

# Pulmonary thromboembolism

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## Abstract

**Objective** – To review the pathophysiology, clinical signs, diagnosis, and treatment of pulmonary thromboembolism (PTE) in small animals.

**Data Sources** – Human and veterinary clinical studies, reviews, texts, and recent research in canine and feline PTE diagnosis and thromboembolic therapeutics.

**Human Data Synthesis** – In humans, clinical probability assessment and point-of-care D-dimer-based algorithms are widely used. Computed tomography pulmonary angiography is the gold standard for PTE diagnosis in humans. Echocardiography is increasingly used for bedside assessment of affected patients. In low-risk human patients anticoagulants alone are recommended while patients with cardiogenic shock are treated with thrombolytics followed by anticoagulation.

**Veterinary Data Synthesis** – PTE is associated with numerous predisposing conditions causing hypercoagulability, blood flow stasis, or endothelial injury. Identifying at-risk patients is key to diagnosis in small animals. Thromboelastography provides a method for identifying hypercoagulable patients. Computed tomography pulmonary angiography may replace selective pulmonary angiography as the imaging technique of choice for PTE diagnosis. PTE therapy consists of supportive treatment combined with appropriate, individualized thromboembolic pharmacotherapy for acute treatment and chronic management. Thrombolytic therapy for PTE remains controversial but may be indicated in hemodynamically unstable acute PTE. Thromboprophylaxis in specific conditions is rational although evidence of efficacy is limited. Prognosis depends upon degree of cardiopulmonary compromise and patient response to therapy. Mortality rates in small animals are unknown.

**Conclusions** – New diagnostic techniques and advances in therapy offer significant potential for improvements in the identification and treatment of PTE in small animals. Further study must be directed to validating new diagnostic modalities and evaluating therapeutic regimens.

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**Keywords:** angiography, CT, D-dimers, PTE, thromboelastography

## Introduction

The purpose of this article is to review the pathophysiology, clinical signs, diagnostic modalities, and therapeutic options for pulmonary thromboembolism (PTE) in small animals. This review was compiled from available original and retrospective studies and review articles in the human and veterinary medical fields. Articles were retrieved with a combination of search engines including but not limited to Public Medline,

Institute for Scientific Information Web of Knowledge, Centre for Agricultural Bioscience, and Ovid abstracts. Relevant articles retrieved were reviewed and where appropriate their bibliographies searched for additional pertinent articles. Attempts were made to assess the relevance of human studies to veterinary patients and to make recommendations in accordance with the principles of evidence-based medicine.

PTE is the obstruction of a pulmonary vessel or vessels by a thrombus. The term *pulmonary thromboembolism* encompasses both local thrombus formation (primary pulmonary thrombosis) and translocation of a thrombus formed elsewhere in the vascular system (pulmonary embolism). Emboli may consist of tissue, aggregates of cells, bacteria, fat, parasites, hair, foreign bodies, or blood clots.<sup>1</sup> Pulmonary thrombosis and pulmonary embolism are difficult to differentiate, partic-

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ularly where no thrombotic or embolic processes can be identified in the right heart or systemic veins.<sup>1</sup> The pathophysiological sequelae are similar and this has led to widespread use of the term PTE to describe both conditions. Some authors consider pulmonary thrombosis to be less common in small animals than pulmonary embolism, although very few reports of venous thrombosis exist.<sup>2</sup> The true incidence of PTE in dogs and cats is unknown; however, it is likely underdiagnosed and may be more common than the literature suggests.

In a retrospective case series of 29 dogs admitted to a referral institution with confirmed pulmonary embolism, there was antemortem suspicion of PTE in 11 of 17 (65%) dogs with compatible clinical signs but PTE was suspected in only 11 of 29 (38%) dogs in which PTE was subsequently diagnosed at necropsy.<sup>3</sup> This study suggested a prevalence of PTE in dogs of 0.9% over a 10-year period. In another study, PTE was suspected before necropsy in 4 of 16 (25%) cats with respiratory signs but PTE was suspected in only 4 of 29 (14%) cats in which it was subsequently diagnosed postmortem.<sup>4</sup> A subsequent postmortem study of PTE in cats suggested a prevalence of 0.06% over a 24-year period.<sup>5</sup> The suggested prevalence of PTE in dogs of 0.9% is likely an underestimate, since in experimental models 50% of canine thrombi lyse within 3 hours of death.<sup>6</sup> Thrombi in dogs lyse far more rapidly than in humans due to greater net plasminogen activator activity, greater platelet lytic activity, and secretion of plasminogen activator by the pulmonary endothelium.<sup>7</sup>

PTE has been associated with numerous conditions and disease states in both dogs and cats (Table 1).<sup>8-21</sup> When considering how these disease states predispose patients to PTE, all of these disorders can be categorized according to how they impact on Virchow's triad, namely hypercoagulability, blood flow stasis, or endothelial injury,<sup>22,23</sup> although in vivo it is unlikely that alteration of a single component would be sufficient to incite thrombosis. The pathophysiology of venous thrombi likely involves more than 1 abnormality in Virchow's triad,<sup>24</sup> however, this approach is still of value in conceptualizing risk factors in individual patients. With respect to PTE in humans, the most important component of Virchow's triad is hypercoagulability, which occurs in >25% of patients with thromboembolism.<sup>25</sup> This likely reflects the high prevalence of heritable primary hypercoagulability syndromes in humans that affect between 2% and 11% of the general population.<sup>23</sup> To date, no such syndromes have been described in small animals. As can be seen from Table 1, the majority of disease processes and risk factors associated with PTE in small animals predispose patients to PTE by conferring a hypercoagulable state.

**Table 1:** Recognized risk factors for pulmonary thromboembolism (PTE) and disease processes with a known association with thromboembolic disease in the dog with proposed mechanisms.

Disease process/ risk factor	Hyper- coagulable state	Vascular flow abnor- malities/ stasis	Endothelial injury/ dysfunction
Corticosteroid administration* <sup>4,8,9</sup>	✓		
Diabetes mellitus <sup>10</sup>	✓		
Dirofilariasis <sup>11,12</sup>	✓		✓
DIC* <sup>3,4,12</sup> (secondary to other disease)	✓		
Endocarditis <sup>3</sup> (tricuspid/pulmonic)	✓		✓
Feline infectious peritonitis* <sup>5</sup>	✓		✓
Hyperadrenocorticism <sup>3,12-14</sup>	✓		
Hypothyroidism <sup>10</sup>	✓		
IMHA* <sup>3,4,15,16</sup>	✓		?
Indwelling venous catheters* <sup>3,4,12</sup>		✓	✓
Myocardial disease <sup>3,5,8</sup>	✓	✓	✓
Neoplasia* <sup>3-5,8,9</sup>	✓	✓	
Pancreatitis* <sup>4,5,9</sup>	✓		✓
Protein-losing enteropathy* <sup>4</sup>	✓		
Renal amyloidosis/ PLN* <sup>3,4,10,14,17-19</sup>	✓		
Sepsis* <sup>3,4,8,9</sup>	✓		✓
Surgery <sup>20</sup>	✓	✓	✓
Trauma* <sup>21</sup>		✓	✓

\*Those conditions also associated with an increased risk in the cat are marked. Question mark signifies the role of this mechanism in the associated disease process is uncertain.

Interestingly, 2 studies have shown that the majority (59% and 64%) of dogs with PTE had >1 predisposing condition, while approximately half (47%) of cats with PTE have multiple disease processes present.<sup>3,4,12</sup>

PTE may induce several pathophysiological sequelae resulting in hypoxemia, hyperventilation, and dyspnea. The arterial hypoxemia seen in patients with PTE is secondary to multiple abnormal ventilation:perfusion (V:Q) ratios within affected lungs occasionally complicated by diffusion impairment resulting from interstitial and alveolar edema.<sup>26,27</sup> The V:Q mismatches occur due to small airway constriction, reduced surfactant production, and the development of pulmonary edema and atelectasis. Small airway constriction occurs in both nonperfused and nonembolized areas of lung, which may lead to airway closure and alveolar collapse.<sup>28-30</sup> Surfactant production is reduced in dogs with experimental PTE, likely secondary to reduced delivery of surfactant components to type II pneumocytes.<sup>31-33</sup> Loss of surfactant leads to transudation of fluid into

alveoli causing pulmonary edema, which has been termed congestive atelectasis.<sup>34</sup> Pulmonary edema may also develop in nonembolized regions due to increased hydrostatic pressure coupled with increased microvascular permeability induced by humoral factors such as lipoxigenase products from activated neutrophils.<sup>35–37</sup> Rarely pulmonary infarction and pleural effusion may result from complete occlusion of distal pulmonary vascular branches.<sup>38,39</sup>

The cardiovascular consequences of PTE are dependent upon the degree of pulmonary vascular occlusion. There is a substantial reserve capacity in the pulmonary vasculature, which likely accounts for the subclinical nature of many pulmonary thromboembolic events.<sup>1</sup> In healthy dogs, >60% of the pulmonary vasculature must be occluded before any change in pulmonary vascular resistance (PVR) reduces pulmonary arterial flow.<sup>40</sup> Reflex vasoconstriction secondary to alveolar hypoxia, humoral factors such as serotonin released from activated platelets and neurogenic reflexes may also contribute to the increase in PVR.<sup>41–44</sup> Significant pulmonary vascular occlusion leads to pulmonary arterial hypertension and increased right ventricular (RV) afterload. Severe, acute changes in RV afterload result in RV dilatation and dysfunction. As the right ventricle dilates, the interventricular septum shifts toward the left resulting in poor filling and reduced diastolic distensibility, a concept known as ventricular interdependence. The consequent reduction in left ventricular filling decreases cardiac output leading to signs of forward failure (hypotension, cardiogenic shock). If the patient survives an acute crisis but has residual pulmonary hypertension then the clinical signs of backward failure (hepatomegaly, ascites, pleural effusion) may develop over the medium to long term.

