Reversal of echocardiographic right-sided heart pathology in a dog with severe pulmonary hypertension: a case report

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Abstract: Pathologic right-sided heart changes are a common echocardiographic finding in patients with pulmonary hypertension (PH). Canines with PH may have right heart pathology documented via echocardiographic color Doppler interrogation including tricuspid valve regurgitation, pulmonic valve insufficiency, elevated pulmonary arterial systolic pressure, elevated pulmonary arterial diastolic pressure, and alterations in ejection profiles. Two-dimensional echocardiographic findings may include right ventricular hypertrophy, interventricular septal flattening, paradoxical interventricular septal motion, pulmonary artery dilation, and potentially abnormal left heart dimensions. In veterinary medicine, much confidence is given to the measurement of pulmonary arterial systolic pressure estimated from tricuspid valve regurgitation to grade the severity of PH and monitor its improvement with little emphasis placed on the integration of two-dimensional echocardiographic right and left heart pathology in conjunction with Doppler findings. To the authors’ knowledge, marked improvement and/or resolution of echocardiographic-documented right heart pathology have not been previously reported in the veterinary literature. This case report documents profound echocardiographic improvement of right-sided heart disease in a dog with severe PH.

Keywords: canine, pulmonary hypertension, tricuspid valve regurgitation, right heart hypertrophy, sildenafil

Introduction
Pulmonary hypertension (PH) is a global term for a complex hemodynamic condition leading to a progressive increase in pulmonary vascular pressures. PH is defined as an estimated pulmonary arterial systolic pressure (PASP) greater than 30 mmHg or pulmonary arterial diastolic pressure greater than 19 mmHg. It can be classified as increased precapillary resistance (pulmonary arterial hypertension, resulting from abnormalities on the arterial side of the pulmonary vascular system) or increased postcapillary resistance (pulmonary venous hypertension, resulting from left-sided heart disease leading to pulmonary capillary hypertension). In dogs, PH may be a consequence of various disease processes, including an idiopathic cause, primary cardiac disease, intra- and extracardiac shunts, heartworm disease, respiratory disease, and thromboembolic disease. Clinical signs associated with PH include tachypnea, cough, respiratory distress, weakness, fatigue, exercise intolerance, syncope, and right-sided congestive heart failure.1–3

In health, the right ventricle (RV) and pulmonary circulation function as a coupled unit. In diseased states, the normally thin-walled, distensible RV becomes incapable of completely matching, or coupling, its contractile performance to...
increased pulmonary vascular resistance (PVR), resulting
in right ventricular–pulmonary artery (PA) uncoupling.
Two-dimensional echocardiographic findings including
RV hypertrophy (eccentric and concentric), right atrial
hypertrophy, interventricular septal flattening, paradoxical
interventricular septal motion, and PA dilation support the
diagnosis of PH.4 Eccentric and/or concentric RV hypertrophy
may occur with acute and chronic RV pressure
overload. The degree to which they occur can help indicate
chronicity and underlying pathology.1,3–7 The causes of
PH can be narrowed down from a noninvasive, thorough
echocardiographic interpretation.

Echocardiography provides the most informative and
least invasive means of evaluating cardiac structure and
function in the veterinary clinical setting when PH is
suspected. Objective maximum velocity measurements of
tricuspid valve regurgitation and pulmonic valve insuffi-
ciency are the most commonly used criteria to make a
diagnosis of PH in veterinary medicine. Pairing echocar-
diographic Doppler interrogation findings with subjective
assessment of right- and left-sided cardiac structures,
measurements of right ventricular systolic function, and
right ventricular ejection profiles can provide a more com-
prehensive evaluation and perhaps a more specific cause
for the PH present.

