

Canine pulmonary hypertension

Part 1: An in-depth review of its pathophysiology and classifications

This complex syndrome is not as uncommon as we once thought. Understanding its pathophysiology and classification schemes—both clinical and functional—will help you better manage this condition in your patients.

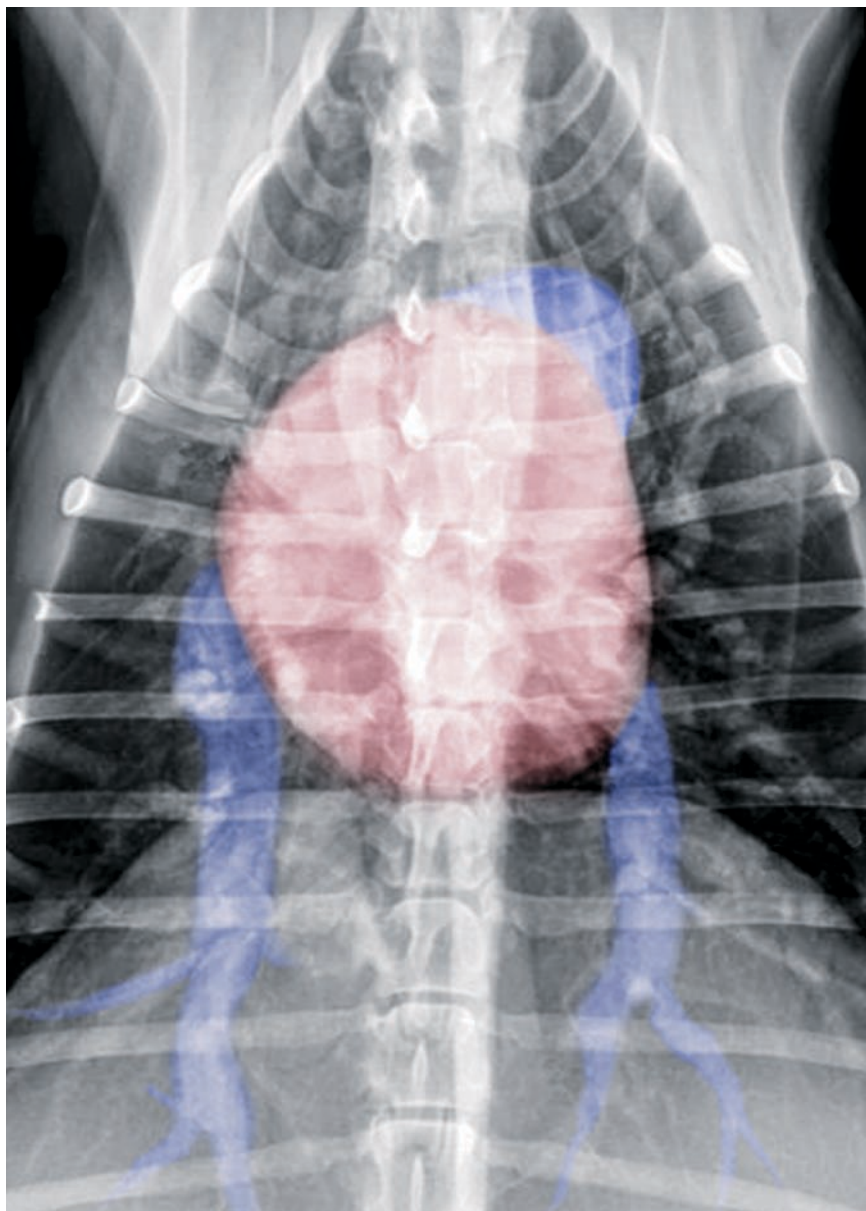
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Although previously thought to be uncommon, canine pulmonary hypertension is now diagnosed with relative frequency.¹ Understanding the pathophysiology of pulmonary hypertension is paramount to successful treatment. Canine pulmonary hypertension should also be recognized as a complex syndrome that is often associated with severe underlying systemic disease.

In this article, we review the anatomy of the pulmonary vascular system and discuss the regulation of pulmonary arterial pressure. We also describe the clinical and functional classifications of pulmonary hypertension.

