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Heart Failure

Heart failure occurs when the cardiovascular system is unable to meet the metabolic demands of the body, or when it can only do so at elevated filling pressures, and subsequent decompensation develops by one or more mechanisms. Thus, heart failure is neither a specific disease nor a diagnosis. It is a progressive condition initiated by decreased cardiac performance that leads to compensatory mechanisms designed to preserve tissue perfusion and cellular metabolism. These mechanisms lead to maladaptive changes that further decrease cardiac performance, initiating a vicious cycle causing failure of the heart as a pump. As a result, normal peripheral perfusion can only be maintained at elevated filling pressures. Heart failure can occur as a result of systolic dysfunction, diastolic dysfunction, or both. Commonly, both systolic and diastolic dysfunction are present, especially in advanced disease states. Clinical signs that may develop as a result of these conditions can be thought of in terms of low output (forward) or congestive (backward) heart failure (CHF).

Initial changes in cardiac chamber dimension (volume) or wall thickness that occur are best understood in relation to preload (the tension imposed by venous return on the ventricular walls at end-diastole) and afterload (the tension imposed on the ventricular walls at end-systole). Alterations in preload or afterload may be caused by structural cardiac abnormalities, systemic compensatory mechanisms, or both. Volume overload states, such as those that occur with chronic valvular disease/valvular insufficiencies, patent ductus arteriosus, atrial or ventricular septal defects, peripheral left-to-right shunts, anemia, or hyperthyroidism, cause an increase in preload that leads to eventual ventricular chamber enlargement (dilation) via eccentric myocyte hypertrophy. Pressure overload states, such as those that occur with pulmonary or systemic hypertension, pulmonic or aortic stenosis, or aortic coarctation, cause an increase in afterload that leads to ventricular wall thickening via concentric hypertrophy. Neither volume nor pressure overload is synonymous with heart failure; either state may result in heart failure, depending on the severity of the overload and the degree of compensation.

SYSTOLIC FAILURE

Systolic cardiac failure occurs when normal ventricular filling is accompanied by a decrease in forward stroke volume, reflecting an inherent decrease in myocardial contractility. This may ultimately result in signs of decreased cardiac output such as weakness, hypotension, and compromised organ perfusion. Myocardial failure may be identified on echocardiographic examination as a decrease in ejection fraction or percent fractional shortening, caused by an increase in end-systolic diameter with a normal or increased end-diastolic diameter. However, these indices of systolic function are heavily impacted by ventricular preload, and more advanced imaging options (such as strain imaging or tissue Doppler) may be needed to characterize contractile function in the face of concurrent volume overload. Additionally, regional or diffuse wall thinning and decreased wall motion may be observed, which can be further quantified through use of these more advanced imaging options.

Primary myocardial failure, or idiopathic dilated cardiomyopathy (DCM), is a diagnosis of exclusion. This disease may be noted in several dog breeds but is most commonly seen in Doberman Pinschers, and current research is helping to define a genetic basis for this condition. Idiopathic DCM is also seen rarely in the cat. Some clinicians feel that idiopathic DCM may be the longterm result of unidentified viral infections or myocarditis. While DCM traditionally has been thought of in relation to systolic dysfunction, it is now known that diastolic dysfunction also occurs relatively early in the disease process.

Secondary myocardial failure often results from one or more insults leading to cardiomyocyte damage with subsequent cardiac remodeling and fibrosis. Etiologies include prolonged tachycardia (supraventricular or ventricular tachycardias), infiltrative disease (neoplasia), myocardial infarction, nutritional deficiency (taurine, carnitine, selenium [as seen with white muscle disease]), myocarditis (viral, rickettsial, spirochetal, parasitic, fungal), sepsis, drugs (doxorubicin), toxins

(lead, cobalt, gossypol), or rarely endocrine disease (severe hypothyroidism). Additionally, chronic pressure or volume overload states can lead to myocardial remodeling and subsequent failure.

DIASTOLIC FAILURE

Diastolic failure occurs when elevated ventricular filling pressures accompany normal or compensated systolic function. Elevations in cardiac filling pressures are transmitted to the pulmonary or systemic circulation, ultimately resulting in transudation of fluid and signs of congestion (edema or effusion). In the absence of pericardial or extracardiac disease leading to ventricular compression or restriction, diastolic dysfunction reflects an inherent abnormality in ventricular relaxation, which may be detected relatively early in cardiac disease processes using Doppler echocardiographic techniques. Diastolic dysfunction may occur in diseases resulting in cardiac compression (pericardial effusion, pericarditis, neoplasia), a stiff or noncompliant ventricle (hypertrophic cardiomyopathy, restrictive cardiomyopathy), myocardial infiltration (neoplasia), or remodeling secondary to chronic volume or pressure overload conditions.

Functional CHF may also occur if a tumor or other anatomic obstruction impedes venous return to one or both atria. Pericardial disease or effusion leading to decreased ventricular filling may also be thought of as an extracardiac cause of congestive and subsequent low output heart failure. Iatrogenic volume overload (ie, with aggressive diuresis) can lead to CHF in the absence of primary myocardial systolic or diastolic dysfunction; however, this situation can be thought of as "pseudodiastolic dysfunction" because the ventricle is unable to increase its compliance enough to avoid elevated filling pressures.

COMPENSATORY MECHANISMS

Systemic blood flow and oxygen delivery to peripheral tissues and organs is under strict neuroendocrine control. Compensatory mechanisms act rapidly to correct any decreases in blood flow or pressure. These mechanisms provide short-term benefit to metabolically active cells but longterm injury to the cardiovascular and ultimately systemic body systems when chronically activated. Regardless of the underlying mechanism of cardiac disease, the cascade of events leading to heart failure is initiated by a perceived decrease in cardiac output by baroreceptors, mechanoreceptors, or chemoreceptors in the cardiovascular system and peripheral tissues. This may occur secondary to chronic valvular disease, DCM, or any of the aforementioned primary or secondary cardiac disorders. Even high output states such as anemia or hyperthyroidism may fulfill this model, as peripheral tissues perceive a metabolic deficit and seek correction via an increase in cardiac output.

