Positive Inotropes

By **Sonya G. Gordon, DVM, DVSc, DACVIM (Cardiology), Associate Professor, Department of Small Animal Clinical Science, Texas A and M University**
Ashley B. Saunders, DVM, DACVIM (Cardiology), Associate Professor of Cardiology, College of Veterinary Medicine and Biomedical Sciences, Texas A and M University

Positive inotropes increase the strength of cardiac muscle contraction by increasing the quantity of intracellular calcium available for binding by muscle proteins, by increasing the sensitivity of contractile proteins to calcium, or a combination of both (eg, pimobendan). This, in turn, augments contractile protein interaction in the myocardial cell. Intracellular calcium can be increased by altering the Na^+/Ca^{2+} exchange pump, by increasing production of cyclic adenosine monophosphate (cAMP) via stimulation of adenylate cyclase, or by decreasing degradation of cAMP via inhibition of phosphodiesterases.

Cardiac Glycosides

The probable mechanism of action for the modest inotropic effect of digoxin is inhibition of the membrane-bound Na^+/K^+-ATPase pump; when this occurs, Na^+ increases in the cell, the exchange of Na^+ for Ca^{2+} via the Na^+/Ca^{2+} exchange pump is augmented, and there is a small increase in calcium influx. The increased intracellular calcium in turn leads to increased release of Ca^{2+} from the sarcoplasmic reticulum and increased contractility of the cardiac muscle. However, because these changes are modest, digoxin does not result in significant inotropy, and the availability of more potent oral positive inotropes has superseded its use for this indication.

Digoxin also has a combination of both proarrhythmic and antiarrhythmic properties. The alterations in the ratio of intracellular and extracellular electrolytes caused by digoxin can result in increased automaticity and cardiac arrhythmias. Negative chronotropic effects are due to decreased conduction velocity in the atrioventricular (AV) node via increased parasympathetic tone, as well as direct effects that help slow AV nodal conduction and prolong the AV nodal cell refractory period. Digoxin also has parasympathomimetic effects on the sinoatrial node and atria. In addition, it potentiates vagal (cholinergic) activity in the heart. The changes in conduction can lead to AV nodal blockade and reductions in heart rate (ventricular response rate) when digoxin is used to treat supraventricular arrhythmias, including atrial fibrillation. However, digoxin is rarely efficacious as a single agent for this indication. Digoxin has a narrow therapeutic window, and at toxic levels it can directly slow sinus nodal activity due to increased sensitivity to acetylcholine. Because the atria are sensitive to acetylcholine, atrial conduction is also enhanced in the diseased heart, which can then lead to atrial arrhythmias. Digoxin is believed to improve vascular baroreceptor responsiveness, thereby minimizing sympathetic activation in heart failure states. This is accomplished via decreasing plasma

catecholamine concentrations, which affect both sympathetic nerve activity and plasma renin activity, thereby minimizing sympathetic activation. In this way, digoxin may be considered to be a neuromodulator. Lastly, digoxin also has been reported to have a mild diuretic effect via the Na^+/K^+ ATPase pumps present in the renal tubular epithelial cells.

Preparations and Disposition:

The oral form of digoxin is the most widely used preparation. Other preparations are available but not used routinely in veterinary medicine.

Absorption of oral digoxin is variable; ~60% of the tablet formulation is absorbed. With little hepatic metabolism, almost all the absorbed drug reaches the vasculature. Absorption is slowed by food. Digoxin is distributed slowly and concentrated in cardiac tissues, and ~25% is bound to plasma proteins. It is primarily eliminated unchanged via the kidneys (15% is metabolized and excreted via the liver); its half-life (~23–39 hr in dogs, and extremely variable in cats) is strongly influenced by renal function. Steady state is reached after ~5 half-lives, and maintenance doses should theoretically achieve a therapeutic serum concentration within 2–4 days.

Drug Interactions and Toxicity:

A number of medications can increase plasma digoxin concentrations, including aspirin, quinidine, chloramphenicol, aminoglycosides (eg, neomycin), amiodarone, anticholinergics, diltiazem, esmolol, flecainide, tetracycline, and spironolactone. Furosemide, hydrochlorothiazide, amphotericin B, and glucocorticoids deplete body potassium and thus potentiate digitalis intoxication and proarrhythmic effects. Administration of β-adrenergic agonists (eg, dobutamine) also increases the risk of proarrhythmia. Longterm administration of phenobarbital may decrease digoxin concentrations by increasing clearance. Calcium channel blockers and β-blockers will potentiate action on the AV node conduction, increasing risk of AV block.