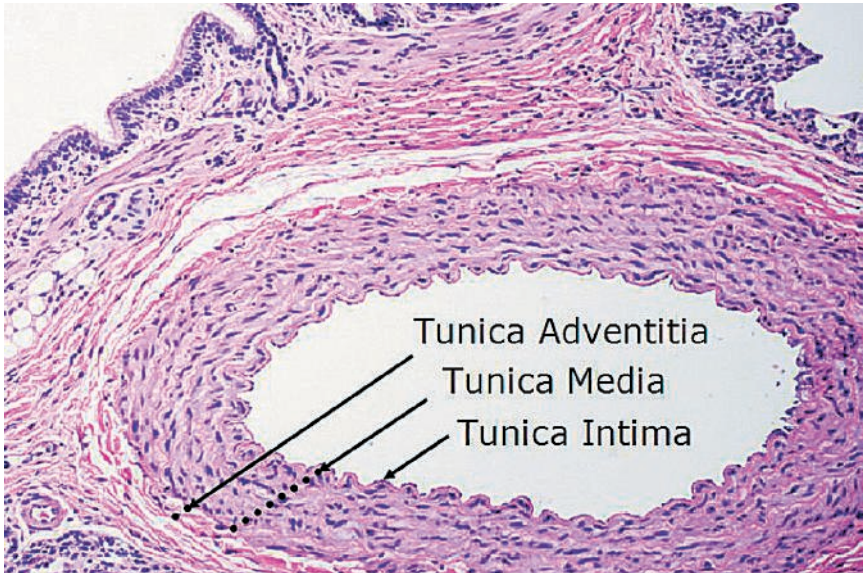
DEFINITION

Any elevation of pulmonary arterial pressure above normal constitutes pulmonary hypertension.² More specifically, pulmonary hypertension can be defined as pulmonary arterial systolic

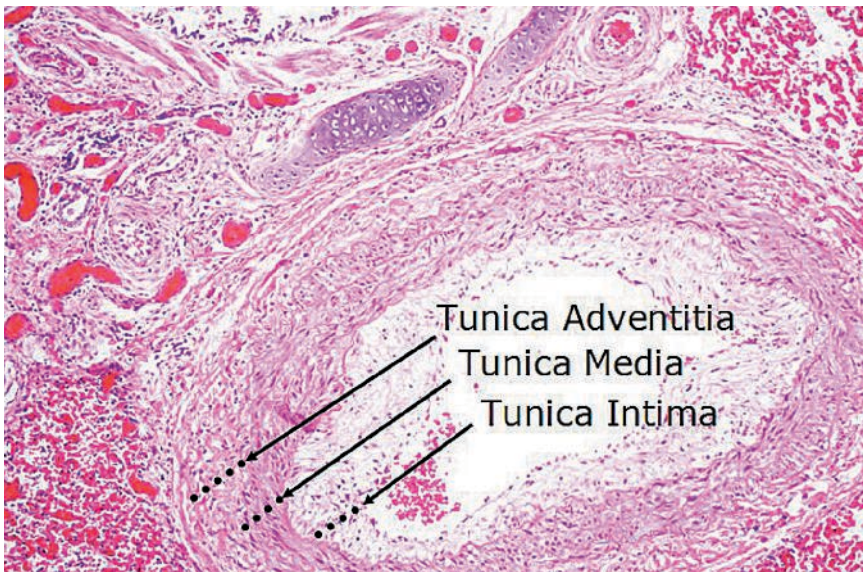


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1. A photograph of a cross section of a normal canine pulmonary artery. The tunica adventitia, media, and intima layers are all normal in thickness and cell structure (hematoxylin-eosin stain; 10X magnification). (Image courtesy of Pam Mouser, DVM, MS, DACVP, Angell Animal Medical Center's Department of Pathology.)



2. A photograph of a cross section of a canine pulmonary artery in a patient with documented pulmonary hypertension. The tunica adventitia and intima layers are both thickened, supporting the clinical diagnosis of pulmonary hypertension (hematoxylin-eosin stain; 10X magnification). (Image courtesy of Pam Mouser, DVM, MS, DACVP, Angell Animal Medical Center's Department of Pathology.)

pressure > 30 mm Hg, pulmonary arterial diastolic pressure > 15 mm Hg, or pulmonary arterial mean pressure > 20 mm Hg.³ Although it is possible to obtain these measurements directly through right-sided cardiac catheterization, this procedure typically requires heavy

sedation or anesthesia, is considered high risk in unstable patients, and can be costly.⁴ Alternatively, pulmonary arterial pressures can be assessed by transthoracic echocardiography, which includes subjective assessment of cardiac changes and Doppler analysis of tricus-

pid valve regurgitation and pulmonary valve insufficiency.