### **Clinical Signs**

The clinical signs seen in animals with PTE ought to be predictable based on our understanding of the pathophysiological consequences of pulmonary vascular occlusion. In reality, clinical signs of PTE are highly variable, inconsistent, and nonspecific. The degree of physiological impairment and thus the severity of clinical signs reflect both the magnitude of the PTE and the patient's compensatory ability – the pulmonary physiologic reserve. Complicating the picture may be clinical signs attributable to the underlying disease process, which has predisposed the patient to thrombus formation. The most common signs are dyspnea, tachypnea, and depression. Other signs include coughing or hemoptysis or both, cyanosis, syncope, collapse, and sudden death.

In dyspneic patients, physical examination may reveal harsh lung sounds and crackles suggestive of interstitial or alveolar edema formation. Alternatively lung and heart sounds may be muffled if a pleural effusion is present. In eupneic patients lung field auscultation will likely be unremarkable. On cardiac auscultation, tachycardia with a split second heart sound may be noted, or more commonly a loud second heart sound associated with pulmonary hypertension. Signs compatible with backward heart failure (jugular distension or pulsation, ascites) or forward heart failure (poor peripheral pulse quality, pallor, prolonged capillary refill time) may be present. The clinician should suspect a PTE in any patient with no history of cardiopulmonary disease who becomes acutely dyspneic, particularly if the patient is known to have a predisposing disease process or risk factor (Table 1).

### **Diagnosis**

#### **CBC/serum biochemistry**

Basic tests are typically of limited value in the diagnosis of PTE. Serum biochemical tests may be useful to identify predisposing conditions such as hyperadrenocorticism, protein-losing nephropathy or enteropathy, diabetes mellitus, or hypothyroidism. CBCs may reveal a nonspecific inflammatory leukogram. Polycythemia, myeloproliferative disorders, and essential thrombocythemia, which can predispose patients to thrombosis, may be identifiable from a CBC and smear examination.<sup>45</sup> Secondary thrombocytosis is not a predisposing factor for thrombosis, although primary essential thrombocythemia may be, particularly if other risk factors exist.<sup>46,47</sup> Thrombocytopenia or schistocytosis, as markers of disseminated intravascular coagulation may increase the index of suspicion for PTE.<sup>48</sup>

#### **Arterial blood-gas analysis**

Typical blood gas changes associated with PTE include hypoxemia, hypocapnia, and an increased alveolar-arterial oxygen tension gradient (A-a PO<sub>2</sub> difference). In one study, hypoxemia occurred in 80% of dogs with PTE, 47% were hypocapnic, and 100% had an increased alveolar-arterial gradient.<sup>3</sup> Blood gas values in cats with PTE have not been reported to date. Hypoxemia secondary to PTE may be poorly responsive to oxygen therapy.<sup>26,42</sup> While simple V:Q mismatch is an oxygen-responsive condition, when extensive it may lead to intrapulmonary shunt and decreased oxygen responsiveness.<sup>34</sup> Poor oxygen responsiveness was documented in 4 of 9 patients assessed in one study.<sup>3</sup> Arterial blood-gas analysis may help to raise the index of suspicion for PTE, but it is typically of insufficient discriminant value to positively diagnose or exclude

PTE. That is to say, blood gas values may be normal in cases of PTE, and the typical findings are nonspecific. The utility of arterial blood-gas analysis in the diagnosis of PTE in humans is controversial.<sup>49,50</sup> Some authors have suggested that using the A-a gradient may be more sensitive than solely looking for hypoxemia.<sup>23,51</sup> The A-a gradient is generally used for patients breathing room air and is calculated by subtracting the measured arterial oxygen partial pressure from the calculated alveolar partial pressure [ $A-a = \{PAO_2 = FiO_2(P_{atm} - P_{H_2O}) - (PaCO_2/R)\} - PaO_2$ ], where normal is <10 mm Hg. Arterial blood-gas analysis may be useful in assessing disease severity, monitoring response to therapy, and in determining prognosis. The degree of hypoxemia is known to be directly proportional to the extent of thromboembolic occlusion.<sup>52</sup> Two recent publications have suggested that humans with confirmed PTE who have an A-a gradient >53 mm Hg or an arterial:alveolar oxygen tension ratio <0.49 have a poor prognosis.<sup>53,54</sup> It is unknown whether similar relationships exist in small animals.

#### Survey thoracic radiography

Suter in 1984 outlined 5 key objectives for assessing thoracic radiographs in suspected PTE cases: (a) to confirm the suspicion of PTE; (b) to report the effects of thrombosis; (c) to demonstrate the lesion extent and location; (d) to identify complications of PTE; (e) to rule out other differentials for respiratory distress.<sup>1</sup> Abnormal radiographic appearances described in dogs with PTE include many different radiographic changes.<sup>37</sup> Pulmonary infiltrates are the most common radiographic abnormality in PTE. They are typically alveolar or alveolar interstitial in appearance seen in one or multiple areas.<sup>38</sup> These infiltrates likely represent edema, atelectasis, hemorrhage, or infarction and often have indistinct borders. Regional oligemia or hypovascular lung areas (Westermarck sign; Figure 1)<sup>38,55</sup> are rare findings that appear as areas of radiolucency best identified on dorsoventral or ventrodorsal radiographs.<sup>1</sup> These hyperlucent areas represent regions of reduced blood flow distal to sites of thromboembolic occlusion. Where pulmonary infarction occurs, distinct pleural based, wedge-shaped densities appear. Other potential abnormalities include uneven vessel diameter including pulmonary arterial enlargement, lobar vein or artery attenuation, pleural effusion, and right-sided cardiomegaly.<sup>5,38</sup>

Many small animals with PTE will have normal thoracic radiographs;<sup>1</sup> however, thoracic radiographs are still indicated as part of the diagnostic investigation of all patients with suspected PTE. Radiographic equipment is readily available; survey thoracic radiographs are easy to perform and interpret and may enable

identification of an alternative cause for the patient's cardiovascular or respiratory signs. Most dogs and most cats with PTE reported in the literature have had abnormal thoracic radiographs.<sup>12,13,15-17,56</sup> In canine studies, between 9% and 27% of dogs with PTE had normal radiographs.<sup>3,12,38</sup> In one feline study of 29 cats, 13 of 14 cats with thoracic radiographs available for review had abnormalities detected,<sup>4</sup> and in a recent postmortem study of 17 cats all 5 cats that had thoracic radiography performed had abnormalities identified.<sup>5</sup> Since patients with PTE may have normal radiographs,<sup>1</sup> the finding that most patients suspected to have PTE reported in the literature have had radiographic abnormalities identified may reflect our inability to detect small emboli. In other words, abnormal thoracic radiographs may only be associated with cases of severe PTE.<sup>38</sup> It has been suggested in both the human and the veterinary literature that PTE should be suspected in all markedly dyspneic patients with normal thoracic radiographs.<sup>17,57</sup> In addition, it is prudent to suspect PTE in patients with pulmonary infiltrates if these cannot adequately be explained by another disease process and the clinical index of suspicion for PTE is high.



**Figure 1:** Dorsoventral thoracic radiograph from a dog with pulmonary thromboembolism showing an area of regional oligemia affecting the right caudal lung lobe.

### Coagulation profiles

Routine coagulation profiles including prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time, fibrinogen, fibrin degradation products (FDPs), and thrombocyte counts were previously recommended as part of the initial diagnostic workup of patients with suspected PTE.<sup>58</sup> However, since routine coagulation profiles were typically normal in recent retrospective studies<sup>3</sup> and changes are non-specific, the utility of these tests in aiding PTE diagnosis has been justifiably questioned.<sup>59</sup>

PT and aPTT times, which represent the extrinsic and common and the intrinsic and common pathways, respectively, have been reported in several studies of PTE in dogs. The results have been inconsistent and often normal.<sup>3,14</sup> One retrospective study of PTE in cats reported clotting times in 6 of 29 cases. Prolongations of PT and aPTT occurred in 2 of 6 and 6 of 6 cats, respectively.<sup>4</sup>

Antithrombin (AT) is an inhibitor of the coagulation factor serine proteases (a serpin). AT inhibits factors IIa, IXa, Xa, Xia, and XIIIa.<sup>60</sup> In hypercoagulable patients in which active thrombin production is occurring, plasma AT activity is reduced by consumption. Urinary AT loss has been linked to the hypercoagulable states associated with protein-losing nephropathy and hypercortisolemia.<sup>10,13,17,18,61</sup> AT assays are unfortunately not as widely available as other coagulation tests. Some authors suggest that AT activity can be used as an accurate guide to the risk of thrombosis although there is no consensus on risk stratification based on AT activity. Some sources suggest activity levels of 75–50% moderately increase the risk of thrombosis, while an activity below 50% is associated with a marked risk.<sup>62</sup> Feldman and others suggested that AT activity <60% carries a moderate risk of thrombosis, while AT activity <30% carries an immediate risk of thrombosis.<sup>47</sup> These values are extrapolated from humans and have not been prospectively evaluated for prediction of PTE in dogs or cats.

### FDPs and D-dimers

Abnormalities of FDPs have not been widely identified in small animals with PTE.<sup>4,63</sup> FDPs are the molecules created by plasmin cleavage of fibrinogen and fibrin and include fragments X, Y, D, and E.<sup>64</sup> FDPs indicate that degradation of fibrinogen or fibrin has occurred following activation of plasmin. Increased FDP concentrations are present in liver failure, dysfibrinogenemia, excessive fibrinolysis, and DIC as well as in thrombosis and have been found to be increased in cats with a variety of disease processes with secondary DIC and thrombosis.<sup>63</sup> Hence, the principal drawback of FDPs is their lack of specificity.<sup>64</sup> FDPs can be measured in

plasma or serum, but plasma assays of FDPs in dogs appear to be more sensitive than serum FDP assays for the diagnosis of both DIC and thromboembolism.<sup>65,66</sup>

D-dimer assays are the focus of much research in recent human studies of PTE and in veterinary studies of thromboembolic disease and DIC.<sup>63,64,67</sup> D-dimers are similar to FDPs in that they are markers of fibrinolysis. In contrast to FDPs, however, D-dimers are specific for the breakdown of insoluble cross-linked fibrin by plasmin. When fibrin, cross-linked by FXIIIa, is cleaved by plasmin, a series of cross-linked oligomers of varying molecular weights known as X-oligomers are produced.<sup>64</sup> The smallest X-oligomer fragment is the D-D/E fragment representing two cross-linked fibrin D-domains and an associated E domain. The term D-dimer actually represents a range of X-oligomers that express this cross-linked D-domain epitope. Because D-dimers require activation of both thrombin and plasmin for their formation only D-dimers indicate that physiologic or pathologic thrombosis has occurred. Furthermore, because only cross-linked fibrin molecules can be broken down into X-oligomers, assays for D-dimers are specific for fibrinolysis following thrombus formation.