This case is the first clinical report that describes
marked clinical, two-dimensional, and color Doppler
echocardiographic improvement in a dog treated for PH.
Other veterinary studies have shown positive responses
to treatments, including resolution of syncopal events,
improved exercise tolerance, decreased PA pressure,3,8
decreased pressure gradients through the tricuspid valve,9
and increased quality of life despite a lack of significant
change in other variables.3 Much focus is also given to
observing reduction in peak tricuspid regurgitant flow
velocity (PTRFV) as estimated via continuous wave inter-
rogation of tricuspid valve regurgitation using the simplified
Bernoulli equation. However, this value alone is incomplete
in assessing the severity and potential outcome of disease.4
PTRFV does not reliably decrease despite improvement in
clinical signs.4,5,10 In human medicine, PASP is a poor
measure of RV afterload, explaining why PA pressure is
also a poor predictor of clinical RV failure and prognosis.
PH may still be considered severe if persistent pathological
changes in RV shape and size, RV systolic dysfunction, and
abnormal interventricular septal motion are present despite
insufficient tricuspid or pulmonic valve regurgitation and
elevated PA pressures.4

Case report
A 2-year-old castrated male Chihuahua was presented to
the Cardiology Service for initial evaluation of labored
breathing. Pertinent medical history includes a diagnosis of
rabies vaccine-induced ischemic dermatopathy via dermal
histopathology by a board-certified veterinary dermatolo-
gist 1 year prior to presentation. The condition was treated
with immunomodulatory, antibiotic, and antifungal therapy.
Ten months after the treatment was instituted, additional
dermal histopathology showed scarring with no persistent
evidence of ischemic dermatopathy. All therapies were
discontinued.

The patient was presented to the Cardiology Service with
a several-day history of increased respiratory rate, decreased
appetite, and lethargy. Upon initial evaluation, the patient was
alert and responsive. Vitals included a heart rate of 140 beats
per minute, respiratory rate of 60 breaths per minute, and
body temperature of 36.67°C (98°F). Physical examination
revealed a new-grade V/VI right apical systolic heart murmur,
mild tachypnea with mild respiratory effort, normal
bronchovesicular sounds, and severe generalized multifocal
alopecia with scarring. Thoracic radiographs revealed gen-
eralized cardiomegaly and main PA enlargement evidenced
by a bulge at the 1–2 o’clock position on the ventrodorsal
projection. There was a moderate, diffuse unstructured
interstitial pulmonary pattern, with heavier infiltrates evenly
distributed throughout the right hemithorax.

Echocardiography revealed a mildly thickened mitral
valve with mild valve regurgitation, small left ventricle
(LV) internal dimensions in diastole and systole, and nor-
mal left atrium (LA) size. Color Doppler interrogation of
the LA revealed diastolic inflow turbulence from right PA
compression. Severe eccentric hypertrophy of the RV, mild
concentric hypertrophy of the RV, severe enlargement of the
right atrium (RA), paradoxical interventricular septal motion,
systolic interventricular septal flattening, and reduced LV
internal diameters were noted (Figure 1 and Table 1). The
tricuspid valve was mildly thickened with severe tricuspid
valve regurgitation present (Figures 2 and 3). The right
ventricular-to-right atrial pressure gradient at the end of
systole was estimated from PTRFV using continuous wave
Doppler and the modified Bernoulli equation at 5.68 m/s,
corresponding to an estimated right ventricular end-systolic
pressure (RVESP) of 129 mmHg (approximates PASP in the
absence of RV outflow obstruction) (Figure 2 and Table 2).
The pulmonic valve appeared structurally normal. Mild
pulmonic valve insufficiency was present, and an interroga-
tion with continuous wave Doppler revealed an elevated end
pulmonary arterial diastolic pressure of 43 mmHg (3.36 m/s).
The main PA and branches were moderately to severely
dilated. Right ventricular outflow tract (RVOT) and PA
tracing showed a laminar flow of 1 m/s with mid-systolic
notching, suggesting increased PVR (Figure 4 and Table 2).