Pulmonary arterial pressure depends on several factors, including right ventricular cardiac output (or pulmonary blood flow), pulmonary vascular resistance, and pulmonary venous pressure.³ An increase in blood flow to the pulmonary arteries, such as in congenital shunts, leads to increased pulmonary arterial pressure. Augmented activity of vascular smooth muscle, increased blood viscosity, and the presence of vascular obstruction all result in increased pulmonary vascular resistance and, thus, increased pulmonary arterial pressure. Pulmonary venous pressure, which becomes elevated in advanced left-sided heart disease, also contributes to increased pulmonary arterial pressure. Based on the variety of factors that contribute to and control pulmonary arterial pressure, it is clear that pulmonary hypertension may develop as the result of many underlying diseases.

PULMONARY VASCULAR ANATOMY

The pulmonary vascular system is characterized as low pressure, low resistance, and high capacitance.⁵ Normal pulmonary arteries are elastic with distensible walls. They are composed of an inner tunica intima, middle tunica media, and outer tunica adventitia (Figure 1). The tunica intima consists of a single layer of endothelial cells, collagen, and occasional fibroblasts. The tunica media is thicker and is a combined layer consisting of elastin, collagen, and smooth muscle fibers. The tunica adventitia consists of collagen.⁶

Several characteristic histopathologic lesions are associated with pulmonary hypertension. These most often include concentric thickening and muscularization of the tunica intima and hypertrophy with fibrosis and proliferation of smooth muscle of the tunica media (Figure 2). In severe cases, plexiform lesions (irregularly shaped outgrowths that project from the intimal layer into the lumen of the blood vessel) may develop, and vessel wall necrosis can occur.⁷

TABLE 1

The Physiologic Factors That Affect Pulmonary Arterial Tone and Platelet Function*

Physiologic Factor	Effect on Pulmonary Arterial Tone		Effect on Platelet Function	
	Vasoconstriction	Vasodilation	Activation	Inhibition
Alveolar hypoxia	X			
Alpha-adrenergic receptor stimulation	X			
Beta-adrenergic receptor stimulation		X		
Prostacyclin		X		X
Prostaglandin E ₁		X		X
Prostaglandin F _{2α}	X			
Prostaglandin A ₂	X			
Thromboxane	X		X	
Nitric oxide		X		X
Endothelin-1	X		X	
Serotonin	X		X	
Angiotensin II	X		X	

*Source: References 1-3 and 8-12.

PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION

Pulmonary hypertension develops when there is an imbalance among the factors that control pulmonary arterial vasoconstriction, vasodilation, platelet activation, and smooth muscle cell proliferation (Table 1).³ By understanding these factors, practitioners are better able to choose the therapy or combination of medications that is most likely to help reduce pulmonary arterial pressure. For instance, by understanding the roles that prostaglandins, endothelin, and nitric oxide play in pulmonary vessel constriction and dilation, you can choose the best therapy for your patient.

Alveolar hypoxia

Alveolar hypoxia elicits pulmonary vessel vasoconstriction, a response unique to the pulmonary system. Vasoconstriction allows deoxygenated blood to be shunted to areas of the lung that are better

ventilated and improves ventilation-perfusion matching, which is thought to be a beneficial physiologic response in acute instances but, in chronic conditions, may lead to pulmonary hypertension.

Pulmonary vasculature tone is controlled by potassium, calcium, and chloride channels. The activity of these channels is affected by local oxygen tension. Poor oxygen tension, or hypoxia, leads to vasoconstriction mainly in small pulmonary arteries and arterioles, leading to increased pulmonary vascular resistance.² If oxygen tension remains poor over a long period, pulmonary vasoconstriction results in increased pulmonary arterial pressure and pulmonary hypertension.