Rapid, accurate, bedside D-dimer assays now play a pivotal role in decision making in humans with clinical signs compatible with PTE. The recommendations of the Prospective Investigation of Pulmonary Embolism Diagnosis investigators was that a rapid, quantitative D-dimer ELISA be performed before any further diagnostic testing for all patients presenting with possible PTE except those with a high clinical probability assessment.<sup>68</sup> Human patients with a high clinical probability assessment (eg, history of thromboembolic disease, deep vein thrombosis, dyspnea) undergo thoracic imaging and do not require a D-dimer test. In patients with a low clinical probability assessment, the need for further diagnostic testing is based upon the results of the D-dimer assay. A positive D-dimer test result will prompt thoracic imaging, while a negative test result suggests no further investigation or therapy for PTE is required. The large-scale multicenter investigations that have yielded such authoritative recommendations are unlikely to be forthcoming in veterinary medicine.

Nonetheless, D-dimer research in small animals has produced some significant results. A semiquantitative latex agglutination D-dimer assay had a sensitivity of 100% and a specificity of 97% for the diagnosis of DIC in dogs.<sup>67</sup> In the same study, an immunoturbidometric D-dimer assay had sensitivity and specificity values of 85% and 77% for DIC diagnosis and measurement of FDPs compared favorably with the D-dimer assays. D-dimers have been used to differentiate clinically ill dogs with thromboembolic disease from clinically ill

dogs with no evidence of thrombosis.<sup>63</sup> The same latex agglutination assay employed in the study by Stokol et al<sup>67</sup> was used to investigate the utility of D-dimers in thromboembolic disease. The sensitivity and specificity values of this assay for the diagnosis of thromboembolic disease were 36% and 98.5% using a cutoff value of >2000 ng/mL, 80% and 94% using a cutoff value of >1000 ng/mL and 100% and 70% using a cutoff value of >500 ng/mL.<sup>63</sup> In this study no patient with thromboembolic disease had increased FDPs using an assay with a reported sensitivity and specificity of 85% and 100% for the diagnosis of DIC.<sup>67</sup>

While there may be differences in the patient populations and disease processes between these 2 studies, one might expect better correlation of the FDP results given that DIC and thromboembolic disease are so closely related. Despite the discrepancy over the FDP assays recent investigations suggest that the latex agglutination D-dimer assay is highly suited to testing patients with a clinical index of suspicion for PTE. As a screening test, using a cutoff of >1000 ng/mL would appear to be most appropriate in minimizing the number of false-negative results, while ensuring that patients with PTE are not missed. This strategy would also aid in reducing the numbers of patients that would unnecessarily undergo further testing.

One potential disadvantage of using the latex agglutination assay as a discriminatory test for further diagnostic testing is availability and the inherent delay in obtaining a result. Point-of-care (POC) tests offer the ability to determine analyte values at the bedside, allowing them to be used for clinical decision making in unstable patients. A canine D-dimer POC test has been evaluated for the detection of D-dimers in patients with thromboembolic disease.<sup>69</sup> The POC test evaluated correlated well with a canine D-dimer ELISA assay, however, there was significant overlap in the values for the 3-patient populations assessed – DIC, thromboembolic disease, and intracavitary hemorrhage. The authors concluded that the POC test quickly and reliably detected dogs with DIC or acute thromboembolic disease but conceded that positive results might also be seen in patients with hemorrhage.<sup>69</sup> Unfortunately at the time of writing, this assay is no longer commercially available.

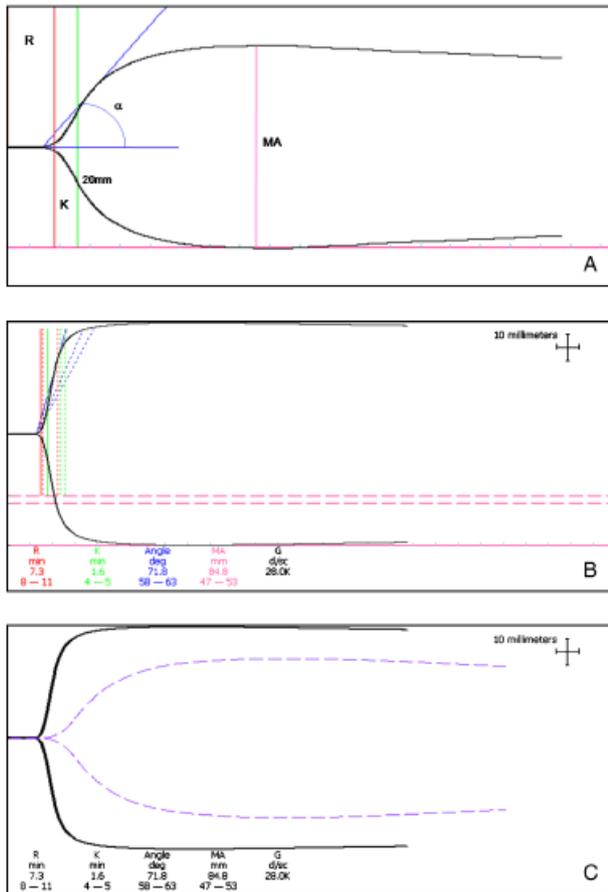
D-dimers are labile and change dynamically dependent upon the underlying thrombotic and fibrinolytic processes. An experimental canine study demonstrated that following induction of PTE, D-dimer levels were significantly increased at 30 minutes post-embolization and remained significantly greater than controls for 24 hours.<sup>70</sup> Plasma D-dimer concentrations were greatest at 2 hours post-embolization and were >2000 ng/mL at both 1 and 2 hours post-embolization.<sup>70</sup>

### Thromboelastography

Several relatively new technologies are available with the ability to detect hypercoagulable states. Two of these techniques being investigated for a role in veterinary diagnostic testing are thromboelastography (TEG) and thromboelastometry (ROTEM).<sup>71–73</sup> A third technique, the Impact Cone and Plate(let) Analyzer, is currently in an experimental stage in human clinical patients but has not been used in veterinary patients to date.<sup>74</sup> TEG was first described in 1948 and has since been used in various human clinical medicine settings, particularly liver transplantation, cardiac surgery, and in intensive care.<sup>75–77</sup> TEG provides a global evaluation of coagulation and fibrinolysis by means of a graphical representation of clot formation and lysis from which information about clot quality and the dynamics of its formation and dissolution can be obtained.<sup>72</sup> TEG provides a rapid (within 30 min) bedside summation of the function of platelets, coagulation proteases, coagulation inhibitors, and of the fibrinolytic system. TEG can be used to identify hypocoagulable states, hypercoagulability, and hyperfibrinolytic states.<sup>78–81</sup> A tissue factor activated TEG assay has been validated for use in dogs.<sup>82</sup> There are several reports of its use in cats<sup>83,84</sup> and work validating the technique in cats has recently been presented in abstract form.<sup>85</sup> There are no veterinary reports of the use of TEG in PTE to date.

Both the TEG and ROTEM setups consist of a heated cup (37°C) in which a small (0.36 mL) blood sample is placed. A pin suspended from a torsion wire (TEG) or an optical detector (ROTEM) is placed into the sample cup. The cup and pin are oscillated through an angle of 4°45' with a cycle length of 10 seconds. With TEG the cup oscillates relative to the pin, while in ROTEM the pin rotates with the cup remaining stationary. As coagulation occurs the viscoelastic changes within the sample create torque forces on the pin. These are electrically transduced to a recording device or computer terminal to produce the characteristic TEG/ROTEM tracings (Figure 2). These two devices produce comparable but not interchangeable results.<sup>86,87</sup> TEG/ROTEM have not been evaluated for the detection of PTE in small animals to date; however, their power to graphically illustrate hypercoagulability at the bedside means that they may be superior to conventional tests such as AT and D-dimer assays in detecting patients who are at risk for PTE.

TEG tracings consist of 3 zones: precoagulation, coagulation, and fibrinolysis. Numerous objective measurements can be made from the TEG tracing but 4 key values are routinely recorded. There are 2 measurements of clot formation, the reaction time (*R*) which evaluates the intrinsic pathway, and the clot formation time (*K*), a measure of the speed of clot development.



**Figure 2:** (A) A normal thromboelastography (TEG) tracing illustrating the measurement of the normal TEG parameters: Reaction time (R) – 0–2 mm. Clot formation (K) time – 2–20 mm. Alpha angle ( $\alpha$ ) – angle of tangent to maximum clot formation rate. Maximum amplitude (MA) – maximum divergence of the tracing lines. Clot elasticity (G) – reflects MA value. (B) A markedly hypercoagulable thromboelastography tracing from a patient with immune-mediated hemolytic anemia. Tracing produced from unactivated, recalcified, citrated whole blood. Note the shortened reaction (R) and clot formation (K) times and the increased alpha angle ( $\alpha$ ), maximum amplitude (MA) and clot elasticity (G) values. (C) The TEG tracing from B is reproduced here with a normal tracing for direct comparison. The degree of hypercoagulability of this patient is readily discernable.

