The myofilament calcium (Ca$^{2+}$) sensitizers are a class of positive inotropic, vasodilating drugs ("inodilators") that augment myocardial contractility by increasing the Ca$^{2+}$ sensitivity of the contractile apparatus without altering intracellular Ca$^{2+}$ concentration (1). Ca$^{2+}$ sensitizers (including levosimendan, pimobendan, sulmazole, EMD 57033, and MCI-154) have received considerable attention for the treatment of acute and chronic congestive heart failure because, unlike β$_{1}$-adrenoceptor agonists or cardiac phosphodiesterase (PDE) III inhibitors that stimulate cyclic adenosine monophosphate (cAMP)-mediated signaling and increase intracellular Ca$^{2+}$ concentration, these drugs do not adversely affect myocardial oxygen supply-demand relations (2), produce cardiotoxicity, or predispose to the development of arrhythmias (3).

Levosimendan was developed over a decade ago, and based on a large body of accumulated experimental and clinical evidence, appears to be the most promising of these drugs. Levosimendan has already been approved for the treatment of acute exacerbation of chronic heart failure in several European countries following European Society of Cardiology guidelines (4,5). The drug is currently undergoing Phase III clinical trials in the United States (REVIVE study) to evaluate its utility for the acute or chronic management of heart failure, and has received "fast-track" status from the Food and Drug Administration.

The mechanisms by which levosimendan enhances the inotropic state and produces vasodilation have been extensively studied (1). Briefly, levosimendan binds to the regulatory protein troponin C (TnC) (6) and stabilizes the Ca$^{2+}$-bound conformation of TnC, thereby allowing unopposed interaction between actin and myosin filaments and enhancing the rate and extent of myocyte contraction (7). A unique feature of levosimendan-TnC binding is its dependence on intracellular Ca$^{2+}$ concentration that facilitates the interaction between TnC and Ca$^{2+}$ during systole, while simultaneously allowing Ca$^{2+}$ to dissociate from the protein during diastole (8). This Ca$^{2+}$-dependence of TnC binding prevents deleterious abnormalities in relaxation that would otherwise be expected to occur (9). Preservation of lusitropic function is also facilitated by the PDE-inhibiting properties of levosimendan that occur at higher doses of the drug (10). Levosimendan-induced systemic, pulmonary, and coronary vasodilation occurs as a result of at least three distinct mechanisms. Levosimendan opens several types of potassium (K$^{+}$) channels (including voltage-dependent, ATP-sensitive, and Ca$^{2+}$-activated forms) in conductance and resistance vessels, actions that reduce intracellular Ca$^{2+}$ concentration in vascular smooth muscle (11). Levosimendan induces Ca$^{2+}$ desensitization of the contractile apparatus in vascular smooth muscle that does not contain TnC independent of intracellular Ca$^{2+}$ concentration (12). PDE inhibition may also play a role in vasodilation produced by higher doses of the drug.

Unlike other inotropic drugs, levosimendan may exert important antischismic effects by virtue of its actions as a K$_{ATP}$ channel opener. Levosimendan...
activates sarcolemmal (13) and mitochondrial (14) K\textsubscript{ATP} channels in vitro, and these channels play a critical role in myocardial protection against reversible and irreversible ischemic injury (15). Levosimendan reduced myocardial infarct size in a canine model of ischemia and reperfusion in vivo, independent of alterations in systemic hemodynamics or coronary collateral blood flow, and this beneficial action was abolished by the nonselective K\textsubscript{ATP} channel antagonist glyburide (16). Levosimendan enhanced the functional recovery of stunned myocardium after percutaneous transluminal coronary angioplasty in patients with acute myocardial ischemia (17) and was also beneficial for the treatment of cardiogenic shock resulting from stunning of border zone myocardium during infarction (18). Brief administration of levosimendan to patients undergoing coronary artery bypass graft surgery before cardiopulmonary bypass was associated with lower postoperative troponin I concentrations (19). These latter data suggested that levosimendan may be capable of producing pharmacological preconditioning in humans, presumably as a consequence of its actions on the K\textsubscript{ATP} channel.