Alveolar hypoxia also induces growth factors, such as platelet-derived growth factors A and B, vascular endothelial growth factor, endothelin, and serotonin. These factors are associated with endothelial cell proliferation and vascular remodeling, as seen in Figure 2.²

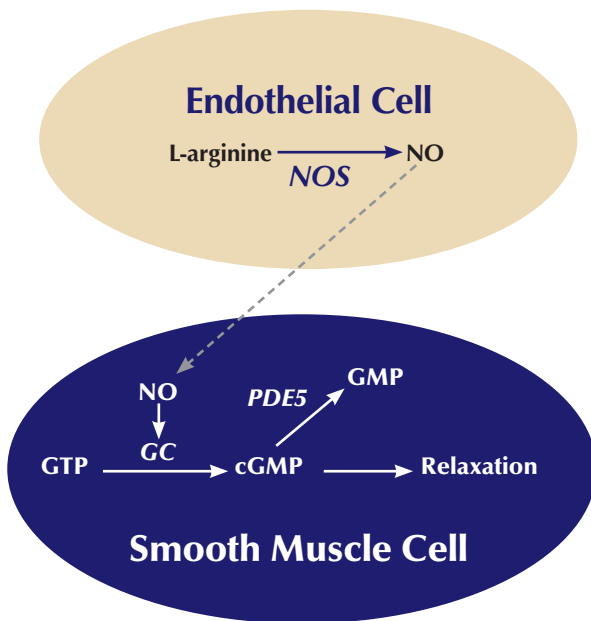
Adrenergic control

Pulmonary arterial vasoconstriction occurs in response to the stimulation of alpha-adrenergic receptors. Alpha-adrenergic receptors found in the pulmonary arteries have a high affinity for their agonists, such as norepinephrine, and, when excessively stimulated, may also cause pulmonary arterial remodeling.² Pulmonary arterial vasodilation occurs in response to the stimulation of beta-adrenergic receptors.

Eicosanoids: prostaglandins and thromboxane

Prostaglandins are hormone-like substances that are actively synthesized, metabolized, and released by the lungs. Prostacyclin and prostaglandin E₁ cause vasodilation and vascular hypertrophy and remodeling and inhibit platelet aggregation. On the other hand, prostaglandin F_{2α} and prostaglandin A₂ cause vasoconstriction.^{2,8}

Thromboxane, a substance derived



3. A schematic demonstrating the actions of nitric oxide in pulmonary vascular endothelial and smooth muscle cells (NO = nitric oxide; NOS = nitric oxide synthase; GTP = guanosine triphosphate; GC = guanylate cyclase; cGMP = cyclic guanosine monophosphate; PDE5 = phosphodiesterase 5; GMP = guanosine monophosphate).

from prostaglandins, is synthesized by and stored in platelets. Thromboxane is associated with vasoconstriction and platelet activation. In people with pulmonary hypertension, there is a documented prostacyclin-thromboxane imbalance with associated pulmonary artery vasoconstriction, thrombosis, and proliferation.⁹

Nitric oxide

Nitric oxide is synthesized in endothelial cells from L-arginine and oxygen by the enzyme nitric oxide synthase. Once produced, nitric oxide is released by the vascular endothelium and travels to smooth muscle cells. There, nitric oxide stimulates the enzyme guanylate cyclase, which catalyzes guanosine triphosphate conversion to cyclic guanosine monophosphate (cGMP), leading to an increase in cGMP concentrations. cGMP inhibits calcium release from the endoplasmic reticulum and causes pulmonary vasodilation (Figure 3). Vasodilation is limited by phosphodiesterase 5 inactivation of cGMP.¹ Nitric oxide also inhibits platelet activation and smooth muscle cell hypertrophy.¹⁰

Endothelin-1

Endothelin-1 is a peptide released by the vascular endothelium in response to changes in blood flow, vascular stretch, oxygenation, and thrombin concentrations. Once released, endothelin-1 causes vasoconstriction, stimulates growth

factors and smooth muscle cell proliferation, and promotes vascular remodeling.⁸ Production of endothelin-1 is inhibited by prostacyclin and nitric oxide.²

Endothelin-1 is considered a potent vasoconstrictor and has been well-studied in human medicine. Circulating endothelin-1 concentrations are elevated in people with pulmonary hypertension, and there is a correlation between endothelin-1 concentrations and the severity of pulmonary hypertension and the prognosis for people with pulmonary hypertension.¹¹ Veterinary studies have also confirmed that endothelin-1 concentrations are elevated in dogs with pulmonary hypertension.¹²