When a decline in stroke volume occurs secondary to cardiac dysfunction, cardiac output decreases. The acute response is an increase in sympathetic tone leading to peripheral vasoconstriction, increased heart rate, and increased cardiac contractility that serve to restore cardiac output and maintain systemic blood pressure. Additionally, the renin-angiotensin-aldosterone system (RAAS) is activated by one or more conditions: decreased renal perfusion, decreased sodium delivery to the macula densa (within the juxtaglomerular apparatus), and increased sympathetic tone. The juxtaglomerular cells release renin, which converts angiotensinogen (synthesized in the liver) to angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, chiefly in the lungs. A separate tissue RAAS exists in the brain, vascular, and myocardial tissues, which can generate angiotensin II independently of the renal, or systemic, RAAS.

Angiotensin II has widespread effects including sodium and water retention via direct tubular effects as well as stimulation of aldosterone synthesis, increased thirst via stimulation of antidiuretic hormone (ADH) release, increased norepinephrine and endothelin release, and stimulation of cardiac remodeling and hypertrophy. These effects cause an increase in circulating blood volume (preload) and peripheral resistance (afterload), and have direct cardiotoxic effects. Additionally, chronically circulating angiotensin II, aldosterone, endothelin, ADH, and catecholamines lead to deleterious effects on the heart and peripheral vasculature via direct remodeling actions, as well as by upregulation of inflammatory cytokines, extracellular matrix components, and proto-oncogenes.

In response to compensatory mechanisms, counter-regulatory systems are in place; namely, the release of atrial natriuretic peptide (ANP) from the atria, and B-type natriuretic peptide (BNP) from the ventricles. ANP and BNP are released in response to stretch of the atrial and ventricular chambers, respectively. Both hormones serve to increase natriuresis (with subsequent diuresis) and decrease systemic vascular resistance, thus countering the effects of the

RAAS. Unfortunately, the effects of ANP and BNP are greatly outweighed by those of the RAAS, especially in advanced stages of CHF. However, there is potential clinical benefit in measurement of circulating ANP and BNP as diagnostic tools for cardiac disease (*see* below).

As circulating blood volume is increased via retention of water and sodium, preload and stroke volume increase, which helps to restore cardiac output. Circulating blood volume is invariably increased in animals with heart failure and chronic RAAS activation, often up to 30% in advanced states. However, this occurs at the expense of elevated diastolic filling pressures, and eventually signs of congestion (edema and effusion) develop. Additionally, increased afterload secondary to peripheral vasoconstriction as described above decreases cardiac output further, and the cycle perpetuates.

CARDIAC BIOMARKERS

A biomarker is an objectively measured trait that may serve as an indicator of normal organ function, disease processes, or response to medical intervention. Biomarkers may provide information about the presence and severity of disease, as well as prognosis. Recent studies in both dogs and cats have shown that elevated blood levels of BNP, ANP, and endothelin-1 are sensitive indicators of cardiac disease that increase proportionately with progressive cardiac disease and CHF. Cardiac troponin I (cTnI), which is released after cardiomyocyte insult, has also been evaluated as a biomarker for CHF but found to be less sensitive than those mentioned above. ANP, BNP, and cTnI have also been evaluated as screening tools for occult DCM (before onset of CHF) in dogs. Elevated levels of BNP were found to be highly sensitive for the detection of occult DCM, while ANP and cTnI were relatively less sensitive. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is released proportionately with BNP in response to elevated cardiac filling pressures or myocardial dysfunction, and its greater stability and longer half-life make it more suitable for use as a diagnostic biomarker. Several studies have demonstrated the usefulness of NT-proBNP in differentiating between cardiac and primary respiratory causes of dyspnea in dogs. NT-proBNP has also been shown to be useful in the diagnosis of CHF in cats, and it may prove to be helpful as a screening tool to identify cats with possible cardiomyopathy that may benefit from an echocardiogram.

CLINICAL MANIFESTATIONS

The hemodynamic changes that occur in heart failure are relatively limited, as are the clinical syndromes resulting from these changes. Much depends on the location(s) of cardiac chamber failure, as well as species differences.

Left-sided Heart Failure

The pulmonary veins drain into the left atrium. Left atrial pressures may increase over time in response to volume overload (from regurgitant blood flow or increased circulating blood volume), mitral valve stenosis, or elevated left ventricular filling pressures. Increases in left atrial pressures are transmitted to the pulmonary veins and, ultimately, to the pulmonary capillaries responsible for alveolar perfusion. As pulmonary capillary hydrostatic pressure continues to increase, Starling forces promote the transudation of fluid and pulmonary edema develops. In dogs, this may manifest as exercise intolerance, nocturnal or general dyspnea, cough, and tachypnea. Syncope may also be noted, especially in small-breed dogs with chronic valvular disease. This may occur in association with coughing (tussive syncope) or a vasovagal-type response to stimulation of left ventricular mechanoreceptors. Coughing may also be triggered in the absence of pulmonary edema secondary to mainstem bronchial compression from left atrial enlargement or from increased airway responsiveness (so-called "cardiac asthma").

In cats, the left atrium also receives partial venous drainage from the pleural and pericardial space. Thus, additional clinical signs of left heart failure in cats may include pleural or pericardial effusion; these conditions seem to occur with more frequency in biventricular failure, however. Small volumes of pericardial effusion are common in cats with heart failure and are generally of no hemodynamic consequence (pericardio-centesis is not usually required). Cats with heart failure are less likely to show signs of overt coughing than dogs, and syncope is rare unless associated with development of arrhythmias. Exercise intolerance can be difficult to define in cats because they are generally sedentary. The most common clinical signs noted are inappetence, behavior changes, dyspnea, and tachypnea, which many owners do not detect until heart failure is advanced.

Right-sided Heart Failure

The right atrium receives systemic and cardiac venous and lymphatic drainage via the cranial and caudal vena cavae and the coronary sinus. Right atrial pressures may increase over time with volume overload (eg, tricuspid insufficiency), tricuspid valve stenosis, or elevated right ventricular filling pressures. Clinical manifestations of right heart failure include jugular venous distension, hepatomegaly, pleural effusion, pericardial effusion, and ascites. Dogs are more likely to develop ascites, while pleural and pericardial effusions are more common in cats. Although the effusions resulting from heart failure are most commonly modified transudates, cats may develop chylous pleural effusion.

