**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 β1 and β2 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.

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