Two further measurements are routinely made, the maximum amplitude (MA) represents maximum clot strength from which clot elasticity (G) is commonly derived and  $\alpha$ , the angle between the R and K points, which corresponds to clot formation rate. These 4 values (R, K, MA,  $\alpha$ ) have been combined using human data to derive an index indicating the coagulability of the patient's blood. This coagulation index has been used in dogs<sup>72</sup> and cats.<sup>88</sup>

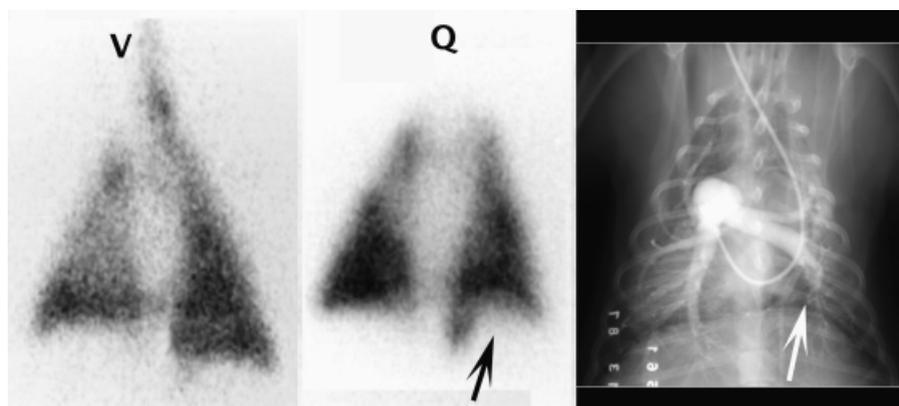
Hypercoagulable patients produce characteristic TEG tracings (Figure 2). These patients typically have short

reaction and clot formation times, steep  $\alpha$  angles, and large MAs. It is unclear which of these abnormalities best relates to thrombotic risk in veterinary patients although MA has been related to postoperative thrombotic risk in human surgical patients.<sup>89</sup> Using TEG, hypercoagulability has been identified in veterinary patients with parvoviral enteritis,<sup>90</sup> neoplasia,<sup>91</sup> and in disseminated intravascular coagulation.<sup>92</sup>

The number of institutions and private practices utilizing TEG has increased significantly in the last few years and a substantial volume of veterinary TEG research has now been published following recognition of the potential of this POC technology. This research should improve our understanding of the results of TEG testing and better inform our diagnostic decision making. Much work remains to be done, however, before the results of TEG testing can be routinely used to guide the selection or monitoring of therapies for thromboembolic disease. TEG is an exciting diagnostic tool because it offers the prospect of cheaply, accurately, and expediently identifying at-risk patients such that specific diagnostic imaging can be appropriately targeted.

### Pulmonary angiography

Selective pulmonary angiography was until recently the *gold standard* for diagnosis of PTE in humans. Until computed tomographic (CT) angiography becomes readily available selective pulmonary angiography is likely to remain the definitive method for identifying PTE in small animals. Selective pulmonary angiography involves rapid bolus injection of contrast material directly into the pulmonary artery (PA) via a PA catheter. This permits radiographic visualization of the pulmonary arterial tree. Intraluminal filling defects, abrupt pulmonary arterial termination, or the complete absence of arterial branches (pruning) are considered diagnostic for PTE (Figure 3).<sup>1,93,94</sup> Less specific changes include regional loss of vascularity, asymmetric blood flow, tortuous PAs, and premature tapering of peripheral vessels.<sup>93,94</sup> Selective pulmonary angiography is a powerful diagnostic tool, because a normal pulmonary angiogram essentially rules out PTE. Although PA catheterization has been described in conscious dogs, due to the invasive nature of this procedure, selective pulmonary angiography is typically performed under general anesthesia in small animals.<sup>95</sup> Clearly general anesthesia may be undesirable in an unstable patient. In such patients, nonselective pulmonary angiography can be performed more easily and more safely. For nonselective pulmonary angiography, contrast medium is injected via a wide-bore jugular catheter. This produces a less sensitive study that is more difficult to interpret due to contrast me-



**Figure 3:** A pulmonary ventilation scan (V), perfusion scan (Q), and pulmonary angiogram from a dog with pulmonary thromboembolism in the right caudal lung lobe. There is a normal ventilation pattern and a wedge-shaped pleural-based perfusion defect (black arrow) indicating V:Q mismatch. This corresponds to an area of decreased blood flow (regional oligemia) noted on the pulmonary angiogram (white arrow). (Adapted from Daniel GB, Berry CR. Pulmonary and Mucociliary Scintigraphy. In: Daniel GB, Berry CR, eds. Textbook of Veterinary Nuclear Medicine. Knoxville: American College of Veterinary Radiology. 304–328.)

dium dilution and superimposition of vascular structures; however, it can be performed in patients where general anesthesia is considered too risky.<sup>1,96</sup>

### Cardiac evaluation

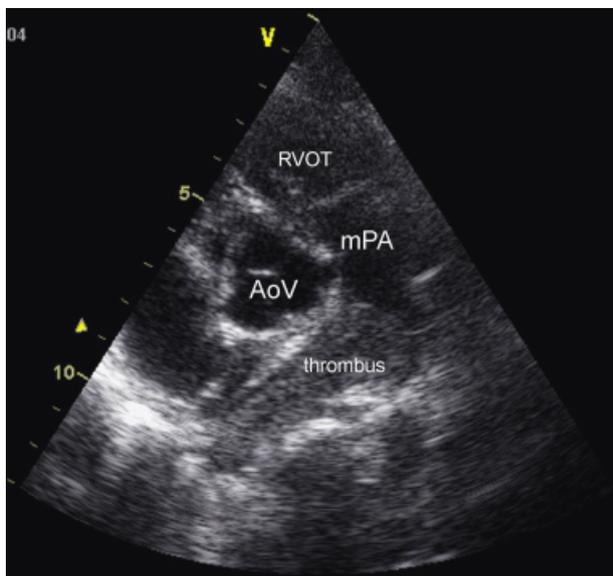
**Electrocardiography:** Electrocardiographic changes have rarely been reported in small animals with PTE and are likely uncommon in acute cases.<sup>97</sup> The most likely rhythm disturbance is sinus tachycardia secondary to sympathetic stimulation associated with hypotension or hypoxemia.<sup>12,17</sup> With myocardial hypoxia or cardiac hypertrophy S-T segment depression or slurring may be identified.<sup>97,98</sup> ECG changes reflecting RV compromise are only likely to appear as a result of severe chronic pulmonary hypertension but include a right axis deviation, an increase in S wave amplitude in leads I and II, increased T wave amplitude and tall, narrow P waves (P pulmonale) secondary to right atrial enlargement.<sup>97,98</sup>

**Echocardiography:** The use of echocardiography in the evaluation of PTE in human medicine is well established. Echocardiography allows identification of cardiac or RV outflow tract thrombosis and also the cardiovascular consequences of PTE. Echocardiography is considered a convenient, safe, noninvasive imaging technique that may provide rapid and accurate assessment of the risk of PTE.<sup>99</sup> Although in one study 94% patients with angiographically confirmed PTE had echocardiographic abnormalities, echocardiography is not recommended as a routine imaging test because other studies have shown that up to 20% of human patients with PTE have normal echocardiograms.<sup>99–102</sup> Despite this, recent large human clinical registries show that echocardiography was still performed in 47–74% of

patients with PTE.<sup>103,104</sup> The strength of echocardiography in the evaluation of patients with acute onset dyspnea or cardiovascular collapse (for which PTE may be a differential) is its established value in the diagnosis of cardiomyopathy, endocarditis, or pericardial tamponade. Thus, in these patients, echocardiography can be used as much to provide evidence for other differentials as for the positive diagnosis of PTE. The report from the Task Force on Pulmonary Embolism suggested that echocardiography was most useful in patients with suspected massive PTE (ie, those associated with cardiogenic shock).<sup>105</sup>

Typical echocardiographic findings in humans with PTE include RV dilatation and hypokinesis, septal flattening and paradoxical septal motion, diastolic left ventricular impairment, pulmonary arterial hypertension, RV hypertrophy, and patency of the foramen ovale. Occasionally direct visualization of a pulmonary arterial, RV or right atrial thrombus is possible (Figure 4). The degree of impairment of RV function is related to the cross-sectional area of the pulmonary vasculature which is occluded. Humans with <30% of their pulmonary vasculature impaired were 6.8 times more likely to have normal RV function on echocardiography.<sup>106</sup> RV hypokinesis was identified in 92% of patients with >30% pulmonary vascular impairment.<sup>106</sup>

Intriguingly in humans with large PTE the apex of the right ventricle appears to be spared the moderate-to-severe hypokinesis that affects the remainder of the right ventricular free wall (RVFW).<sup>107</sup> This abnormality was quantified by assessing RVFW wall motion in sections. This apical sparing, now known as the McConnell sign, had a sensitivity of 77% and a specificity of 94% for the diagnosis of PTE in humans.<sup>107</sup> The McConnell study used computer analysis to trace RVFW



**Figure 4:** Echocardiographic image of a thrombus in the main pulmonary artery extending into the right pulmonary artery (labelled *thrombus*). RVOT, right ventricular outflow tract; AoV, aortic valve; mPA, main pulmonary artery.

motion. Tissue Doppler imaging, designed for assessment of global and regional myocardial function from measurements of myocardial velocities might also be used to assess RVFW motion without the need for additional software.<sup>108</sup> It is unknown whether small animals with PTE also manifest regional RV hypokinesis. Given the potential diagnostic value of such a finding, further study into this area is warranted.