Hemostatic Changes in Heart Failure

Recent studies in both dogs and cats with CHF have demonstrated alterations in platelet function, as well as hemostatic biomarkers such as fibrinogen, D-dimers, antithrombin, von Willebrand's factor, and protein C. Whether the presence of a hypercoagulable state is associated with a worsened prognosis in dogs or cats is unknown, although microemboli have been demonstrated in the myocardium and other organs of dogs and cats with cardiomyopathy at necropsy. Arterial thromboembolism is a devastating complication seen in cats with cardiomyopathy, but it remains unknown whether the development of thrombi in this disease is related to a systemic or only a local intracardiac hypercoagulable state.

Thrombus formation is seen with an increase in the components of Virchow's triad: alterations in blood flow, endothelial damage, and a hypercoagulable state. In the presence of CHF, alterations of blood flow may occur with decreased cardiac output, increased circulating plasma volume, vasoconstriction, and endothelial dysfunction. Additionally, small vessel disease (arteriosclerosis) has been demonstrated in the myocardium of both cats and dogs with cardiac disease. Endothelial damage may occur secondary to cardiac chamber dilation or splitting (most commonly left atrial), shear forces caused by high velocity blood flow (as may occur around stenotic lesions), and vascular remodeling effects of circulating neurohormones. A hypercoagulable state has been demonstrated and may be exacerbated by increased levels of circulating catecholamines.

MANAGEMENT

Management of heart failure is directed at controlling clinical signs related to congestion (pulmonary edema, pleural or pericardial effusion, and ascites), decreased cardiac output, and chronic neurohormonal adaptations. This is accomplished through preload and/or afterload reduction (diuretics and vasodilators), improving cardiac performance (positive inotropes, lusitropes, sympathomimetics, antiarrhythmics), and use of neurohormonal modulators (ACE inhibitors, and potentially β-blockers, aldosterone antagonists, and angiotensin II blockers).

Diuretics

The **loop diuretics** are the single most effective agents available to decrease circulating blood volume and reduce signs of congestion. They act via inhibition of the $Na^+/K^+/2\ Cl^-$ cotransporter in the thick ascending loop of Henle. This leads to increased renal sodium and chloride excretion, with subsequent free water loss. Furosemide is the most widely used loop diuretic. When administered IV, it also directly reduces pulmonary capillary wedge pressure (before onset of diuresis) via local prostaglandin synthesis, which has a vasodilatory effect. The onset of action after IV administration is 5 min, with peak effects occurring at 30 min and lasting ~2 hr. The onset of action after oral administration is 60 min, with peak effects seen at 1–2 hr and lasting ~6 hr.

Emergency therapy of pulmonary edema often requires high doses of IV or IM furosemide (2–8 mg/kg for dogs; 2–4 mg/kg for cats), repeated at 30- to 60-min intervals until clinical signs of congestion are controlled. Because of the concern for hypotension, azotemia, and significant electrolyte disturbances with overzealous furosemide administration, tapering to the lowest effective dosage that controls signs of CHF is recommended once the animal is stable. Mild azotemia and electrolyte and acid-base disturbances (hyponatremia, hypokalemia, and a hypochloremic metabolic alkalosis) are not uncommon and are generally tolerated as long as the animal is eating and drinking. Oral doses used to manage chronic CHF may vary significantly between animals; the lowest possible dosage should be used. In dogs, CHF is often initially controlled at dosages of 1–2 mg/kg, sid-bid while cats are more sensitive to the development of

adverse effects and generally require lower dosages (0.5–2 mg/kg every 12–48 hr). Use of furosemide or other diuretics as sole therapy in longterm management of CHF increases RAAS activation; thus, combination with an ACE inhibitor is recommended.

Furosemide resistance, typically defined by persistent signs of congestion despite dosages of 2–4 mg/kg, PO, tid, may develop in advanced cases of CHF. There are many causes of diuretic resistance, including decreased delivery of the drug to the nephron, activation of the RAAS (which counteracts the effects of diuresis), and hypertrophy of the distal convoluted tubular cells with consequent increases in ion transport in this region of the nephron. GI edema secondary to right-sided CHF may decrease absorption of orally administered diuretics and contribute to diuretic resistance. Animals with resistance to chronic high doses of oral furosemide may thus have an improved diuretic response from SC administration of the drug or from addition of other diuretic agents ("diuretic stacking").

Adverse effects seen with furosemide administration are generally related to dehydration from volume depletion and electrolyte and acid-base abnormalities. Less common adverse effects include vomiting, pancreatitis, and idiosyncratic deafness with rapid IV administration. Animals with preexisting renal disease are more likely to develop adverse effects, and furosemide therapy should be reduced or temporarily withdrawn accordingly. Renal values should be monitored frequently when starting diuretic therapy (on initiation and at least 1 wk later) and should be reassessed every 3–6 mo during chronic administration. Some animals may remain mild to moderately azotemic, which is generally tolerated provided they are eating and drinking adequately.

Additional loop diuretics include torsemide and bumetanide. While there is less experience with these agents, they may prove useful in the management of refractory heart failure in which furosemide resistance has been documented, or when furosemide is not tolerated. Torsemide has a longer duration of action than furosemide and has ancillary aldosterone-blocking effects. Both torsemide and bumetanide are significantly more potent than oral furosemide, but they have not been evaluated extensively for use in veterinary medicine. Anecdotally, starting doses of both agents are approximately one-tenth that of furosemide.