The RVOT acceleration time was shortened and the RVOT
acceleration time to ejection time was decreased (Table 2).
There was no evidence of pericardial or pleural effusion. A
bubble study with agitated saline was negative for intra- and
extrathoracic shunts. A lead II electrocardiogram revealed
a normal sinus rhythm to sinus tachycardia throughout the
study. Findings were consistent with severe PH from pulmo-
nary vascular disease (PVD), a precapillary cause of PH.

Additional testing was performed in an effort to elucidate
an underlying cause for severe PH. Abnormal hematological
findings included a mild regenerative anemia characterized
by a reticulocytosis, neutrophilic, monocytic leukocytosis
with a left shift, and a moderate thrombocytopenia. Abnormal
serum chemistry findings included a mildly increased alkaline
phosphatase, mildly increased alanine aminotransferase, mild
hypoproteinemia, and mild hypoalbuminemia (Table 3).
A thyroid panel and urinalysis were normal. A thromboelas-
togram revealed normal coagulation parameters. Heartworm
and tick-borne disease testing, including polymerase chain
reaction assays, were negative. An anticardiolipin antibody
assay was negative.

Table 1 Echocardiographic two-dimensional parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretherapy</th>
<th>1 month posttherapy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Diastole</td>
<td>Systole</td>
</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>4.23</td>
<td>5.70</td>
</tr>
<tr>
<td>Left ventricular internal</td>
<td>8.35</td>
<td>3.35</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular posterior</td>
<td>5.13</td>
<td>6.46</td>
</tr>
<tr>
<td>wall (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>59.86</td>
<td>51.91</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>11.19</td>
<td>12.92</td>
</tr>
<tr>
<td>Aorta (mm)</td>
<td>8.40</td>
<td>8.71</td>
</tr>
<tr>
<td>Left atrium: aorta</td>
<td>1.33</td>
<td>1.48</td>
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<tr>
<td>Pulmonary artery (mm)</td>
<td>10.08</td>
<td>10.42</td>
</tr>
<tr>
<td>Pulmonary artery: aorta</td>
<td>1.20</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; 2-D, two-dimensional.
Figure 2 Right parasternal long- and short-axis 2-D echocardiographic images with color Doppler and continuous wave color Doppler at the level of the tricuspid valve, respectively. 

Notes: (A) Right parasternal long-axis four-chamber 2-D echocardiographic image with color Doppler at the level of the tricuspid valve. Moderate-to-severe TR, severe eccentric RV hypertrophy, mild RV concentric hypertrophy, and severe RA enlargement are noted. The LV is small and underfilled, pseudo LV concentric hypertrophy is present, and the LA is normal in size. (B) Right parasternal short-axis 2-D echocardiographic image with continuous wave color Doppler at the level of the tricuspid valve. TR peak velocity is measured and RVESP is estimated via the modified Bernoulli’s equation at 129 mmHg.

Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; RVESP, right ventricular end-systolic pressure; TR, tricuspid valve regurgitation; TR \( V_{\text{max}} \), maximum TR peak velocity; TR \( PG \), maximum TR pressure gradient; \( V \), velocity; 2-D, two-dimensional.

was negative. An abdominal ultrasound revealed caudal vena cava and hepatic vein distension, a small amount of anechoic peritoneal effusion, and a hypoechoic, mildly enlarged pancreas, thought to be a variation of normal in this patient.

The patient was discharged with administration of sildenafil 2.40 mg/kg every 12 hours.

The patient was reevaluated by the Cardiology Service 2 days after his initial visit due to new coughing and worsening of labored breathing at home. Physical examination revealed a static heart murmur, diffusely increased bronchovesicular sounds, and soft crackles bilaterally. Compared to the previous visit’s radiographs, there was worsening of the unstructured interstitial pulmonary pattern. The patient was admitted to the hospital, placed in environmental oxygen at 40% for several hours, and sildenafil administration was increased in frequency to 2.40 mg/kg orally every 8 hours. By the
The following morning, the patient was breathing with only mild respiratory effort in room air. An echocardiogram revealed a moderate improvement in RV ESP to 83 mmHg and a subjective decrease in right heart size. The patient was discharged from the hospital with sildenafil as described earlier.