Toxic effects with digitalis glycosides are common and can be lethal. Cats are more sensitive to digoxin than dogs. Probably the most frequent cause of toxicity is inadvertent overdosing. The potential for toxicity is increased with hypokalemia and azotemia. The likelihood and severity of toxicity are related to the severity of cardiac disease. Other factors that would require dosage adjustment to prevent toxicity include renal failure (azotemia), hypothyroidism, decreased muscle mass (a significant amount of digoxin is bound to skeletal muscle), ascites, hypercalcemia, and myocardial failure leading to reduced renal blood flow. Signs of toxicity relate to the GI system (most common adverse effects) or CNS, or manifest as arrhythmias, with digitalis capable of inducing any type of cardiac arrhythmia. GI signs of toxicity include diarrhea, anorexia, and nausea and vomiting due to direct stimulation of the chemoreceptor trigger zone. Frequently, these are the earliest indications of toxicity. Neurologic effects include malaise and drowsiness. Digoxin toxicity can be diagnosed (and avoided) by monitoring plasma drug concentrations. Treatment of intoxication includes discontinuing therapy with digitalis and potassium-depleting diuretics and administering phenytoin (blocks AV nodal effects of digitalis), lidocaine (for ventricular arrhythmias), and if indicated, potassium (preferably PO). Atropine may be useful to treat both clinically significant sinus bradycardia and second- or third-degree heart block induced by cholinergic augmentation. Arrhythmias, clinical signs, and electrolyte abnormalities should be treated as clinically indicated on a case-by-case basis.

Clinical Use:

In general, the availability of other medications with similar activities and more favorable risk-benefit ratios with respect to toxicity have dramatically reduced the clinical use of digoxin in dogs. Digoxin is rarely if ever used in cats for any indication. Current typical clinical indications in dogs are for adjunctive (in combination with another antiarrhythmic) treatment of supraventricular arrhythmias such as atrial fibrillation or flutter, as part of management of chronic, advanced, or refractory CHF, or to treat vasovagal syncope.

Maintenance dosages are 0.003–0.011 mg/kg, PO, bid, for dogs, and 0.005–0.01 mg/kg, PO, every 24–48 hr for cats. In general, initial dosages should be at the lower end of the range and rounded down, and then titrated up, if needed, based on measurement of serum digoxin levels (target serum concentrations 0.8–1.2 ng/mL 8–12 hr after administration). Toxicity can occur even in animals that have levels in the therapeutic range. Levels should be monitored 3–5 days after initial treatment (8–12 hours after administration) and every 6 mo thereafter or sooner if signs of toxicity develop. Digoxin dosages should be calculated based on lean body weight and reduced in obese or cachectic animals and in the presence of ascites. Known electrolyte disorders should be corrected before digitalis glycosides are administered.

Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) inhibitors, also known as inodilators, block the breakdown of cAMP and therefore increase intracellular cAMP concentrations. The result is an increase in myocardial contractility and peripheral vasodilation. Methylxanthine derivatives have been classified as PDE inhibitors, but this is controversial. Of the methylxanthines, theophylline is the most cardiopotent. In addition to their cardiac effects, methylxanthines have significant CNS, renal, and smooth muscle effects, including on bronchial smooth muscle. The use of methylxanthines in cardiac disease is limited to conditions that would benefit from bronchodilation.

Pimobendan is a benzimidazole pyridazinone derivative and is a positive inotrope and balanced systemic arterial and venous dilator. In failing hearts, it exerts positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium. As a PDE 3 inhibitor, pimobendan can potentially increase intracellular calcium concentration and myocardial oxygen consumption. However, the cardiac PDE effects of pimobendan are reportedly minimal at pharmacologic doses in dogs with heart disease, which is a major advantage relative to other inotropic PDE inhibitors such as milrinone. PDE 3 inhibitors such as pimobendan result in balanced vasodilation (combination of venous and arterial dilation) leading to a reduction of both cardiac preload and afterload. In addition, pimobendan may have some direct endothelial-derived vasodilatory effects. The significance of alterations in proinflammatory cytokine concentrations such as tumor necrosis factor-β and interleukins 1β and 6 on the progression of heart failure has been documented in many forms of heart disease. Maladaptive alterations in these cytokine concentrations are associated with increased morbidity and mortality, and pimobendan has demonstrated beneficial modulation of several such cytokines in various models of heart failure. Pimobendan reportedly may have some platelet inhibitory effect in dogs and cats, but the clinical significance of this is not yet clear. Lastly, PDE 3 inhibition in cardiomyocytes leads to more rapid relaxation; thus, pimobendan can also be considered to be a positive lusiotrope.