Thiazide diuretics (eg, hydrochlorothiazide, chlorothiazide) decrease sodium resorption via inhibition of the Na^+/Cl^- cotransporter in the distal convoluted tubule. This results in increased sodium and water delivery to the collecting ducts and subsequent increased hydrogen and potassium excretion. While the thiazides are relatively weak diuretics, they do exert a synergistic effect when administered with loop diuretics and can cause profound electrolyte abnormalities (particularly hypokalemia) and dehydration if not used judiciously. Hydrochlorothiazide is more commonly used, with a recommended dosage of 1–4 mg/kg, PO, sid-bid. It is combined with the potassium-sparing diuretic spironolactone (*see* below) in the product aldactazide, which may also be dosed at 1–4 mg/kg, PO, sid-bid. Many animals do not tolerate dosages at the higher end of this range, and the lowest effective dosage should be used. Chlorothiazide is dosed at 20–40 mg/kg, PO, sid-bid. Thiazide diuretics are generally reserved for those cases in which resistance to furosemide has developed.

Potassium-sparing diuretics are the weakest of the diuretic class, exhibiting little to sometimes undetectable diuretic effect at standard dosages, especially when used alone. Drugs in this class include the aldosterone inhibitors spironolactone and eplerenone, and those that block sodium resorption at the distal tubules, triamterene and amilaride. Spironolactone at sub-diuretic dosages of 0.3–1 mg/kg, sid is advocated by some cardiologists for use in dogs with subclinical DCM or early myocardial failure for its theoretical benefit in blunting the aldosterone-mediated remodeling and fibrosis of the myocardium and vasculature. A large-scale clinical trial in people with heart failure demonstrated significant improvement in morbidity and mortality in patients administered spironolactone versus placebo, in addition to standard heart failure therapy. Eplerenone has demonstrated a myocardial protective effect in dogs with experimentally induced heart failure, although no clinical benefit of aldosterone blockade has been proved in veterinary patients with naturally occurring cardiac disease. A clinical trial using spironolactone in cats with hypertrophic cardiomyopathy (HCM) revealed no decrease in cardiac remodeling or improvement in diastolic function after 4 mo. Furthermore, severe ulcerative facial dermatitis occurred in approximately one-third of the cats receiving spironolactone. Consequently, use of spironolactone as a prophylactic antiremodeling agent in cats is not recommended.

Spironolactone is generally reserved for dogs and cats that are refractory to standard diuretic dosages, those with ascites, or those in which clinically significant hypokalemia has developed. It is dosed at 1–3 mg/kg, PO, sid-bid. Future studies may validate its use in certain cardiac disease entities. Eplerenone, triamterene, and amiloride are not routinely used in the management of cardiac disease in veterinary medicine.

Positive Inotropes

Pimobendan is a novel inodilator approved by the FDA in 2007 for use in dogs with CHF related to atrioventricular valve insufficiency or DCM. It is classified as a phosphodiesterase (PDE) III inhibitor with calcium-sensitizing properties. Increased inotropic effects occur primarily via sensitization of the cardiomyocyte contractile apparatus (mostly troponin C) to calcium, with minimal increases in intracellular calcium. This is in contrast to other positive inotropes (*see* below) that exert their effects predominantly via increased intracellular calcium, which can lead to arrhythmogenesis, tachycardia, and increased myocardial oxygen consumption. Balanced vasodilation occurs via vascular PDE III inhibition, leading to endothelial smooth muscle relaxation and calcium efflux. Additional beneficial effects may include improved myocardial relaxation and diastolic function, anti-inflammatory and anticytokine effects, and neurohumoral modulation.

The combination of increased inotropy with afterload reduction results in a significant improvement in cardiac output and a pronounced reduction in cardiac filling pressures. Clinical improvements seen with pimobendan can be dramatic and may include improved quality of life, improved clinical scores, and longer survival times. No studies to date have investigated the effects of combining pimobendan with an ACE inhibitor, but most cardiologists feel that this combination confers additional clinical benefits. The inotropic effect of pimobendan is significantly greater than that seen with digoxin, and pimobendan has supplanted digoxin as the first choice for inotropic support in CHF in dogs.

There is some debate regarding the use of pimobendan in cats, and there are no published studies to date investigating its use in this species. Pimobendan is not approved for use in cats, and many cardiologists feel it is contraindicated in cats with HCM with no documented systolic dysfunction, especially in the presence of left ventricular outflow obstruction (as seen with systolic anterior motion of the mitral valve or basal septal hypertrophy). Anecdotally, pimobendan has been tolerated in cats with refractory CHF of any cause and may particularly benefit cats with reduced systolic function, as may occur in dilated, restrictive, unclassified, or "end-stage" cardiomyopathy.

Pimobendan is dosed at 0.2–0.3 mg/kg, PO, bid in dogs and cats. With progression of heart failure, many cardiologists increase the dosing frequency in dogs to tid. Adverse effects are rare, and generally occur at high dosages, but may include GI upset or possibly increased arrhythmogenesis. There is no clinical evidence supporting a significant increase in arrhythmias in patients treated with pimobendan; although some studies have demonstrated such a trend, others have refuted this. Pimobendan is not approved for use before the onset of heart failure, and a study in presymptomatic Beagles with experimentally induced mitral regurgitation demonstrated increased valvular lesions in dogs treated with pimobendan compared with dogs treated with benazepril.

The **sympathomimetic amines** (dobutamine, dopamine) improve contractility and cardiac output via β-adrenergic agonist effects and can be invaluable in the acute management of cardiogenic shock or CHF secondary to myocardial failure. Stimulation of the membrane-bound β receptor activates adenyl cyclase, leading to the production of cAMP and subsequent phosphorylation of membrane-bound calcium channels on both the sarcolemma (myocyte membrane) and sarcoplasmic reticulum. These cellular actions increase myocardial contractility and relaxation, as well as oxygen consumption. Effects on ion channels in cardiac pacemaker cells and conduction fibers lead to decreased depolarization threshold, increased heart rate, and increased conduction velocity, all of which predispose to cardiac arrhythmias. In the peripheral vasculature, mixed β_1 and β_2 stimulation has a negligible effect on vascular resistance, although α-adrenergic stimulation (as occurs with dopamine at higher doses) can lead to vasoconstriction.