Approximately 1 month later, the patient was presented for a routine recheck examination. He was reported to be doing very well at home with normal activity, normal appetite, and eupnea. Physical examination revealed resolution of the right-sided heart murmur, a normal respiratory pattern, and normal bronchovesicular sounds. Thoracic radiographs revealed continued cardiomegaly and main PA enlargement, with improvement to a mild, diffuse unstructured interstitial pulmonary pattern. An echocardiogram revealed only trace tricuspid valve regurgitation (unable to estimate RV ESP from trivial regurgitation present) and resolution of pulmonic valve insufficiency. Additionally, there were marked improvements in right heart findings, including only mild RV eccentric and concentric hypertrophy, borderline RA enlargement, normal RV ejection profiles, improved RVOT acceleration time and acceleration time/ejection time, normal interventricular septal motion, and a normal LV dimensions (Figures 1-4; Tables 1 and 2).

### Discussion

The cause of this patient’s PH is most consistent with PVD due to lack of significant changes to the left heart, increased PVR, abnormal PA compliance (notched RV ejections profiles),
In people, interstitial lung disease is a common respiratory manifestation of similar ischemic connective tissue disease, and it has been associated with PH. To date, PH as a manifestation of ischemic connective tissue disease has not been reported in dogs. Although autoimmune disease is a plausible cause for this patient’s PH, other forms of chronic respiratory disease, idiopathic PH, and thromboembolic disease remain possibilities.

Regardless of the cause of PH, adaptations of the right heart secondary to increased afterload occur through mechanisms of hypertrophy and dilation. In the normal heart, the RV adapts to an increase in load with an increase in contractility. Compared to the LV, the RV free wall is much thinner and has greater compliance, making it more sensitive to increased afterload. In patients with PH, stretching of the RV wall leads to adaptive remodeling (concentric hypertrophy) due to increased protein synthesis and increased cardiomyocyte size through the addition of sarcomeres. This adaptation cannot be maintained in the face of sustained pressure overload, and there is eventually a transition to dilation (eccentric hypertrophy). The specific mechanisms underlying the transition from hypertrophy to dilation in the right ventricular failure secondary to PH remain unclear.

The degree of RV concentric hypertrophy versus eccentric hypertrophy can also help to elucidate the chronicity and possible causes of PH. Severe concentric RV hypertrophy is seen more with chronic disease, whereas severe eccentric RV hypertrophy, as seen in this patient, is typically noted in cases of acute RV dilation. RV dilation causes an increase in myocardial oxygen demand while decreasing right-sided heart perfusion, and finally decreasing function.

As with many cases of PH, the underlying cause of this patient’s PH was not definitively determined. This patient suffered from chronic, severe ischemic dermal disease. Ischemic dermatopathy is believed to be the result of vascular abnormalities such as vasculopathy and vasculitis from immunologically induced structural defects in microvasculature. In people, interstitial lung disease is a common respiratory manifestation of similar ischemic connective tissue disease, and it has been associated with PH. To date, PH as a manifestation of ischemic connective tissue disease has not been reported in dogs. Although autoimmune disease is a plausible cause for this patient’s PH, other forms of chronic respiratory disease, idiopathic PH, and thromboembolic disease remain possibilities.