In dogs, pimobendan is extensively metabolized, and both the parent drug and active metabolite are >90% bound to plasma protein. The steady state volume of distribution of pimobendan is 2.6 L/kg, and the terminal elimination half-lives of pimobendan and its active metabolite are 0.5 and 2 hr, respectively. Oral bioavailability is reduced by food until steady state is reached in a few days. Consequently, pimobendan should be administered on an empty stomach at least 1 hr before feeding

for maximal effects when starting therapy. Hemodynamic effects after PO administration on an empty stomach peak in 1 hr and last 8–12 hr; therefore, pimobendan can provide rapid short-term support to dogs with acute or decompensated heart failure. IV preparations are available in some countries.

Pimobendan is approved for treatment of CHF due to dilated cardiomyopathy (DCM) and chronic degenerative mitral valvular disease (DMVD) in dogs. It has also been shown to prolong symptom-free survival in Doberman Pinschers with occult DCM. Pimobendan has an excellent safety profile, and clinical data suggest that it is safe when administered concomitantly with other medications commonly used in treatment of canine CHF. Reported adverse effects are minimal, but the main one is GI intolerance of the chewable tablet formulation. Pimobendan is contraindicated in dogs with known outflow tract obstruction (eg, subaortic stenosis). Pimobendan is not approved for use in cats. A number of retrospective studies in cats, using dosages similar to those used in dogs, suggest it is well tolerated, but there is no definitive proof of efficacy.

The mechanism of action of the bipyridine derivatives **amrinone** and **milrinone** is probably inhibition of PDE and increased levels of intracellular cAMP. Both amrinone and milrinone are available for IV administration and are suitable only for short-term management of CHF. However, with the wide availability and known efficacy of pimobendan, these medications have fallen out of favor for treatment of CHF.

β -Adrenergic Agonists

These drugs cause a positive inotropic effect by activating β-receptors with subsequent stimulation of adenylate cyclase and increased cAMP.

Dopamine is an endogenous catecholamine precursor with selective β_1 activity. However, it also stimulates release of norepinephrine. At low doses, it stimulates renal dopaminergic receptors, which causes increased renal blood flow and diuresis. It is rapidly metabolized by the body and has a half-life of <2 min. Dopamine is available as a solution, which is further diluted with saline or dextrose. It is administered IV, usually by CRI (1–15 mcg/kg/min). Cardiac arrhythmias may develop due to β-adrenergic activity. Indications include cardiogenic or endotoxic shock and oliguria. In cardiogenic shock, infusion of equal concentrations of dopamine and dobutamine may afford more advantages than either drug alone. Both medications should be titrated up slowly while monitoring for arrhythmias, blood pressure, and clinical response to treatment. Dopamine is contraindicated in the face of ventricular arrhythmias and when a pheochromocytoma is suspected. Care should be used in the setting of aortic stenosis. If the animal has recently taken a monoamine oxidase inhibitor, the rate of dopamine metabolism by the tissue will fall and the dosage should be reduced to one-tenth of usual.

Dobutamine is a synthetic drug similar to dopamine, but it does not cause release of norepinephrine and therefore has minimal effects other than β_1 activity. Dobutamine is a more effective positive inotrope than dopamine with less chronotropic effects, although it does not dilate the renal vascular bed. Its plasma half-life is ~2 min. Dobutamine is prepared as a solution to be diluted with 5% dextrose or normal saline. When compared with dopamine, dobutamine is the preferred β-adrenergic agonist for short-term therapy of refractory CHF when pimobendan alone is not successful or insufficient. Dobutamine causes an immediate increase in blood pressure due to increased cardiac output. It is given as a CRI at 2–15 mcg/kg/min; heart rate, blood pressure, and cardiac output should be monitored. In cats, dobutamine has a longer half-life and causes CNS stimulation, so lower infusion rates (0.5–10 mcg/kg/min) should be used. It is rarely indicated in cats.

Compared with other inotropic drugs, **epinephrine**, with its β_1 and β_2 effects, causes the greatest increase in the rate of energy usage and myocardial oxygen demand. This increase in oxygen need may be detrimental to the failing heart. Epinephrine also causes vasoconstriction and bronchodilation. Epinephrine is rapidly metabolized in the GI tract and is not effective after administration PO. Absorption is more rapid after IM versus SC administration. Epinephrine is available in several preparations and is effective after IV, pulmonary, and nasal administration. However, because of the decreased efficiency of cardiac work, epinephrine is not used as a positive inotropic agent but rather for emergency therapy of cardiac arrest and anaphylactic shock. Ventricular arrhythmias should be expected and are a contraindication to using epinephrine except in life-threatening situations.

Isoproterenol is a nonspecific β-agonist that, like epinephrine, increases myocardial oxygen demand. Tachycardia and the potential for other arrhythmias excludes its use in a cardiac patient except for short-term therapy of bradyarrhythmias (eg, AV block). It is typically used as a CRI to effect based on the heart rate desired.