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Drug Therapy of Heart Failure: The Big Picture

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Thoughtful clinicians treating heart disease (or heart failure) would like to be able to answer the following 4 questions before prescribing therapy:

- Is the proposed therapy needed?
- Is the proposed therapy safe?
- Is the proposed therapy effective?
- How will I monitor the safety and efficacy of the proposed therapy?

DEFINITIONS

Heart failure is the term generally used to describe a clinical and hemodynamic syndrome in which the heart is no longer able to pump enough blood to meet the tissue needs at normal venous (e.g., left or right ventricular diastolic) pressures. Heart failure is distinct from heart disease, although a variety of congenital and acquired heart diseases of dogs and cats eventually result in heart failure. Heart failure is a relatively common cause of chronic illness and death in dogs and cats. Once clinical signs of heart failure are evident (e.g., shortness of breath), the prognosis for untreated heart failure is poor regardless of it's cause—hence the answer to the first question above would always be "yes," if the patient's clinical signs were actually caused by heart failure. Exactly when a patient with heart disease can be said to be in heart failure may be difficult to determine. Cardiac output might be normal at rest, but rise inadequately with exercise; ventricular pressures in diastole might be normal at low resting heart rates, but elevated at higher rates. Diastolic pressures might be high at rest, for example, but not so high as to cause pulmonary venous distention radiographically, or fluid accumulation in the lungs or body cavities.

In addition to the hemodynamic changes that can cause fluid accumulation in body cavities or the pulmonary parenchyma, heart failure is generally characterized by the activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, as well as by the elaboration of a variety of inflammatory and vasoactive cytokines. Triggered in part by reductions in cardiac output and the accompanying changes in organ perfusion, arterial blood pressure, and vascular and cardiac distention, these mechanisms appear to be designed to enhance survival following acute hemodynamic compromise (e.g., hemorrhage or dehydration). Their activation may support circulatory function (at a high metabolic cost to the heart muscle) for a variable amount of time, depending on the nature and severity of the initial injury and the initial health of the myocardium. The short-term benefits of these compensatory mechanisms fade quickly with chronic activation of these systems (e.g., from causes other than acute blood or fluid loss), and the resulting damage to the myocardium and vasculature appears to contribute significantly to the progression of heart failure in many heart diseases.

The definition we choose for heart failure becomes more important as our understanding of the pathogenesis of heart failure evolves from a hemodynamic model to one that encompasses subtle neurohormonal, biochemical, and genetic changes that often precede measurable hemodynamic or clinical abnormalities. As we refine our ability to both define and detect heart failure, neurohormonal, biochemical, and genetic changes preceding the onset of clinical signs of heart failure pose attractive therapeutic targets that could alter the course of many heart diseases, postponing or preventing the clinical signs of heart failure. With quantitative testing for biochemical markers of neurohormonal activation widely unavailable, it remains difficult to assess when animals with clinically identifiable heart disease have started down the slope to heart failure. The need for, safety, appropriate timing, and extent of pharmacological intervention aimed at reducing the activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and other vasoactive or inflammatory cytokines

remains incompletely studied in every important heart disease of dogs and cats that can be identified before the onset of clinical signs. There is probably no more controversial topic in veterinary cardiology than the appropriate treatment of dogs and cats with subclinical heart disease.

OVERVIEW OF HEART FAILURE THERAPY

Heart diseases, like most diseases, are most effectively prevented or treated by eliminating their cause, or interrupting their pathogenesis at an early stage in their development. Promising investigations aimed at clarifying the cause and pathogenesis of the diseases that commonly cause heart failure in dogs and cats are in progress at a number of institutions, but practical therapy directed at avoiding or healing the inciting injuries that result in most of these diseases may still be years away. Surgical interventions (e.g., mitral valve repair or replacement) may be lifesaving to dozens, or even hundreds of animals with heart diseases amenable to surgical therapy, but this approach is also unlikely to alter the overall need or demand for effective drug therapy of heart failure in the foreseeable future.

Historically, drug therapy for heart failure can be divided into roughly 3 continuous and variably overlapping eras. Before the 1970's, heart failure therapy most often consisted of the administration of a digitalis glycoside and a diuretic. Advances in understanding the hemodynamic model of heart function and failure led in the late 1970's to the concept of afterload reduction, and the first human clinical trials to show improved survival with vasodilator therapy followed shortly thereafter. Veterinary use of vasodilators to treat heart failure roughly paralleled their usage in human medicine. More recently, drug therapy designed to interrupt the cascade of neurohormonal events that accompanies and contributes to the pathogenesis of heart failure has resulted in clinically significant improvement in survival as well as in the quality of life of both human and veterinary heart failure patients.