Serotonin

Serotonin is produced by the gastrointestinal tract from tryptophan.⁵ Once produced, serotonin is released into circulation and taken up by platelets. Platelets then release serotonin in response to blood vessel wall damage so that serotonin causes local vasoconstriction. As mentioned above, serotonin can act as a growth factor and also causes smooth muscle cell hypertrophy and vascular remodeling.⁸

Angiotensin II

Angiotensin II is a peptide produced by the actions of the angiotensin-converting enzyme (ACE) on angiotensin I. In animal models of pulmonary hypertension, pulmonary hypertension is associated with an increase in ACE expression and activity.² Angiotensin II causes vasoconstriction and vascular remodeling.²

CLINICAL CLASSIFICATION

The Evian Classification Scheme, proposed by the World Health Organization (WHO), categorizes pulmonary hypertension based on similarities in pathophysiologic mechanism, clinical presentation, and treatment options.^{13,14} This scheme has been adopted by the veterinary community.

Clinical class I: pulmonary arterial hypertension

Class I pulmonary hypertension includes patients with pulmonary hypertension due to pulmonary arteriolar vascular disease. In people, the most common form of class I pulmonary hypertension is idiopathic. Although idiopathic pulmonary hypertension has been recognized in dogs, it is rarely reported.¹⁵ In dogs, the most common causes of class I pulmonary hypertension include congenital shunts and heartworm disease.¹⁵

Congenital shunts. Congenital shunts include patent ductus arteriosus, atrial septal defects, and ventricular septal defects. These defects all lead to increased pulmonary blood flow and structural changes in the vascular walls. Specifically, histopathology demonstrates hypertrophy of the small muscular pulmonary arteries and arterioles. Advanced dis-

ease is associated with fibrosis, vessel obliteration, and arteritis.¹⁶

Eisenmenger syndrome describes severe pulmonary arterial hypertension secondary to a congenital cardiac defect. In this condition, a left-to-right cardiac shunt causes severe endothelial dysfunction, which leads to increased pulmonary vascular resistance. This resistance ultimately increases right-sided heart pressures to the point of shunt reversal, and blood flows right to left through the congenital defect. Patients with Eisenmenger syndrome develop severe cyanosis, polycythemia, and congestive heart failure. In human medicine, the development of Eisenmenger syndrome secondary to an unrepaired congenital shunt is associated with a 10- to 12-fold increase in mortality; almost all patients with unrepaired patent ductus arteriosus develop Eisenmenger syndrome.¹⁷

Heartworm disease. Heartworm disease, caused by the nematode *Dirofilaria immitis*, is another common cause of canine class I pulmonary hypertension. Heartworm disease is diagnosed worldwide and occurs when a mosquito bite transmits *D. immitis* larvae to a canine host. Over a period of months, the larvae develop into adult nematodes and relocate to the right side of the heart and the pulmonary artery. Acute signs of pulmonary hypertension can be caused by an embolism of dead adult heartworms and are associated with class IV pulmonary hypertension (see below). But long-term, occlusion of large pulmonary arteries leads to pulmonary vascular proliferation, irreversible structural damage, inflammation, and vascular dysfunction that is typical of class I pulmonary hypertension.¹⁸ French heartworm, caused by *Angiostrongylus vasorum*, has also been associated with canine pulmonary hypertension.¹⁹

Clinical class II: pulmonary venous hypertension

Patients in the class II category develop pulmonary hypertension secondary to

left-sided heart disease. Chronic left-sided heart disease leads to increased left atrial pressure, which in turn leads to increased pulmonary venous pressure. In these scenarios, pulmonary edema and hypoxia develop, and reactive pulmonary arterial hypertension occurs.³ When pulmonary venous pressure exceeds 25 mm Hg, pulmonary arterial pressure increases in an attempt to maintain pulmonary blood flow. Ultimately, pulmonary arteriole hypertrophy and pulmonary artery noncompliance develop.

