternans.[15] Changes in the extent of cooperative gating (coupling) between L-type Ca^{++} channels might impact both membrane voltage and intracellular Ca^{++} dynamics within the heart. Increased coupling between L-type Ca^{++} channels increases the amplitude of Ca^{++} currents and prolongs the action potential, which can promote cardiac alternans.[15] Consequently, beat-to-beat alternation in action potential duration and peak intracellular Ca^{++} concentration can occur.[15] Cardiac alternans is more likely to develop at rapid heart rates. Instability of the action potential, including the T-wave, duration is potentially arrhythmogenic. However, alternation in cardiac mechanical function can occur without apparent electrical alternans.[15]

Subtle evidence for pulsus alternans might be identified on physical examination, such as a strong-weak alternation in arterial pulse strength or murmur intensity on consecutive beats. Because ventricular bigeminy, or other rhythm disturbance, could cause such alternation, it is important to verify regular sinus rhythm electrocardiographically concurrent with physical (or echocardiographic) evidence of suspected alternans. Especially when the heart rate is rapid and fusion complexes are present, ventricular bigeminy might be missed. Late-diastolic, premature ventricular beats in bigeminal distribution are most likely to be confused with true pulsus alternans, particularly if the "weak" beat is not scrutinized for shortening of its preceding PR interval. Electrocardiographic documentation of

regular sinus rhythm when physical evidence of pulsus alternans is present also might show the alternating variation in waveform configuration or duration of electrical alternans.

In the present case, the alternation in peak outflow velocities and free wall motion of both ventricles, in the presence of a regular sinus rhythm, were consistent with alternating contractile strength. Direct ventricular pressure measurements were not obtained. Cardiac translational motion could be a potential source of spurious variation in Doppler recordings of ventricular outflow velocity, especially in situations where the respiratory rate is elevated. Careful transducer positioning, to maintain consistent visualization of anatomic structures throughout the cardiac cycle, is important. In addition, Doppler interrogation of ventricular outflow from more than one view, when possible, can confirm beat-to-beat velocity alternation even if recorded peak velocity is suboptimal.

Some cardiovascular findings in this dog had changed by the second day. Besides the uniform arterial pulses and systolic murmur, there was an overall decrease in murmur intensity and reduction in Doppler peak pulmonary and aortic outflow velocities. Likely contributing to this were a reduction in sympathetic tone with pain control and atenolol administration (albeit at low dose), as well as absence of enhanced contractility on alternating beats induced by the previous pulsus alternans. The appearance of jugular vein pulsations on this examination was attributed to blood volume expansion following fluid therapy, in conjunction with increased RV stiffness; only minimal tricuspid regurgitation was present. Jugular venous distension was not observed.

Myocardial injury associated with sepsis could have caused the cTnI elevation, although myocardial remodeling associated with severe PS could have contributed. To what degree this might have played a role in pulsus alternans development is unknown. Unfortunately, we were not able to obtain subsequent cTnI measurements. Some other laboratory abnormalities, such as hypoalbuminemia and nonregenerative anemia, as well as the dog's poor body condition, suggest more chronic nutritional issues in this case. The trauma and associated infection likely exacerbated these preexisting issues.

In summary, although pulsus alternans often indicates the presence of severe myocardial failure,[3] reduced preload and tachycardia also impact the function of both ventricles and can play an important role in the pathogenesis of this phenomenon. Sepsis can foster conditions that promote pulsus alternans, which careful echocardiographic evaluation can reveal. In the 9-year-old dog of this report, there was marked RV remodeling caused by the severe PS, although RV contractile function appeared only modestly reduced and congestive failure had not developed. Yet the interplay of abnormal cardiac substrate with the effects of sepsis and dehydration allowed biventricular pulsus alternans to become manifest, if only transiently. The setting of RV outflow obstruction might predispose to RV alternans; however, it is important to recognize that pulsus alternans is likely to be a biventricular phenomenon.

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