To date, there is minimal published information on the use of echocardiography in the diagnosis of PTE in small animals. The principal use of the technique in 2 studies was to identify thromboses in the heart or great vessels.<sup>8,15</sup> In a case report of PTE secondary to renal amyloidosis, echocardiography demonstrated right atrial and ventricular enlargement, paradoxical septal motion and a large thrombus in the right PA.<sup>109</sup> Generally, however, this technique is not routinely used in the workup of small animals with suspected PTE. In a recent retrospective study only 5 of 29 dogs (17%) with PTE were studied with echocardiography.<sup>3</sup> In 2 of these dogs there was evidence of RV and pulmonary arterial dilatation and in another dog there was evidence of pulmonary arterial hypertension.<sup>3</sup> Based on the human medical experience, it is reasonable to hypothesize that although the majority of small animals with PTE will have abnormal echocardiograms, the lack of specificity may limit the usefulness of this technique in assessment of PTE. Despite this, however, the noninvasive nature of this technique (in contrast to the majority of other diagnostic tests for PTE) and its utility in identifying

alternative diagnoses, makes echocardiography a vital tool in the investigation of patients presenting in respiratory distress or with cardiogenic shock.

**Troponins:** Assays of cardiac troponin (cTn) (both T and I) are routinely used in humans to assess patients with acute coronary syndromes. Circulating cTn is highly specific for myocardial cell injury. Cardiac troponins are frequently increased in veterinary patients with a range of disease processes including primary, ischemic, congenital and degenerative cardiac diseases, pericardial disease, gastric dilatation-volvulus syndrome, sepsis, trauma, uremia, hyperthyroidism, and some neoplasms.<sup>110</sup> Serum cTn concentration appears to be related to the magnitude of myocardial injury in acute situations such as myocardial infarction, GDV syndrome, and myocarditis.<sup>111–113</sup> There are no reports to date on measurement of cTn in small animals with PTE, although it seems reasonable to predict that they would be elevated. In humans with PTE, prognostication is frequently performed on the basis of blood pressure, RV dysfunction, and PaO<sub>2</sub> ratios as previously described. In humans, echocardiographic RV dysfunction secondary to PTE is associated with elevated cTn concentrations.<sup>114</sup> A recent meta-analysis of 20 studies suggested that humans with PTE and an increased cTn level are at high risk of short-term death and adverse events.<sup>115</sup> To date there are no veterinary studies examining this relationship.

### Nuclear medicine

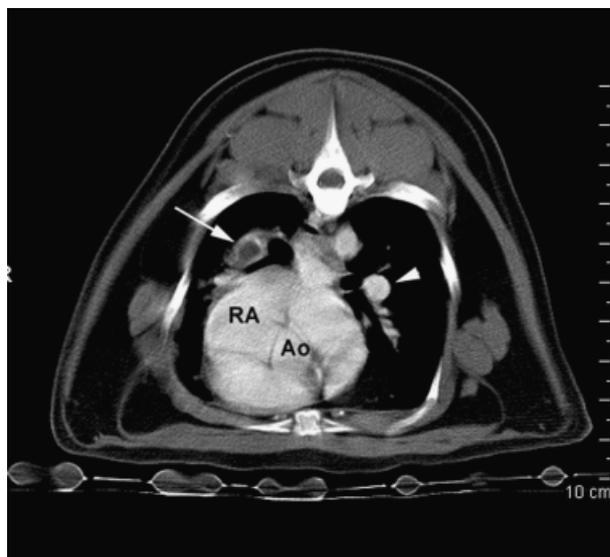
In small animals, ventilation/perfusion (V/Q) scanning has been used for the detection of perturbations in the normal V/Q matching that occur in PTE.<sup>15,16,116–118</sup> Radionuclide blood labelling to evaluate pulmonary perfusion and radionuclide labelling of inspired air to assess ventilation enables areas of V/Q mismatch to be identified. Perfusion scanning is accomplished using an IV injection of technetium-labelled macroaggregated albumin that is distributed in proportion to pulmonary blood flow. Inhomogenous distribution of activity from the decay of technetium-labelled macroaggregated albumin is consistent with abnormal perfusion. A photopenic wedge-shaped, pleural based defect with a lobar or segmental distribution is classical for PTE (Figure 3), however, entire lung lobes may appear photopenic, or if multiple small emboli are present, then a mottled pattern may result.<sup>119</sup> Ventilation scans are uncommonly performed in dyspneic patients and are typically normal in patients with PTE. In many cases only a perfusion scan is performed, which is then compared with thoracic radiographs to identify nonthrombotic pathology that may be affecting perfusion. The advent of multislice spiral CT in the early 1990s

significantly reduced the number of V/Q scans being performed in humans.<sup>120,121</sup> A prospective evaluation of PTE diagnosis Prospective Investigation of Pulmonary Embolism Diagnosis suggested that V/Q scanning was indicated for just a small subset of the population presenting with suspected PTE.<sup>122</sup> In light of this, the limited availability of equipment and expertise and the associated technical difficulties, V/Q scanning may become obsolete.

### CT pulmonary angiography

A study from 1978 reported identification of pulmonary infarcts with a conventional thoracic CT scan.<sup>123</sup> The advent of spiral (also called helical) CT in 1989 and multislice spiral CT in the early 1990s provided the technological advance required to permit rapid, high-resolution imaging of a larger tissue volume without motion artifacts. Early studies of spiral CT angiography detection of PTE in humans reported very high sensitivity (100%) and specificity values (96%).<sup>120,124</sup> Two human reports from 2000 demonstrated consistently high sensitivity (87%) and specificity (91%) values.<sup>125,126</sup> CT angiography scans are particularly good at detecting main, lobar, or segmental pulmonary arterial thrombi in humans; however, sensitivity is poorer (86%) when subsegmental vessels are included.<sup>124</sup> PTE confined to the subsegmental vessels represents only 6% of cases in humans, however, and thus represents a relatively minor limitation to the technique.<sup>127</sup> CT angiography directly identifies the pulmonary embolus as an intraluminal filling defect and enables identification of other conditions that may cause similar presenting signs (Figure 5). Critically, CT angiography is a rapid test which, if normal, essentially rules out PTE as the cause of the patient's respiratory distress.

Spiral computed tomography pulmonary angiography (CTPA) has become part of the basic investigations for PTE recommended by US and UK human medical guidelines.<sup>128,129</sup> CTPA has largely supplanted pulmonary angiography and pulmonary scintigraphy for diagnosis of PTE in humans.<sup>68,130-132</sup> Recently there have been several studies in dogs reporting CT angiography for investigation of the hepatic and portal vasculature as a method for investigating porto-vascular anomalies.<sup>133-135</sup> CTPA has been performed in dogs with a single slice helical CT scanner.<sup>136</sup> This study reported a protocol for CTPA based on contrast injection via a peripheral venous catheter. The study compared pulmonary perfusion scintigraphy for detection of PTE following total hip arthroplasty. While the study did not detect any thrombi (with either technique), the CTPA protocol allowed consistent acquisition of diagnostic quality images and permitted visualization down to the fifth generation of PA branches. A single



**Figure 5:** Transverse CT angiographic image of the heart and pulmonary arteries from a cat. Right is to the left. Contrast medium can be seen filling the heart chambers and the left pulmonary artery (arrowhead). Note the round filling defect representing an embolus in the right pulmonary artery (arrow). RA, right atrium; Ao, aorta. (Adapted from: Davidson BL et al. Pulmonary Thromboembolism in a Heartworm-Positive Cat. *J Vet Intern Med* 2006; 20(4):1037-1041.)

breath hold technique was not attempted in this study. Patients were manually hyperventilated for 4-5 minutes before commencing the CT scan. This protocol limited breathing induced motion artefact to only 7% of slices.

CTPA has been demonstrated to be capable of imaging PTE in an experimental canine model.<sup>70</sup> Both pulmonary thrombi and pulmonary infarcts were identified by CTPA in this study. The advent of multislice CT scanners permits the imaging of more anatomy in less time, likely alleviating the need for breath-hold techniques to eliminate motion artifact. Importantly the scanning speed of multislice CT systems will likely permit scanning of veterinary patients conscious or under sedation obviating the need for potentially hazardous general anesthesia. The power of multislice CT technology being applied to veterinary patients was illustrated by a recent case report using a 16 slice CT scanner to positively identify a descending aortic thrombus secondary to spirocercosis in a dog.<sup>137</sup> The human medical experience suggests that multislice CTPA is the way forward for PTE diagnosis. Advancements in CT technology in which as many as 64 image slices may be acquired simultaneously may revolutionize our ability to detect pulmonary emboli in veterinary patients.

### Imaging techniques of the future

The use of magnetic resonance imaging (MRI) in the diagnosis of PTE is in its infancy in human medicine and thus, it is likely to be some time before such technology is available for use in veterinary species. The safe, noninvasive nature of MRI offers potentially significant advantages over CT; however, since general anesthesia is required for MRI of veterinary patients the utility of MRI-based techniques may be somewhat limited. Nevertheless, several MRI-based techniques for PTE diagnosis have emerged and magnetic resonance angiography appears comparable to CTPA in experimental studies in dogs.<sup>138,139</sup> Direct thrombus imaging using MRI offers the possibility of imaging clots by identifying the thrombus degradation product methemoglobin via a heavily T1-weighted image.<sup>140</sup> Clot-labelling techniques utilizing radiolabelled anti-D-dimer antibodies detected by a tomographic nuclear medicine technique have been performed experimentally in dogs.<sup>141</sup> The feasibility and utility of these techniques remains uncertain.