Table 3 Hematological and biochemical abnormalities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference interval</th>
</tr>
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<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>26.3</td>
<td>38.3–56.5</td>
</tr>
<tr>
<td>Reticulocyte (K/μL)</td>
<td>132</td>
<td>10–110</td>
</tr>
<tr>
<td>WBC (K/μL)</td>
<td>23.7</td>
<td>4.9–17.6</td>
</tr>
<tr>
<td>Neutrophil (μL)</td>
<td>16,116</td>
<td>2,940–12,670</td>
</tr>
<tr>
<td>Band (μL)</td>
<td>474</td>
<td>0–170</td>
</tr>
<tr>
<td>Monocyte (μL)</td>
<td>2,370</td>
<td>130–1,150</td>
</tr>
<tr>
<td>Platelet (K/μL)</td>
<td>72</td>
<td>143–488</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>380</td>
<td>5–260</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>175</td>
<td>18–121</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>5.1</td>
<td>5.5–7.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.3</td>
<td>2.7–3.9</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; WBC, white blood cell.
people and animals. In veterinary medicine, two-dimensional echocardiography can be supportive evidence of changes associated with PH and is often underused in helping to distinguish PH from PVD versus pulmonary venous hypertension and in monitoring response to treatment. In this patient, significant right-sided cardiac pathology associated with PH from primary PVD included profound RV eccentric hypertrophy with minimal concentric RV hypertrophy, severe RA enlargement, interventricular septal flattening in both diastole and systole (most profound in systole), severe tricuspid valve regurgitation, moderate-to-severe main PA enlargement, mild pulmonary valve insufficiency, and abnormal RV ejection profiles with mid-systolic notching in conjunction with a small, underfilled LV (Figures 1–4). A limitation of these subjective changes is that they lack information about the functional capacity and systolic function of the right heart.

In people, right ventricular ejection fraction (RVEF) is considered to be one of the most important measures of RV systolic function. Invasive cardiac right heart catheterization and cardiac magnetic resonance imaging are considered the gold standards for assessment of RV volumes, RVEF, and RV–PA coupling. Echocardiographically, alterations in RV ejection profiles (mid- and later-systolic notching) have also correlated with RV systolic function in human patients. This notching is from early arrival of reflected arterial waves from the noncompliant pulmonary vasculature. Tricuspid annular systolic plane excursion (TAPSE), a method used for evaluation of RV systolic function in people, has recently been characterized in dogs. This method has shown a reasonably good correlation with RVEF. Although not measured in this patient, in future patients, it would be interesting to compare qualitative right heart improvements to semiquantitative TAPSE.

RV mass decreased in people undergoing pulmonary endarterectomy to treat chronic thromboembolic PH. Sildenafil has also been shown to affect heart mass in PH. Sildenafil is a highly selective phosphodiesterase-5 inhibitor that causes PA vasodilation by increasing vascular concentrations of cyclic guanosine monophosphate, resulting in nitric oxide-mediated vasodilation. Sildenafil decreases PA pressure and PVR. It may also have effects on pulmonary vascular remodeling. Two mechanisms have been proposed to explain its effects. The first is due to a decrease in PVR, resulting in a decrease in RV wall stress. The second mechanism involves blocking the intrinsic catabolism of cyclic guanosine monophosphate, suppressing chamber and cardiomyocyte hypertrophy. Investigators using sildenafil as treatment in experimentally induced PH in rats recently found that sildenafil prevented and partially reversed ultrastructural, molecular, and functional remodeling of failing RV myocytes. In this patient, causes of the profound improvement in clinical signs and structural right heart improvements remain speculative. It is possible that the inciting cause of the severe PH subsided or that the improvement was multifactorial, including resolution of the inciting cause, oxygen therapy, and sildenafil. Regardless of the cause of both the PH and the reasons for improvement, the remarkable echocardiographic improvements of the right heart are noteworthy.

Conclusion

To the authors’ knowledge, significant echocardiographic improvement in right-sided cardiac pathology has not been reported in dogs with severe PH. Echocardiography provides the most informative and least invasive method of evaluating cardiac structure and function in the veterinary clinical setting. The complex, asymmetric geometry of the right heart can make echocardiographic techniques more challenging, but they continue to prove a useful tool in the absence of invasive and expensive techniques such as cardiac catheterization and cardiac magnetic resonance imaging. Right heart changes associated with PH have traditionally been thought to be irreversible, but there is a recent trend toward more thorough assessment of the right heart and its utility in making diagnoses, prognoses, and monitoring treatment.

Disclosure

The authors report no conflicts of interest in this work.

References