Dobutamine is administered IV as a continuous rate infusion at 2.5–20 µg/kg/min diluted in 5% dextrose. Dosages >15 µg/kg/min are rarely required and can be associated with increased tachyarrhythmias. Starting at a lower dosage with uptitration every 15–30 min as required is recommended. Concurrent ECG monitoring is strongly recommended, and a reduction or withdrawal of dobutamine is recommended should arrhythmias worsen. Because dobutamine increases

conduction through the AV node, additional caution is advocated in atrial fibrillation. Dobutamine may preferentially increase myocardial flow, as compared with dopamine, which tends to increase renal and mesenteric flow. Dobutamine also tends to cause less tachycardia than dopamine. Dopamine is administered as a continuous rate infusion at 2–8 µg/kg/min; higher dosages (>10 µg/kg/min) are associated with hypertension and tachycardia. Gradual uptitration is recommended, as with dobutamine. Both dopamine and dobutamine may cause GI upset. These agents are less commonly used in cats, although the same general treatment strategy may be followed, while starting at more conservative infusion doses (about 1 µg/kg/min) for both dobutamine and dopamine.

The **bipyridine compounds** (milrinone, amrinone) are PDE III inhibitors. Inhibition of PDE III reduces the degradation of cAMP, with subsequent effects similar to those seen with sympathomimetic amines. These agents are generally reserved for patients with severe refractory myocardial failure, because their use is associated with a higher level of mortality than that seen with the sympathomimetic amines. Due to lack of dependence on β-receptor stimulation, PDE III inhibitors are unaffected by β-receptor downregulation or uncoupling that may occur with progressive cardiac disease, and may be useful in clinical situations when benefits of sympathomimetic therapy are less than expected. Additionally, vascular PDE III inhibition and lack of α-adrenergic stimulation results in vasodilation. Adverse effects noted with PDE III inhibitors include tachycardia, tachyarrhythmias, thrombocytopenia, GI upset, and hypotension at higher dosages. Amrinone is dosed at 1–3 mg/kg, IV, or as a continuous rate infusion at 10–80 µg/kg/min. Milrinone is significantly more potent than amrinone, but its use in veterinary medicine is restricted due to cost and limited experience.

Cardiac Glycosides

The **digitalis glycosides** (digoxin and digitoxin) are relatively weak inotropes, have a narrow nontoxic therapeutic range, and are associated with significantly more adverse effects than pimobendan. Digitoxin is no longer commercially available. Although used increasingly less for its inotropic effects since the introduction of pimobendan, digoxin still plays an important role in cardiac disease, particularly in atrial fibrillation or supraventricular tachycardia with concurrent CHF, because it is the only available pharmacologic agent that slows AV nodal conduction without concurrent negative inotropic effects. (For a complete discussion, see Cardiac Glycosides.)

Rapid (IV) digitalization commonly results in toxicity and is not recommended. Digoxin may be administered at a conservative starting dose of 0.003–0.005 mg/kg, PO, bid. Adequate serum levels are not achieved for 3–4 days, and a digoxin level should be checked 5–7 days after initiation of therapy, 8 hr after the last dose is given. Further dosage adjustments should be conservative and ultimately based on the animal's serum digoxin level and clinical response. If digoxin is used in cats, it may be started at one-fourth of a 0.125-mg tablet every third day for cats <5 kg, and every other day for cats >5 kg. Some larger cats may ultimately tolerate doses as high as one-fourth of a 0.125-mg tablet, sid. An elixir form is available, although cats generally dislike the taste.

Adverse effects are increasingly likely at higher serum levels, and generally occur in order of GI, cardiac, and CNS derangements. Because of its ability to slow electrical conduction as well as increase intracellular calcium, digoxin can cause almost any cardiac arrhythmia, and it is contraindicated in cases of AV block, significant bradycardia, and rapid ventricular tachycardia. If adverse effects are noted, the drug should be temporarily discontinued (usually for 1–2 days) and the dosage subsequently reduced by ∼30%.

Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors competitively inhibit ACE, which converts angiotensin I to angiotensin II. This blunts the increase in systemic vascular resistance, adverse cardiac remodeling and hypertrophy effects, and aldosterone release caused by angiotensin II. ACE inhibitors are modest balanced vasodilators. They may reduce systemic vascular resistance up to 25%, improving cardiac output and reducing regurgitant fraction in mitral regurgitation. Additional benefits include a reduction in left ventricular filling pressures and thus pulmonary venous congestion. It is thought that the beneficial effects of ACE inhibitors are primarily due to neurohormonal modulation, in addition to hemodynamic benefits. Studies in dogs with CHF have demonstrated improved clinical scores when an ACE inhibitor was added to standard therapy

(diuretics with or without digitalis glycoside), with more dramatic improvements generally seen in dogs with DCM than in those with CVD. A trend toward prolonged survival was also seen in some studies.

In general, cardiologists agree that an ACE inhibitor is indicated in CHF. The benefit of ACE inhibitor therapy before the onset of CHF is more controversial and should be based on the individual patient and underlying disease. It may be appropriate to initiate therapy in any dog with clearly depressed systolic function (ie, occult DCM) in hopes of delaying ongoing remodeling, or in dogs with CVD and documented hypertension (systemic blood pressure >160 mm Hg), but there are no well controlled studies to support this claim. Studies of ACE inhibition in cats are limited, and none has shown a true statistical benefit to ACE inhibition beyond what is gained from standard diuretic therapy in cats with CHF. Furthermore, no benefit has been shown in delaying the progression of occult HCM. These studies have low patient numbers, however, and most cardiologists do prescribe an ACE inhibitor in addition to appropriate background therapy for cats in CHF.

Adverse effects of ACE inhibition are generally related to a reduced glomerular filtration rate (GFR) in hypovolemia or preexisting renal insufficiency, as angiotensin II promotes renal efferent arteriolar constriction in the face of reduced renal perfusion. Most commonly, adverse effects are noted in animals with azotemia related to poor cardiac output, overzealous diuretic administration, or preexisting renal insufficiency. Anorexia, vomiting, and lethargy may occur. Although cough is a common adverse effect of ACE inhibitor therapy in people, this is not seen in dogs and cats. Some animals may develop transient azotemia or hyperkalemia after starting ACE inhibitor therapy. For this reason, it is recommended that renal values and electrolytes be checked before starting an ACE inhibitor and 5–7 days later.