### Diagnostic approach

PTE is suspected in many patients but confirmation of this diagnosis is comparatively rare. This is likely due to the inconsistency and variability of the clinical signs; the poor specificity of readily available diagnostic tests, and the lack of availability of those tests with better diagnostic accuracy. In human medicine the major limitation is not the lack of availability of diagnostic testing but rather the difficulty in identifying those patients with the greatest need for these tests. Algorithms incorporating coagulation parameters have been used widely in humans to this end.<sup>142–144</sup> Similar algorithms have been suggested for defining clinical probability of PTE in dogs.<sup>145</sup> The first step in making a diagnosis is to identify patients with consistent clinical signs and known risk factors such as outlined in Table 1. Further diagnostic testing should be expedited in patients with known risk factors. All patients with consistent clinical signs should have thoracic radiographs ideally in combination with arterial blood-gas analysis to identify patients with a normal respiratory system or other pulmonary pathologies. In rare cases a diagnosis of PTE may then be possible without further diagnostic testing. In patients with radiographic changes consistent with but not pathognomonic for PTE further imaging will be necessary to exclude other disease processes and to positively diagnose PTE. An initial echocardiogram followed by angiography or scintigraphy is rational. At-risk patients with clinical signs but without radiographic abnormalities should have additional imaging studies performed, particularly if arterial blood-gas analysis shows hypoxemia, hypocapnia, or

an increased A-a gradient. Echocardiography is noninvasive, can be performed at the bedside and may identify patients that would most benefit from advanced imaging. Selection of additional imaging will be dependent upon availability and operator capability. In patients with clinical signs but without known risk factors coagulation testing with D-dimers, AT activity, or TEG may help identify patients with evidence of thrombin activation, AT depletion, or hypercoagulability. Results from an experimental study suggest that D-dimers should be measured as soon as possible after a suspected PTE event.<sup>70</sup> Recognition of a dyspneic, hypercoagulable patient should prompt re-evaluation for predisposing conditions and additional imaging to look for PTE. Overall, PTE remains a diagnostic challenge and a subset of patients will be difficult to diagnose even with a logical diagnostic evaluation. A consensus driven, evidence-based algorithmic approach has proved effective in humans and a similar mechanism would undoubtedly be of value in small animals.

### Therapy for PTE

Therapeutic decision making in individual animals with PTE is problematic. The uncertainty of PTE diagnosis in many patients has resulted in a shortage of evidence upon which to base therapeutic recommendations, making formulation of treatment protocols challenging. Where PTE is diagnosed or the clinical index of suspicion is sufficiently great, therapy for PTE may consist of supportive treatment and thromboembolic pharmacotherapy (Table 2). Successful treatment for acute PTE is typically followed by chronic anticoagulant or antiplatelet therapy. In humans with PTE, risk stratification based on clinical assessment, oxygenation status, anatomic clot size, cardiac function, biomarkers, and the presence of pulmonary hypertension is key to successful treatment.<sup>146</sup> In low-risk patients anticoagulant therapy alone is recommended while high-risk patients particularly those with hemodynamic instability secondary to massive PTE are treated with thrombolytics followed by anticoagulation. Therapy for thromboembolic disease is based on the concepts of Virchow's triad – hypercoagulability, blood flow stasis, and endothelial dysfunction. Therapies designed to address flow stasis are principally supportive; for instance, treating the underlying neoplastic or myocardial disease. Abnormalities of flow stasis may also require pharmacotherapy to prevent thrombus propagation. Specific drug therapies for endothelial dysfunction are not available. This predisposing factor is addressed by treatment of the primary disease potentially with the addition of pharmacotherapy as for flow stasis. Dis-

eases promoting hypercoagulability require treatment of the underlying disease and pharmacotherapy to treat existing thrombi, limit propagation, and prevent recurrence.

### Supportive therapy

In a small percentage of patients PTE is immediately fatal and thus despite thrombolytic therapy survival is unlikely.<sup>147,148</sup> In normal dogs thrombi lyse within hours.<sup>6</sup> Although this rapid lysis may not occur in clinical patients, supportive therapy may be sufficient to permit survival while fibrinolysis occurs.<sup>6,93</sup> As such, supportive measures should be considered essential to any putative PTE patient. Oxygen therapy should be given to all dyspneic or hypoxemic patients. Mechanical ventilation may be necessary if oxygen therapy alone cannot resolve the hypoxemia. Should mechanical ventilation be required efforts must be made to minimize the detrimental impact of positive intrathoracic pressure on PVR (which may already be increased in this patient population). Because delivery of oxygen to tissues depends upon cardiac output as well oxygen content, perfusion must be optimized to maximize tissue oxygenation. Judicious, targeted use of fluid therapy, guided by measurement of arterial and central venous pressure and venous lactate concentrations may be used to improve cardiac output and tissue oxygen delivery. Clinicians must be cautious, however, because overdistension of the RV with fluid therapy may impair coronary perfusion and LV filling. The use of echocardiography to determine RV filling may help to guide fluid administration.<sup>149</sup>

Bronchodilators such as theophylline may be beneficial. In addition to bronchodilation, theophylline may induce pulmonary vasodilation, improve diaphragmatic contractility, and reduce respiratory muscle fatigue.<sup>59</sup> Very little has been published about vasopressor therapy in acute PTE. In a canine model, norepinephrine was superior to phenylephrine in increasing cardiac output and RV coronary blood flow.<sup>150</sup> Positive inotropes such as dobutamine may be considered in cases of cardiogenic shock; however, these drugs may increase PA pressures and susceptibility to arrhythmias.<sup>151,152</sup> Venodilator therapy may be useful to treat the reflex pulmonary vasoconstriction which contributes to increased PVR in PTE cases. Inhaled nitric oxide has been shown to decrease mean pulmonary artery pressure in canine models and in humans.<sup>153</sup> Although no clinical trials in veterinary patients have been undertaken to date, this therapy shows promise in humans to reduce RV afterload, improve hemodynamics and allow time for recovery.<sup>154</sup> Several veterinary studies have shown beneficial effects of sildenafil (a specific phosphodiesterase type 5 inhibitor) in patients

with pulmonary hypertension.<sup>155,156</sup> Sildenafil has been shown in canine PTE models to produce selective pulmonary arterial vasodilation thereby attenuating pulmonary hypertension.<sup>157-160</sup> In a human case report, oral sildenafil administered to a patient with recurrent massive PTE decreased mean pulmonary artery pressure and improved cardiac index<sup>161</sup> although to date it has not been adopted as standard of care.<sup>149,162</sup> No veterinary studies have yet been published examining sildenafil use in clinical PTE cases. Based on the documented benefits of sildenafil for canine idiopathic pulmonary hypertension, its use in suspected PTE cases may be considered if pulmonary hypertension is documented echocardiographically. Potential side effects of sildenafil therapy in dogs include systemic hypotension, vomiting, and inguinal cutaneous flushing. Co-administration with heparin may increase the risk of hemorrhage, while coadministration with nitrates can cause marked systemic hypotension and should be avoided.

### Thrombolysis

Thrombolysis is the dissolution of thrombi within the vascular system by the serine protease plasmin. Plasmin is produced physiologically from plasminogen by urokinase and tissue plasminogen activator (t-PA). Therapeutic thrombolysis involves the administration of supraphysiologic doses of plasminogen activators systemically or locally at the thrombosis site. Thrombolytic agents increase the conversion of plasminogen to plasmin and help to overcome plasmin inhibition by plasminogen activator inhibitor 1.<sup>163</sup> In PTE thrombolytic drugs may reverse right-sided heart failure by inducing rapid thrombus dissolution, prevent ongoing neurohumoral factor release, improve systemic and pulmonary hemodynamics, and reduce the likelihood of recurrence.<sup>148</sup>

Available pharmacologic agents include streptokinase, anisoylated plasminogen streptokinase complex (anistreplase), urokinase, t-PA (alteplase), and modified recombinant t-PA (reteplase and tenecteplase). These agents vary in their pharmacokinetics, thrombolytic activity, and fibrin specificity (preference for fibrin-bound versus circulating plasminogen). Fibrin-specific thrombolytics have increased clot lysis efficacy, a longer duration of activity, and a reduced risk of hemorrhage compared with less specific agents.<sup>164</sup> Veterinary experience with thrombolytics to date is limited to anecdotal reports involving streptokinase, urokinase, and alteplase only. Prospective clinical trials are needed to determine the safety and efficacy of these agents in veterinary patients. No consensus on their administration exists and the use of these drugs remains controversial. Clinicians must determine the

**Table 2:** Supportive, thrombolytic and thromboembolic pharmacotherapies for pulmonary thromboembolism (PTE) in dogs and cats

Drug	Drug type	Mechanism of action	Indications in PTE therapy	Canine dosage	Feline dosage	Route	Frequency	Treatment considerations	Ref
Dobutamine	Adrenergic positive inotrope	$\beta_1$ adrenergic receptor agonist	Myocardial failure - cardiogenic shock	1–10 $\mu$ g/kg/min	1–3 $\mu$ g/kg/min	IV CRI	–	Monitor ECG	238,239
Sildenafil	Pulmonary vasodilator	PDE 5 inhibitor	Pulmonary hypertension	0.3–3 mg/kg	?	PO	q 6–8 h	Experimental	155
Theophylline (Aminophylline)	Methylxanthine bronchodilator	PDE 4 inhibitor	Bronchoconstriction	9–11 mg/kg	2–5 mg/kg	IV	Single dose	Dilute and give slowly	240,241
Alteplase	t-PA	Directly converts plasminogen to plasmin	Thrombolysis	0.4–1.0 mg/kg q1 h 4–10 doses over 1–2 days	0.25–1.0 mg/kg/hr Total dose 1.0–10.0 mg/kg	IV CRI	–	Risk of hemorrhage	169,178
Streptokinase	Thrombolytic	Plasminogen: streptokinase complex converts plasminogen to plasmin	Thrombolysis	90,000 IU over 30 min then 45,000 IU/h over 6–12 h	90,000 IU over 20 min then 45,000 IU/h CRI over 2–24 h	IV CRI	Do not repeat within 6 months	Risk of hemorrhage	168,169
Urokinase	Thrombolytic	Directly converts plasminogen to plasmin	Thrombolysis	4,400 IU/kg over 10 min then 4,400 IU/kg/hr CRI for $\geq$ 12 hr	–	IV	–	Not peer-reviewed	171,175
Dalteparin	Parenteral anticoagulant LMWH	Indirect anti-Xa activity via AT	Acute PTE therapy Maintenance anticoagulation	150 IU/kg	150 IU/kg	SC	C – q 8 h F – q 4 h	Monitoring only possible with anti-Xa assay	180
Enoxaparin	Parenteral anticoagulant LMWH	Indirect anti-Xa activity via AT	Acute PTE therapy Maintenance anticoagulation	0.8 mg/kg	1.5 mg/kg	SC	C – q 6 h F – q 6 h	–	83, 180
UFH	Parenteral anticoagulant Heparin	Binds and potentiates AT inactivation of IIa and Xa	Acute PTE therapy	250 U/kg	175–475 U/kg	IV	C – q 6 h F – q 6–8 h	Target 1.5–2.5 $\times$ aPTT baseline or anti-Xa 0.35–0.7 U/mL	196, 197,242-244
			Thromboprophylaxis during warfarin therapy induction	18 U/kg/h 200–500 U/kg	18 U/kg/h 200–500 U/kg	IV CRI SC	CRI q 8 h	–	–