There is general agreement in veterinary cardiology on the necessity for careful clinical diagnosis of the underlying heart disease, and assessment and regulation of the heart failure patient's hemodynamic state. The hemodynamic state (e.g., the cardiac output, systemic and pulmonary arterial and venous pressures and resistances) of heart failure patients can be modified with drugs that reduce the preload (e.g., diuretics or venous dilators), reduce the afterload (arterial vasodilators), slow the heart rate (digitalis glycosides, calcium channel blockers, beta adrenergic receptor blockers), or alter the contractility (e.g., digitalis glycosides or catecholamines to increase contractility; beta adrenergic receptor blockers to decrease it). After the major hemodynamic problems have been successfully addressed by manipulating these determinants of cardiac output, most cardiologists turn their attention to interventions aimed at prolonging survival by reducing the long term activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the inflammatory and vasoactive cytokines that have been shown to be elevated in heart failure. Table I summarizes the dosages, routes of administration, and major mechanisms of action of the drugs commonly used in heart failure therapy in dogs, table II summarizes the same information for cats.

Table 1. Drugs Commonly Used to Treat Heart Failure in Dogs

Drug	Dosage	Route of Administration	Major Action(s)
Dobutamine	2.5–20 µg/kg/min	Constant IV infusion	Positive inotrope
Nitroprusside	2.5–10 µg/kg/min	Constant IV infusion	Preload & afterload reduction
Furosemide	1–4 mg/kg q8–24h	Oral or parenteral (IV, subcutaneous (SQ), or intramuscular (IM)	Preload reduction
Nitroglycerine	2.5–10 mg/24h patch, 12 h on, 12 h off	Transcutaneous patch	Preload reduction
Hydralazine	0.5–2.0 mg/kg q12h, start low and titrate to desired arterial pressure	Oral	Afterload reduction
Amlodipine	1.25 mg/(small dog)–2.5 mg/(large dog) total dose to start, titrate to desired arterial pressure	Oral	Afterload reduction
Digoxin	0.006 mg/kg q12 h (not to exceed 0.25 mg/dog q12h without serum digoxin measurement)	Oral	Mild positive inotrope, reduces sympathetic nerve activity, restores baroreceptor sensitivity, slows heart rate (vagal effect)
Enalapril	0.5 mg/kg q12h	Oral	Angiotensin converting enzyme inhibitor (renin-angiotensin-aldosterone [RAAS] inactivation), mild preload and afterload reduction
Spironolactone	0.1–2.0 mg/kg q12h	Oral	Aldosterone antagonist (RAAS inactivation), mild preload reduction
Carvedilol	1.625–3.25 mg /dog q12h to start, q12h, titrate weekly to final dose of 12.5 mg q12h (small dog) or 25 mg q12h (large dog)	Oral	Sympathetic Nervous System (SNS) inactivation, antioxidant, mild afterload reduction, slows heart rate
Atenolol	6.25 mg /dog q12h to start, titrate weekly to 25 mg q12h (small-med dog) or 50 mg q12h (large dog)	Oral	SNS inactivation, slows heart rate
Diltiazem	0.5–1.25 mg/kg q8h	Oral	Slows heart rate

Drug	Dosage	Route of Administration	Major Action(s)
Diltiazem	0.25 mg/kg	IV	Slows heart rate
Morphine Sulfate	0.05 mg/kg q 3 minutes to effect (0. 1–0.3 mg/kg total q4–6 h)	IV	Pain relief, anxiolysis, mild preload reduction
Acepromazine	0.01–0.03 mg/kg not to exceed q6h	Parenteral (IV, SQ, IM)	Anxiolysis, preload reduction

Table 2. Drugs Commonly Used to Treat Heart Failure in Cats

Drug	Dosage	Route	Major Action(s) or Indication
Furosemide	1–4 mg/kg q8–48h	Oral or parenteral (IV, subcutaneous (SQ), or intramuscular (IM)	Preload reduction
Nitroglycerine	2.5–5 mg/24h patch, 12 h on, 12 h off	Transcutaneous patch	Preload reduction
Digoxin	¼ of a 0.125 mg tablet q48h	Oral	Mild positive inotrope, slows heart rate (vagal effect), indicated for dilated cardiomyopathy, some restrictive cardiomyopathy
Enalapril	0.5 mg/kg q24h	Oral	Angiotensin converting enzyme inhibitor (renin-angiotensin-aldosterone [RAAS] inactivation), mild preload and afterload reduction
Esmolol	0.5 mg/kg (peak effect by 2 minutes, ultrashort acting)	IV bolus	SNS inactivation, slows heart rate (hypertrophic obstructive cardiomyopathy as a test dose)
Atenolol	6.25 mg/cat q12–24h	Oral	SNS inactivation, slows heart rate
Diltiazem (Dilacor ®)	30 mg/cat q12h ½ of a 60 mg tablet, inside of a 180 mg or 240 mg capsule	Oral	Slows heart rate
Diltiazem	0.25 mg/kg	IV	Slows heart rate
Butorphenol	0.05 mg/kg q 3 minutes to effect, 0.1–0.4 mg/kg total q2–6h	IV	Pain relief

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KEYWORDS

Heart disease, heart failure, renin-angiotensin-aldosterone system, sympathetic nervous system, drug therapy