Enalapril is the only approved ACE inhibitor in the USA for dogs with CHF. It is generally started at 0.5 mg/kg, PO, sid or 0.25 mg/kg, bid in dogs with mild heart failure; dosage may subsequently be increased to 0.5 mg/kg, bid in dogs with moderate to severe heart failure. Longterm dosing in cats is recommended at 0.5 mg/kg, PO, sid. Clinical benefits are not commonly seen before 2–3 wk. Renal values should be monitored periodically (at least every 6 mo) while on longterm ACE inhibitor therapy.

Other ACE inhibitors used for the treatment of heart failure include benazepril (0.25–0.5 mg/kg, PO, sid-bid), captopril (0.5–2.0 mg/kg, PO, bid-tid), and lisinopril (0.5 mg/kg, PO, sid-bid). Unlike enalapril and other ACE inhibitors that are renally excreted, benazepril undergoes significant hepatobiliary elimination (up to 50% in dogs and 85% in cats). Whether benazepril is safer or more effective in patients with renal insufficiency remains to be seen.

Vasodilators

Vasodilators exert a positive effect in CHF through reduction of preload or afterload. The **nitrates** (sodium nitroprusside, nitroglycerin ointment, isosorbide dinitrate) act via the common end pathway of increased nitric oxide production, with subsequent activation of cyclic guanosine monophosphate (cGMP) and endothelial smooth muscle relaxation. Sodium nitroprusside is a potent mixed vasodilator, acting on both the arterial and venous systems. The combination of sodium nitroprusside with dobutamine may be especially useful in cases with cardiogenic shock and severe pulmonary edema. While sodium nitroprusside dramatically and acutely reduces preload and afterload, its use is limited by the need for close monitoring and administration as a continuous rate infusion. The major adverse effect is systemic hypotension (with or without weakness, tachycardia, or vomiting); thus, concurrent blood pressure monitoring is recommended. Sodium nitroprusside is diluted in 5% dextrose, and started at 1 µg/kg/min, with careful uptitration every 5–10 min to desired effect. A dosage of 5–7 µg/kg/min is usually sufficient to control clinical signs, and rarely is >10 µg/kg/min required. Prolonged administration (>16 hr) increases the risk of cyanide toxicity.

If nitroprusside therapy is unavailable or undesired, nitroglycerin ointment and isosorbide dinitrate are effective preload reducing agents, although clinical effects are generally less impressive. Adverse effects are also less common, although similarly associated with hypotension. Depression may be seen in a percentage of canine and feline patients. Nitroglycerin is absorbed transcutaneously, and gloves must be worn during administration. It is applied at approximately ¼ in. per 10 lb (dogs and cats) every 6–8 hr on a hairless region such as the inner pinna or inguinal region. The latter may be preferable in animals with poor peripheral perfusion, in which the pinnae and extremities may be cool to the touch. The drug should be wiped or cleaned off after 8–12 hr or before the next dose is given. Isosorbide

dinitrate is less commonly used. It is generally chosen in patients refractory to therapy with ACE inhibitors. It is administered at 0.2–1.0 mg/kg, PO, tid. Tolerance to nitrates has been demonstrated in experimental canine models.

Hydralazine is a potent arterial vasodilator typically reserved for animals refractory to therapy with ACE inhibitors, or in acute CHF when nitroprusside is unavailable. Its presumed mechanism of action is via production of vasodilatory prostaglandins. Hydralazine may reduce systemic vascular resistance up to 40%. Because of an increased tendency for adverse effects related to hypotension (tachycardia, weakness, vomiting, diarrhea), hospital monitoring during the initiation of therapy is often recommended. The recommended starting dosage is 0.5 mg/kg, PO, bid with gradual uptitration to effect, as high as 2.0 mg/kg, PO, bid. In cats, it can be given at 2.5 mg/cat, PO, sid-bid.

Amlodipine is a calcium channel blocker with peripheral vascular selectivity and moderate vasodilatory effects. Direct cardiac effects (reduced inotropy and conduction) are uncommon at standard dosages. Amlodipine has a relatively slow onset of action and is typically reserved for animals that are refractory to, or unable to tolerate therapy with an ACE inhibitor or for those with moderate to severe systemic hypertension. Adverse effects are generally related to hypotension and are uncommon when uptitration is done gradually. In dogs, therapy is initiated at 0.1 mg/kg, PO, bid and uptitrated weekly to a target of 0.2 mg/kg, sid-bid. In cats, therapy is generally started at 0.625 mg (one-fourth of a 2.5-mg tablet), sid and gradually uptitrated to effect, up to 1.25 mg, bid in some cases.

Phosphodiesterase type V (PDE-V) inhibitors (sildenafil, tadalafil) are mixed vasodilators with pulmonary selectivity. Their mechanism of action is similar to that seen with nitrates, with a common increase in the second messenger cGMP. PDE-V inhibitors are used in the treatment of moderate to severe pulmonary arterial hypertension. Studies in dogs have demonstrated modest clinical improvement with minimal improvement in pulmonary artery pressures. Anecdotally, PDE-V inhibitors seem to provide the most notable clinical benefit to animals with syncope secondary to pulmonary hypertension. Adverse effects are uncommon but may include GI upset and hypotensive-related effects (especially when combined with other nitrates, which is contraindicated). A major drawback regarding clinical use of PDE-V inhibitors is expense, particularly in larger patients. Sildenafil is administered at 1–2 mg/kg, PO, bid-tid in dogs and cats. Tadalafil is administered at 1 mg/kg, PO, sid-bid.

Antiarrhythmics

A detailed discussion of antiarrhythmic therapy is covered elsewhere (see Antiarrhythmics). Many antiarrhythmics have negative inotropic effects, with the potential to worsen active CHF. This is most likely to occur with the use of calcium channel blockers or β-blockers in the treatment of supraventricular tachyarrhythmias. Therapeutic decisions can be challenging when it is suspected that the presence of a tachyarrhythmia is worsening CHF by reducing the time for ventricular filling during diastole. This is further confounded by the fact that animals in heart failure generally have elevated sympathetic tone, which can worsen tacharrhythmias. Thus, there is some debate as to whether mild to moderate tachyarrythmias (heart rate of up to 180 bpm) in heart failure should be treated, or simply observed while awaiting better therapeutic control of heart failure.