Warfarin	Oral anticoagulant	Inhibits VKOR	Maintenance anticoagulation	0.2 mg/kg then 0.05–0.1 mg/kg	0.1–0.2 mg/kg	PO	q 24 h	Target 1.5–2.5 × PT baseline	180
Aspirin	Oral antiplatelet	Inhibits COX-1 preventing TXA2 mediated platelet activation	Thromboprophylaxis	0.5 mg/kg	5 mg total dose	PO	C – q 24 h F – q 72 h	Monitor for bleeding or GI side effects	180
Clopidogrel	Oral antiplatelet	P <sub>2</sub> Y <sub>12</sub> ADP receptor antagonist	Thromboprophylaxis	?	18.75 mg/kg	PO	q 24 h		236
Abciximab	Injectable antiplatelet	GP1Ib/IIla receptor antagonist	Thromboprophylaxis	?	0.25 mg/kg bolus then 0.125 µg/kg/min CRI	IV CRI	–	Experimental	222

Dosages, routes of administration, indications and main mechanism of action are included. See relevant sections of the text for a full discussion of the use of these drugs in management of the PTE patient. aPTT, activated partial thromboplastin time; AT, antithrombin; C, canine; COX-1, cyclo-oxygenase-1; CRI, continuous rate infusion; F, feline; GI, gastrointestinal; LMWH, low-molecular-weight heparin; PDE, phosphodiesterase; PRN, pro re nata (as required); t-PA, tissue plasminogen activator; TXA<sub>2</sub>, thromboxane A<sub>2</sub>; UFH, unfractionated heparin. Question marks signify no published dose identified.

potential benefits and risks of administration for individual patients.

Streptokinase, a purified streptococcal protein binds plasminogen in a 1:1 complex promoting the conversion of other plasminogen molecules to plasmin.<sup>165</sup> Streptokinase is not fibrin specific and readily binds circulating plasminogen potentially inducing a systemic lytic state. Streptokinase has been used both experimentally and clinically in cats with aortic thromboembolism (ATE), although its use was associated with increased mortality.<sup>166,167</sup> Streptokinase has been used effectively in 4 dogs with thrombosis<sup>168</sup> and in 1 dog with PTE.<sup>3</sup>

Urokinase is produced commercially from cultured human neonatal kidney cells; it is no longer commercially available in the United States. Urokinase directly converts plasminogen to plasmin.<sup>169</sup> It is more fibrin specific than streptokinase but may also bind circulating plasminogen with the associated risk of hemorrhage.<sup>170</sup> The clinical use of urokinase has been described in 12 cats with ATE of which 42% survived to discharge.<sup>171</sup> Urokinase was not associated with serious hemorrhage in that study. Urokinase has been used experimentally in dogs<sup>172–174</sup> and has been reported in 1 dog with PTE.<sup>175</sup>

t-PA directly converts plasminogen to plasmin. The t-PA products are fibrin specific, activating bound plasminogen more rapidly and more effectively than that in circulation. At pharmacologic concentrations, however, a systemic lytic state can still occur and all t-PA products are associated with a risk of hemorrhage in humans.<sup>170,176</sup> Hemorrhage associated with t-PA administration requires treatment with cryoprecipitate, fresh frozen plasma, or the fibrin-binding antifibrinolytic drug ε-aminocaproic acid.<sup>176</sup> Alteplase (a recombinant form of human t-PA) is derived from mammalian cell culture and has the shortest half-life of the available thrombolytics.<sup>163</sup> Modified recombinant t-PAs including reteplase and tenecteplase have longer half-lives with minimal improvements in fibrin specificity.<sup>177</sup> There are no reports of their use in veterinary clinical patients. Alteplase has been used in 6 cats with ATE of which 3 survived to discharge.<sup>167</sup> Successful use of alteplase has been reported in 1 dog with ATE.<sup>178</sup> Canine PTE has been treated with t-PA therapy in experimental animals.<sup>179</sup>

A recent, comprehensive, evidence-based review of thromboembolic therapies was unable to make specific recommendations on the use of thrombolytic agents in PTE based on the available veterinary literature.<sup>180</sup> The American College of Chest Physicians suggests that thrombolytics are not appropriate for most humans with PTE.<sup>181</sup> Results from the International Cooperative Pulmonary Embolism Register suggest

that thrombolytic usage in humans with PTE is uncommon (33/108 patients with massive PTE).<sup>182</sup> Thrombolytic therapy may be indicated in veterinary patients with hemodynamically unstable acute PTE. Should thrombolytic therapy be required in veterinary patients, alteplase, which is fibrin specific, suitable for rapid infusion with a short half-life may be preferable.<sup>180</sup> Thrombolytic therapy should only be administered where continuous hemodynamic monitoring is available.<sup>169</sup>

### Thromboembolic pharmacotherapy

Minimizing thrombus propagation and prevention of recurrence are the aims of thromboembolic treatment of patients with PTE. Evidence suggesting that embolization itself may stimulate thrombus propagation makes this aspect of therapy particularly important.<sup>183</sup> Arterial and venous thromboses were previously considered separate pathophysiological entities; however, this distinction is likely an oversimplification since they share common features, risk factors, and both contain platelets and fibrin.<sup>184</sup> There is evidence of overlapping efficacy of antiplatelet and anticoagulant agents in the treatment of both venous and arterial thromboembolic conditions.<sup>185,186</sup> Thromboembolic therapies are classified into parenteral and oral anticoagulants and parenteral and oral antiplatelet agents.

Rapidly initiated parenteral anticoagulation is the foundation for treatment of humans with acute PTE.<sup>146</sup> Parenteral anticoagulants including unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and synthetic selective FXa inhibitors such as fondaparinux<sup>187</sup> have been evaluated for treatment or prevention of PTE in humans. The injectable direct thrombin inhibitors (DTI) argatroban and lepirudin are indicated for treatment of heparin-induced thrombocytopenia and thrombosis in humans.<sup>149</sup> Although canine thrombosis models have been used to evaluate pharmacokinetics and safety profiles of the DTI melagatran, no information on veterinary clinical usage is available.<sup>188,189</sup>

UFH, a mixture of variably sized glycosaminoglycan molecules, complexes with and amplifies the activity of AT.<sup>190</sup> Heparin:AT complexes inhibit FIIa (thrombin) and FXa most actively, but factors IXa, XIa, XIIa, and XIII are also inhibited. Only heparin molecules with more than 18 monosaccharide units are capable of inactivating thrombin.<sup>191</sup> Thrombin inactivation prevents fibrin formation and reduces thrombin-induced platelet activation.<sup>192–194</sup> Variation in the distribution of heparin molecules in UFH leads to variation in the biologic effects and pharmacokinetics of the preparation. It is this unpredictability that necessitates close monitoring of the aPTT or activated clotting time to achieve the desired therapeutic activity while minimizing the risk

of hemorrhage. The pharmacokinetic properties of UFH in dogs are similar to those in humans but a reliable regimen for high-dose heparin treatment in dogs may not be feasible.<sup>195</sup> Variations in parameters influencing heparin pharmacokinetics in sick patients make it unfeasible to design generally applicable dosing recommendations, emphasizing the need to closely monitor and tailor the heparin dose to the individual. The recommended degree of prolongation of the aPTT is 1.5–2.5 times initial values in dogs.<sup>196,197</sup> Heparin has a narrow therapeutic index and severe bleeding complications can result from exceeding the therapeutic range. These target intervals have not been shown to indicate efficacy in cats. IV UFH therapy titrated to a predefined aPTT endpoint remains the most widely used strategy for the initial management of PTE in humans.<sup>146</sup> This is often performed based on a nomogram (a graphical calculation device) such as that described by Raschke *et al.*<sup>198</sup> The Seventh ACCP Conference on Antithrombotic and Thromboembolic Disease suggested that IV UFH or SC LMWH were appropriate (Grade 1A) for acute nonmassive PTE in humans.<sup>181</sup>

LMWHs are produced from UFH by chemical or enzymatic depolymerization. They were developed to have more consistent biologic effects and pharmacokinetics than UFH. As the size of the LMWHs reduces, the proportion of molecules of sufficient length to bind both AT and thrombin decreases. As a result LMWHs have reduced anti-FIIa activity and are principally indirect anti-FXa agents and therefore have minimal effect on aPTT.<sup>199</sup> The pharmacokinetic profiles of available LMWHs vary and preparations are not interchangeable.<sup>190</sup> In humans LMWHs have a predictable dose response and a longer half-life than UFH allowing intermittent fixed dose administration without routine anti-FXa activity monitoring. These drugs are also highly bioavailable after SC administration allowing less invasive administration.<sup>200</sup> LMWH pharmacokinetics have been evaluated in normal healthy dogs and therapeutic anti-FXa levels can be achieved, although it is unclear whether achieving these target levels is required for adequate anticoagulation.<sup>201,202</sup> LMWH also appears highly bioavailable in dogs when injected SC.<sup>203</sup> The pharmacokinetics of LMWHs in cats are much less predictable, however, and high dosages frequently administered are required to achieve human therapeutic anti-FXa activities.<sup>83</sup> In humans LMWHs are approved by the FDA for treatment of deep vein thrombosis with or without symptomatic pulmonary embolism. No studies have evaluated the efficacy of LMWH in the resolution of naturally occurring PTE in dogs or cats.