The clinical efficacy of levosimendan in patients with heart failure resulting from ischemic heart disease (20,21), dilated cardiomyopathy (21), and acute myocardial infarction (22) has been well documented. Levosimendan causes dose-dependent improvements in systemic and pulmonary hemodynamics in patients with heart failure concomitant with a reduction in clinical symptoms (21); but the myofilament Ca\textsuperscript{2+} sensitizer does not produce hypotension, exacerbate ongoing ischemia, or contribute to mortality by increasing the incidence of arrhythmias (22). In contrast, a major clinical trial of the PDE III inhibitor, milrinone, in patients admitted for an acute exacerbation of chronic heart failure demonstrated that milrinone did not alter inhospital or 60-day mortality when compared with placebo, caused more frequent episodes of hypotension requiring intervention, and increased the incidence of arrhythmias as compared to placebo (23). When compared with the \(\beta\)-adrenoceptor agonist, dobutamine, levosimendan also produced more favorable alterations in hemodynamics and reduced mortality in patients with low-output heart failure (24) and in those with cardiogenic shock after percutaneous coronary intervention (25). The relative superiority of levosimendan when compared with dobutamine described in these studies (24,25) may be related to the antiinflammatory and antiapoptotic effects of the myofilament Ca\textsuperscript{2+} sensitizer (26). Similar to the findings in the setting of heart failure, levosimendan has also been shown to increase cardiac performance concomitant with reductions in pulmonary capillary occlusion pressure and systemic vascular resistance in patients with normal (27) and depressed (28,29) left ventricular (LV) function undergoing cardiac surgery with or without (30) cardiopulmonary bypass.

In the current issue of Anesthesia & Analgesia, De Hert et al. (31) provide further evidence that levosimendan produces beneficial hemodynamic effects in patients with preoperative LV dysfunction (ejection fraction <30%) undergoing LV dysfunction after cardiopulmonary bypass. Despite the inherent problems associated with a strict comparison between drugs of differing pharmacological action and relative potency, the authors demonstrate that the combination of IV infusions of levosimendan (0.1 g kg\textsuperscript{-1} min\textsuperscript{-1}) and dobutamine (5 g kg\textsuperscript{-1} min\textsuperscript{-1}) produces very similar cardiovascular effects to those observed with the combination of milrinone (0.5 g kg\textsuperscript{-1} min\textsuperscript{-1}) and dobutamine during the first 24 h after cardiopulmonary bypass. The data further suggest that levosimendan-dobutamine may augment stroke volume index to a greater degree than milrinone-dobutamine 12 and 24 h after bypass, although these results may most likely be attributed to the greater reductions in systemic vascular resistance observed in patients receiving the combination of levosimendan and dobutamine. Loading doses of levosimendan or milrinone were not administered, but infusions of these drugs were initiated upon removal of the aortic cross-clamp preceding a prolonged reperfusion before separation from bypass. Thus, steady-state plasma concentrations of levosimendan and milrinone were probably established before bypass was discontinued. Perhaps of more importance, the results indicate that the total doses of dobutamine and norepinephrine (used to treat mean arterial blood pressure <60 mm Hg) required during the first 48 h after cardiopulmonary bypass, the total duration of inotropic drug treatment, the duration of mechanical circulatory support (intraaortic balloon counterpulsion was required in four of 15 patients per group), and time to tracheal extubation were significantly less in patients receiving levosimendan-dobutamine when compared with those treated with milrinone-dobutamine. The beneficial hemodynamic effects of levosimendan have been shown to persist for at least 24 h after discontinuation of a continuous infusion as a result of a biologically active metabolite (OR-1896) (32), and it is likely that the accumulation and prolonged effect of this metabolite may, at least partially, account for these dramatic differences between levosimendan- and milrinone-treated patients.

PDE III inhibitors such as milrinone have been a mainstay in the pharmacological management of LV dysfunction after cardiopulmonary bypass for many years. These drugs are commonly used in combination with the \(\beta\)-adrenoceptor agonists to provide a synergistic positive inotropic effect in the presence of bypass-induced down regulation of the \(\beta\)-adrenoceptor and dysfunctional adenylyl cyclase-mediated signal transduction (33). Because the mechanism of action of levosimendan is not dependent on this signaling pathway, the drug may have the distinct advantage of enhancing myocardial contractility by acting directly at the level of the contractile apparatus. In addition, levosimendan may reduce the development of arrhythmias and the incidence of cardiotoxicity that often occur with other clinically used inotropic drugs, because increases in
intracellular Ca\(^{2+}\) concentration do not occur with the myofilament Ca\(^{2+}\) sensitizer at typical therapeutic doses. K\(_{ATP}\) channel-mediated antiischemic effects and prolonged drug action resulting from an active metabolite also represent potentially important benefits of levosimendan in patients with LV dysfunction after cardiac surgery. Thus, the recent findings of De Hert et al. (31) are certainly promising, and support the work of previous investigations (28,29). Nevertheless, PDE III inhibitors and \(\beta_1\)-adrenoceptor agonists have a well-established record of clinical efficacy in the treatment of perioperative LV dysfunction. Given the success of these drugs in this setting, a fundamental question remains: Is another positive inotropic drug with vasodilating properties truly required to successfully treat these patients? Thus, whether the theoretical advantages of levosimendan will ultimately translate into improved outcome in cardiac surgical patients with LV dysfunction is unknown and will require additional investigation to define.

REFERENCES