There is little debate as to whether severe sustained tachyarrhythmias (heart rate >180–200 bpm) should be treated. As previously mentioned, digoxin is the treatment of choice in most patients with atrial fibrillation or supraventricular tachycardia in the setting of CHF. However, effects of digoxin are generally not seen for 3–5 days and, in many cases, it is only moderately effective at reducing the ventricular response rate to atrial fibrillation. Diltiazem or β-blockers such as atenolol are often added to digoxin for their ability to further slow AV nodal conduction and reduce the ventricular response rate (β-blockers should not be used if active CHF is present). If the addition of diltiazem or a β-blocker results in worsening signs of congestion, these agents should be withdrawn until the animal is no longer in CHF. Other options for the treatment of atrial fibrillation or supraventricular tachycardia in CHF include procainamide or amiodarone (see Antiarrhythmics).

Treatment of significant ventricular arrhythmias (successive ventricular beats demonstrating R-on-T phenomena) or tachycardia (>160–180 bpm) in CHF is generally attempted with class IB antiarrhythmics (lidocaine or mexilitine) or amiodarone. All of these agents possess minimal or mild negative inotropic effects. Sotalol, a class III antiarrhythmic

with β-blocking properties, may also be used, although it possesses more negative inotropic effects and may not be tolerated if significant myocardial dysfunction or CHF are present.

Chronic bradyarrhythmias as seen with AV block (high grade second or third degree) or sick sinus syndrome may also lead to CHF, and in these animals, pacemaker implantation is the treatment of choice. If pacemaker implantation is not a viable option, anticholinergics or sympathomimetics may be administered. Propantheline is an oral anticholinergic that is dosed at 0.25–0.5 mg/kg, PO, bid-tid. Adverse effects include tachycardia and GI upset. Theophylline is a nonselective PDE inhibitor with modest chronotropic effects, dosed at 9 mg/kg, PO, tid-qid in dogs, and at 4 mg/kg, PO, bid-tid in cats. A sustained-release formula is also available, which is dosed at 10–15 mg/kg, PO, bid in dogs, and at 20 mg/kg, PO, every 24–48 hr in cats. Adverse effects may include restlessness, excitability, tachycardia, or GI upset. Terbutaline is a β-agonist that also possesses modest chronotropic effects and has similar adverse effects to those seen with theophylline. It is dosed at 1.25–5 mg, PO, tid in dogs, and 0.625 mg, bid in cats. Attempts to overcome clinically significant bradyarrhythmias with oral therapy are often unrewarding, although overall clinical signs may improve in some patients.

β-Adrenergic Blockers as Cardioprotective Agents

It remains to be seen whether β-blockers will improve morbidity and mortality in animals with cardiac disease, but studies in people indicate that there is sound theoretical and experimental basis to support their efficacy. Clinical trials in dogs with DCM or CVD have not shown significant clinical or neurohormonal benefits from administration of carvedilol, a third-generation β-adrenergic blocker. Dogs with experimentally induced heart failure have shown measurable improvements in cardiac performance after administration of metoprolol, but these were models of ischemic cardiomyopathy, which is an uncommon cause of DCM in dogs.

Many cardiologists are using β-adrenergic blockers in dogs with demonstrated systolic or diastolic dysfunction, and it is believed that better clinical results may be obtained if these agents are started earlier in the course of disease and gradually uptitrated. In animals with occult disease or compensated heart failure, they seem to be well tolerated when careful uptitration is followed, stopping at the highest tolerated dose that does not cause weakness, lethargy, or other clinical signs associated with hypotension or reduced cardiac output. Carvedilol and metoprolol are the most commonly used agents in this setting. Carvedilol is generally started at 0.2–0.4 mg/kg, PO, bid in dogs, and gradually uptitrated every 1–2 wk to a maximal dosage of 1.5 mg/kg, bid. Metoprolol is started at 0.5 mg/kg, PO, bid-tid in dogs, and uptitrated to 1 mg/kg, PO, bid-tid. The recommended dosage of metoprolol in cats is 2–15 mg, PO, tid. Atenolol (6.25 –12.5 mg/cat, bid) may also be considered for myocardial protection in cats. There are some data associating the use of atenolol in cats with HCM and CHF with a poorer outcome, and consideration should be given to dosage reduction or withdrawal if CHF develops.

Nutritional Considerations

Important metabolic changes may occur in animals with heart failure. Upregulation of the RAAS leads to increased plasma volume, largely mediated by increased sodium retention. Increased production of inflammatory cytokines such as tumor necrosis factor and interleukin 1 may promote increased metabolic demand and contribute to anorexia, thus worsening "cardiac cachexia." Studies in people and a recent one in dogs have shown that patients with CHF who lost weight during the course of these studies had a poorer prognosis. In some patients, nutrient deficiencies (taurine, carnitine, coenzyme Q_{10}) have been associated with decreased myocardial performance. Decreased levels of circulating fatty acids have been documented in people and dogs with heart failure. The overall nutritional goals in the management of animals with heart failure should therefore include supplying adequate calories, modulating the production of proinflammatory cytokines, managing sodium balance, and supplementing nutrients that may be deficient.

The idea that **sodium restriction** reduces circulating plasma volume and thus preload is well established. However, sodium restriction is known to activate the RAAS, and there is some debate as to the role of sodium restriction in animals with asymptomatic cardiac disease or mild or moderate CHF. In contrast, there is almost universal acceptance that moderate to severe sodium restriction is indicated in animals with advanced CHF. Only mild sodium restriction (<80 –90 mg/100 kcal) is recommended in patients with moderate to severe cardiac remodeling not yet in CHF (International

Small Animal Cardiac Health Council [ISACHC] Class IB). It is also important to counsel owners to avoid foods and treats with high sodium content, because an acutely high sodium load (as can occur in animals fed human snacks or table foods) may precipitate CHF in animals with compensated heart disease. For animals in mild to moderate heart failure (ISACHC Class II), moderate sodium restriction (50–80 mg/100 kcal) is recommended. In patients with severe refractory CHF, more aggressive sodium restriction (<50 mg/100 kcal) is recommended. This becomes a therapeutic challenge with some animals in which cardiac cachexia is now present, because lower sodium foods can be less palatable.