Fondaparinux is a synthetic, selective, AT-dependent indirect FXa-inhibitor with no anti-FIIa activity.<sup>204</sup>

Fondaparinux has been evaluated in a large randomized-controlled trial of humans with acute PTE.<sup>187</sup> This trial compared UFH with fondaparinux and documented no difference in major bleeding between treatments although there was a trend towards fewer PTE recurrences with fondaparinux. This trial formed the basis for FDA approval of fondaparinux as a bridge to warfarin therapy in humans with acute PTE. Once the initial PE episode has been treated, oral anticoagulation is indicated for at least 6 months in humans.<sup>181</sup> To the authors' knowledge no studies of fondaparinux have been performed in dogs or cats.

To date there are no clinical trials in small animals evaluating anticoagulants for PTE. As such recommendations are difficult to make and require extrapolation from humans or from studies of other thromboembolic diseases. Further research is urgently required in this area. It is unknown whether treatment efficacy for arterial thromboembolism will reflect efficacy in PTE. Of the available drugs, most veterinary experience exists with the use of UFH, although a wide range of dosages have been published.<sup>180</sup> A recent evidence-based review suggested that UFH should be considered for the initial in-hospital therapy of PTE; although enoxaparin or dalteparin can be considered as alternatives to UFH.<sup>180</sup>

Oral anticoagulants act by inhibiting coagulation factors. Warfarin has long been the mainstay for oral anticoagulation in human medicine but it is notoriously difficult to achieve adequate anticoagulation with this drug while minimizing bleeding risk. Warfarin has a narrow therapeutic index, variable patient dose-response and numerous interactions with other drugs.<sup>205</sup> As a result of these concerns several new oral anticoagulants are in clinical development including the FXa inhibitors rivaroxaban and apixaban<sup>206</sup> and the oral DTI dabigatran.<sup>207</sup> Ximelagatran an orally active DTI underwent an extensive human clinical trial program with efficacy demonstrated in venous thromboembolism and stroke.<sup>208</sup> Hepatotoxicity and adverse cardiovascular events observed in several studies led to the withdrawal of ximelagatran from all markets in 2006.<sup>207</sup> Currently no oral DTI or Xa-inhibitors are approved by the FDA in humans or veterinary species.

Warfarin, the most commonly used therapeutic vitamin K antagonist inhibits vitamin K epoxide reductase preventing recycling of vitamin K epoxide to hydroquinone.<sup>209,210</sup> Depletion of hydroquinone prevents  $\gamma$ -carboxylation of FII, FVII, FIX, and FX leading to accumulation of decarboxylated proteins with greatly reduced procoagulant activity and hence anticoagulation.<sup>211-213</sup> Warfarin also inhibits the vitamin K-dependent anticoagulant proteins C and S. This can lead to

paradoxical thrombosis because protein C has a shorter half-life than the procoagulant factors. Short-term heparinization is therefore recommended during initiation of warfarin therapy.<sup>205</sup> Warfarin therapy is indicated for long-term thromboprophylaxis and is of little value in an acute setting. Like UFH, warfarin has a narrow therapeutic index and severe, life-threatening hemorrhage is a perpetual risk. As such therapeutic drug monitoring using the PT is essential for all patients receiving warfarin. The international normalized ratio (where  $INR = [\text{patient PT} / \text{mean normal PT}]^{ISI}$ ) was developed to standardize warfarin monitoring by adjusting for different thromboplastin activities.<sup>214</sup> The effects of warfarin on the INR in dogs have been studied<sup>215</sup> and warfarin has been used clinically in both cats and dogs.<sup>216</sup> Oral anticoagulant therapy with warfarin has been undertaken for dogs following cardiac valve replacement,<sup>217</sup> however, the risks of inadequate anticoagulation or fatal hemorrhage are high. Warfarin therapy adjusted to achieve a PT prolongation of 1.25–1.5 times baseline may be considered for PTE. UFH should be administered concurrently with warfarin for the first 5–7 days of therapy, targeted to an aPTT value 1.5–2 times baseline or anti-FXa activity between 0.35 and 0.70 U/mL. Subcutaneous injections of the LMWHs enoxaparin or dalteparin may be considered alternatives to warfarin therapy in dogs.<sup>180</sup>

The vital role of platelets in hemostasis is now well recognized and platelets are known to play a far more active part than solely providing a surface for coagulation factors to interact on.<sup>218</sup> Platelet activation is mediated by collagen, ADP, serotonin, arachidonic acid metabolites, and thrombin. Oral antiplatelet agents include the thromboxane synthesis inhibitor aspirin and the thienopyridine P<sub>2</sub>Y<sub>12</sub> ADP receptor antagonists ticlopidine<sup>219</sup> and clopidogrel. Aspirin<sup>220</sup> and clopidogrel<sup>221</sup> have been used to reduce thromboembolic risk in small animals with known predisposing conditions. The  $\alpha_{IIb}\beta_3$  integrin receptor antagonists abciximab, tirofiban, and eptafibatide are all injectable antiplatelet agents. Of these agents only abciximab has been used safely in cats.<sup>222</sup> Eptifibatide causes fatal cardiotoxicity in cats and should not be used.<sup>223</sup>

To date, only oral antiplatelet agents have been studied in veterinary medicine and this is likely to remain the case until further work evaluating the injectable platelet agents is performed. Antiplatelet agents are most suited to use as long-term maintenance therapy potentially in combination with other drugs, and as thromboprophylactic agents in at-risk patients. Few studies have employed antiplatelet agents in combination with anticoagulants;<sup>137,220,224</sup> however, an approach directed at multiple therapeutic targets has pathophysiological appeal.

Aspirin irreversibly acetylates platelet cyclooxygenase-1, inhibiting the enzyme and preventing the conversion of arachidonic acid to prostaglandin H<sub>2</sub>, the precursor for thromboxane A<sub>2</sub> (TXA<sub>2</sub>) in platelets which induces platelet aggregation. Platelet function is therefore very sensitive to inhibition by aspirin and the drug produces an antithrombotic state over a wide dose range.<sup>225–228</sup> Aspirin pharmacodynamics in humans, dogs, and cats are similar, however, feline aspirin pharmacokinetics are different due to a relative glucuronate deficiency. This causes a prolonged elimination half-life in the cat (38 h) compared with humans (15–20 min) and dogs (7 h).<sup>180</sup>

Aspirin therapy has long been recommended for feline ATE although no studies have documented efficacy. A recent retrospective study suggested a reduced dose of 5 mg per cat every 72 hours may be safer than previously recommended high doses.<sup>229</sup> Early evidence regarding aspirin in heartworm disease is contradictory to more recent studies that have failed to demonstrate a benefit<sup>230</sup> or suggest that prostaglandin inhibitors may be contraindicated in heartworm disease.<sup>231</sup> Current recommendations are that aspirin not be used in the treatment of heartworm-infected dogs.<sup>232</sup> Aspirin (0.5–5 mg/kg q 12–24 h) should be considered in the treatment of dogs with protein-losing nephropathy and nephrotic syndrome.<sup>233</sup> A 2005 retrospective study of 151 dogs with immune-mediated hemolytic anemia compared ultralow-dose aspirin, UFH, or a combination of the 2 and found that dogs that received aspirin had significantly better survival rates than dogs that did not.<sup>220</sup> Dogs receiving UFH in this study had significantly different laboratory values from those on aspirin, however, which may have confounded the results. Based primarily on this single study, aspirin (0.5 mg/kg/d) has been recommended for dogs with IMHA,<sup>180</sup> however, given the potential treatment bias in this study the efficacy of ultralow-dose aspirin therapy needs prospective evaluation.

The thienopyridines ticlopidine and clopidogrel were discovered by phenotypic screening since both are inactive *in vitro* and rely on active metabolites for their *in vivo* efficacy.<sup>234</sup> Concerns over myelotoxicity associated with ticlopidine has led to it being largely superseded by clopidogrel. The active metabolite of clopidogrel causes cumulative inhibition of platelet function following repeated daily administration. In humans, clopidogrel may be marginally more effective than aspirin, while combining both agents may produce beneficial additive effects.<sup>235</sup> The clinical activity and pharmacodynamics of clopidogrel have been evaluated in cats and significant antiplatelet effects are achievable.<sup>236</sup> A multicenter double-blinded prospective study of cats with thromboembolism secondary to myocardial dis-

ease is currently underway.<sup>237</sup> An interim analysis of the FATCAT study comparing aspirin with clopidogrel for reduction cardiogenic embolic events suggested a potential difference between these two drugs; however, the study is currently still enrolling.<sup>221</sup> With limited evidence of efficacy for either aspirin or clopidogrel, evidenced-based recommendations for treatment of PTE cannot be made. Aspirin is indicated for thromboprophylaxis in IMHA, PLN, and feline myocardial disease and is a rational therapeutic choice in patients with PTE associated with these disease processes.

## Conclusion

Given the complex pathogenesis of PTE, this disorder will likely remain a challenging diagnosis to confirm. There is still much work to be done in evaluating many of the diagnostic steps in small animals, particularly the use of POC evaluation of coagulation including TEG and D-dimers, and imaging techniques, chiefly echocardiography and spiral CT pulmonary angiography. Better evaluation of coagulation status may improve our ability to identify at-risk patients and as a result improve the detection of PTE. Because PTE likely carries a substantial mortality rate and is potentially rapidly fatal, the importance of early detection cannot be overstated. Once we are better able to confirm a diagnosis of PTE in small animals, therapeutic clinical trials of thrombolytics, anticoagulants, and antiplatelet agents will be essential in order to improve our treatment of this condition. Until such time therapy for PTE should consist of close monitoring, good supportive therapy, and judicious, individualized empirical use of thrombolytics, anticoagulants, and antiplatelet agents.

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