Left-sided heart disease is the most common cause of pulmonary hypertension overall in both people and dogs.^{13,15} While causes of left-sided heart disease may include dilated cardiomyopathy, degenerative mitral valve disease is a more common cause of canine pulmonary hypertension. In a study of 60 dogs with pulmonary hypertension, 38 dogs (63%) had pulmonary hypertension due to degenerative mitral valve disease, while only two dogs (3%) had pulmonary hypertension due to dilated cardiomyopathy.²⁰ Other studies indicate that anywhere from 14% to 31% of dogs with degenerative mitral valve disease develop pulmonary hypertension.^{21,22} Although less common, class II pulmonary hypertension has been reported in people and dogs with myocarditis and atrial distention secondary to atrial fibrillation.^{8,23}

Clinical class III: pulmonary disease or hypoxia

Pulmonary hypertension may also occur secondary to primary pulmonary disease or chronic hypoxia. These patients are considered class III. The respiratory diseases most frequently associated with class III pulmonary hypertension in people are chronic obstructive airway disease, interstitial lung disease, and sleep-disorder breathing.⁸ In dogs, class III pulmonary hypertension has been associated with pulmonary fibrosis, pneumonia, tracheobronchial disease, and neoplasia.²² Given the breed predilection, it is not surprising to find that up to 40% of West Highland white

terriers with chronic interstitial lung disease have some degree of pulmonary hypertension.²⁴

Clinical class IV: thromboembolic disease

Class IV pulmonary hypertension is caused by a thrombotic or embolic event. In people with class IV pulmonary hypertension, pulmonary artery obstruction has been associated with thromboembolism, tumors, and foreign bodies. In dogs, pulmonary thromboembolism has been associated with immune-mediated hemolytic anemia, neoplasia, protein-losing nephropathies and enteropathies, hyperadrenocorticism, sepsis, and trauma.^{15,23} Given the possibility of worm emboli, heartworm disease can be included in this category as well.¹⁵

Clinical class V: miscellaneous

Class V pulmonary hypertension encompasses the miscellaneous causes of pulmonary hypertension. In people, class V includes conditions that indirectly alter cardiac blood flow (e.g. primary polycythemia vera), granulomatous diseases, and diseases that lead to the destruction of pulmonary parenchyma.¹³ In veterinary medicine, class V pulmonary hypertension is rarely reported; however, the most common conditions are likely those that cause pulmonary vasculature compression, such as neoplasia.

FUNCTIONAL CLASSIFICATION

While the clinical classification scheme groups pulmonary hypertension patients into classes based on the underlying cause of pulmonary hypertension, the functional classification scheme groups these patients into classes based on the severity of pulmonary hypertension-induced clinical signs (Table 2). This schematic was also developed at the 1998 WHO Evian meeting and is used in human medicine to help determine when to institute therapy, to decide which treatments may be most beneficial, and to provide an objective treatment goal.²⁵

TABLE 2

WHO Functional Classification Scheme of Pulmonary Hypertension

Class	Decreased Activity	Dyspnea, Lethargy, Syncope	Right-Sided Heart Failure
I			
II	+	+	
III	++	++	
IV	+++	+++	+++

Although not explicitly evaluated in dogs, the information can be easily extrapolated from people to dogs.

Functional class I

This class includes patients with pulmonary hypertension that do not suffer any decrease in physical activity and can exercise without signs of dyspnea, fatigue, chest pain, or syncope.

Functional class II

Class II patients are comfortable at rest but suffer a mild decrease in activity associated with dyspnea, fatigue, chest pain, or syncope.

Functional class III

These patients have pulmonary hypertension that results in marked limitations in physical activity and have severe dyspnea, fatigue, chest pain, or syncope even with minimal activity. These patients are comfortable at rest.

Functional class IV

The final class includes patients with pulmonary hypertension that are unable to participate in physical activity, and any activity leads to severe signs. These patients are symptomatic at rest and have right-sided heart failure secondary to pulmonary hypertension.

CONCLUSION

Canine pulmonary hypertension is a complex condition caused by an im-

balance in pulmonary arterial vasoconstriction and vasodilation and is associated with enhanced platelet actions and vascular remodeling. Patients with pulmonary hypertension may be classified into clinical groups based on the underlying cause of disease and into functional groups based on the severity of signs. Ultimately, the classification schemes should help practitioners diagnose pulmonary hypertension, formulate an effective treatment plan, and evaluate a patient's prognosis. ❖

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