Supplementation with **n-3 fatty acids** has shown multiple benefits in people with CHF, and a recent study in dogs suggests antiarrhythmic benefits as well. These fatty acids may reduce circulating inflammatory cytokine levels and seem to improve appetite in some dogs with cardiac cachexia. Daily doses of 40 mg/kg EPA and 25 mg/kg DHA are recommended.

Taurine supplementation is indicated in animals with documented taurine deficiency and DCM. The incidence of DCM has declined dramatically in cats since taurine deficiency was identified as a primary cause in the late 1980s. Taurine deficiency is still documented in some cats with DCM fed noncommercial diets. Supplementation at 250 mg, sid-bid can be started in cats while awaiting results of plasma and whole blood taurine levels. Dogs are able to synthesize endogenous taurine, so deficiency is less common in this species. However, breeds such as the American Cocker Spaniel, Golden Retriever, and Newfoundland are relatively predisposed to taurine deficiency, especially when fed lamb and rice, or high-fiber low-protein/taurine diets. Whole blood and plasma taurine levels should be obtained in any dog suspected of having a taurine-deficient cardiomyopathy, and supplementation can be started at 500–1,000 mg, PO, bid-tid while awaiting results.

l-Carnitine plays an important role in fatty acid metabolism and energy production. Carnitine deficiency has been documented in a family of Boxers, and carnitine has been supplemented in other breeds with DCM with some anecdotal success. It is unclear whether this deficiency is a cause, or a result of cardiomyopathy in these dogs. Diagnosis of carnitine deficiency is difficult and requires an endomyocardial biopsy. Supplementation is also expensive, and given our limited knowledge of the role carnitine plays in canine cardiomyopathy, supplementation is not routinely recommended. Nevertheless, supplementation can be offered at 50–100 mg/kg, PO, bid-tid to dogs with DCM, especially Boxers.

Coenzyme Q$_{10}$ is involved with mitochondrial energy production and possesses general antioxidant properties. Anecdotal benefits of supplementation in people and dogs with DCM have been reported, but well-controlled studies are lacking, and some reports are conflicting. The current recommended dosage in dogs is 30–90 mg, PO, bid.

Oxygen Therapy

The presence of pulmonary edema in animals with CHF increases the alveolar-arterial diffusion distance for oxygen to pulmonary capillaries. Supplemental oxygen administration increases the alveolar-arterial diffusion gradient and thus increases arterial oxygen content. Oxygen may be administered via oxygen cage, flow-by method, nasal cannula, or oxygen collar (constructed by covering the ventral 50–75% of an Elizabethan collar with plastic wrap and taping oxygen tubing along the ventral aspect of the collar). The oxygen cage may prove least stressful for the patient but is expensive because high flows of oxygen are required to achieve therapeutic concentrations (>40% inspired oxygen). The oxygen collar has the potential to achieve very high concentrations of inspired oxygen (up to 80%) but may require light sedation to increase patient compliance.

Thoracocentesis

Pleural effusion decreases the available area for alveolar ventilation and thus arterial oxygenation. Thoracocentesis is the most effective treatment in animals with significant volumes of effusion and respiratory distress. However, caution should be taken in particularly stressed patients, which may require pretreatment with oxygen, a moderate furosemide dose, and light sedation. Diuretic therapy is relatively ineffective at resolving large volumes of pleural effusion acutely,

and hypovolemia with azotemia is likely to develop if such a treatment strategy is used (ie, administering large enough doses of diuretics sufficient to significantly reduce pleural effusion).

Abdominocentesis

Ascites may produce abdominal discomfort and worsen dyspnea by reducing available lung capacity. In animals with continued ascites in which increasing diuretic therapy is not an option, abdominocentesis may be performed every 2–4 wk to improve patient comfort and quality of life.

Ancillary Therapy

Bronchodilators (theophylline, terbutaline) are generally reserved for patients with chronic airway disease, which is not uncommon in older small-breed dogs. Caution should be taken in animals with CHF, especially with tachyarrhythmias, due to the sympathomimetic effects of these agents. In dogs with CVD and syncope, theophylline has been used with some success for its vagolytic effects. Dosages of theophylline and terbutaline are as previously described under treatment for bradyarrhythmias (*see* above).

Cough suppressants may help reduce coughing related to mainstem bronchial compression secondary to left atrial enlargement. Coughing may also be seen with reactive airway disease (cardiac asthma). However, caution must be taken in patients with CHF, because suppressing a cough may mask worsening pulmonary edema. Common antitussive agents used for dogs with cardiac disease include butorphanol at 0.05–0.3 mg/kg, PO, tid-qid or hydrocodone at 0.22 mg/kg, PO, bid-tid.

Anxiolytic therapy may be required for animals with severe respiratory distress secondary to CHF. Morphine has traditionally been recommended to alleviate anxiety in dogs and people with acute CHF because of its concurrent sedative and venodilating (and thus preload reducing) properties. Morphine may be used at a dosage of 0.1–0.25 mg/kg, SC. The most common adverse effects include respiratory depression and nausea or vomiting. Morphine is generally avoided in cats, because it may induce agitation and dysphoria. Butorphanol is a partial opiate agonist/antagonist with minimal cardiovascular effects. A sedative dosage of 0.2–0.5 mg/kg administered IM or IV can be used in cats and dogs. Butorphanol may also be combined with a benzodiazepine (midazolam or diazepam), with the latter also dosed at 0.2–0.5 mg/kg, IM or IV. Phenothiazine tranquilizers (eg, acepromazine) may be used to alleviate severe anxiety; however, they induce vasodilation via a blocking effect and should be used cautiously, if at all, in animals with severe hemodynamic compromise or systemic hypotension. A low dosage of 0.01–0.1 mg/kg, IM or IV can be used if potent anxiolysis is required.

Last full review/revision July 2011 by Suzanne M. Cunningham; Daniel J. Hall

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