Comparison of the effects of levosimendan, pimobendan, and milrinone on canine left ventricular-arterial coupling and mechanical efficiency

Abstract We examined and compared the effects of levosimendan, a new myofilament calcium sensitizer with phosphodiesterase inhibiting activity, pimobendan, and milrinone on left ventricular-arterial coupling and mechanical efficiency in 21 experiments performed in open-chest, barbiturate-anesthetized dogs instrumented for measurement of aortic and left ventricular (LV) pressure (micromanometer-tipped catheter), \(+dP/dt\), and LV volume (conductance catheter). Myocardial contractility was assessed with the end-systolic pressure-volume relation (Ees) and preload recruitable stroke work (Msw), generated from a series of differentially loaded LV pressure-volume diagrams. LV-arterial coupling and mechanical efficiency were determined by the ratio of Ees to effective arterial elastance (Ea; the ratio of end-systolic arterial pressure to stroke volume) and the ratio of stroke work (SW) to pressure-volume area (PVA), respectively. Levosimendan (0.75, 1.5, and 3.0 \(\mu\)g\-kg\(^{-1}\)-min\(^{-1}\)) significantly (\(p < 0.05\)) increased heart rate, \(+dP/dt\), and ejection fraction (EF) and decreased mean arterial pressure (MAP), pressure-work index (PWI; an estimate of myocardial oxygen consumption), and LV systolic and end-diastolic pressures (LVSP and LVEDP) and volumes (EDV and ESV). Levosimendan-induced augmentation of myocardial contractility (Ees, Msw and \(+dP/dt\)) and reductions in LV afterload (Ea) caused increases in the Ees/Ea ratio (0.61 ± 0.10 during control to 3.3 ± 0.7 during the high dose) consistent with enhancement of LV-arterial coupling. Levosimendan increased SW/PVA (0.48 ± 0.05 during control to 0.84 ± 0.04 during the high dose), indicating this drug improves the transfer of myocardial potential energy to external work. Levosimendan also increased the ratio of SW to PWI (109 ± 18 during control to 255 ± 50 mmHg·min·100 g during the high dose), suggesting that myocardial metabolic efficiency was improved as well. Like levosimendan, pimobendan and milrinone (10, 20, and 40 and 1.0, 2.0, and 4.0 \(\mu\)g·kg\(^{-1}\)-min\(^{-1}\), respectively) increased HR, \(+dP/dt\), EF, Ees, and Msw and decreased MAP, LVSP, LVEDP, EDV, ESV, and Ea. In contrast to levosimendan, neither agent reduced PWI. Pimobendan and milrinone caused dose-related increases in Ees/Ea, SW/PVA, and SW/PWI. The results indicate that levosimendan, pimobendan, and milrinone augment myocardial contractility, produce venous and arteriolar vasodilation, and enhance LV-arterial coupling and mechanical efficiency in open-chest, barbiturate-anesthetized dogs.
Levosimendan and LV-arterial coupling


**Introduction**
Levosimendan \[(R)-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile\] is a new drug in the myofilament Ca\(^{2+}\) sensitizer class of positive inotropic compounds (19). Levosimendan has been shown to augment myocardial contractility by binding to troponin C and stabilizing the Ca\(^{2+}\)-bound conformation of this regulatory protein without directly affecting actin-myosin interaction (11, 18, 38), mechanisms of action that are similar to those of pimobendan and sulmazole (6, 13, 22, 41, 55). Unlike other myofilament Ca\(^{2+}\) sensitizers, however, levosimendan-induced increases in the binding affinity of Ca\(^{2+}\) to troponin C are dependent on intracellular Ca\(^{2+}\) concentration. Myofilament Ca\(^{2+}\) sensitivity is enhanced in the presence of higher Ca\(^{2+}\) concentrations found during systole but is relatively unchanged at low intracellular Ca\(^{2+}\) concentrations in diastole (16, 17). Similar to other myofilament Ca\(^{2+}\) sensitizers (6, 13, 53), levosimendan partially inhibits cardiac and vascular smooth muscle phosphodiesterase (PDE) isoforms, actions that contribute to the positive inotropic and lusitropic effects of higher doses of this drug (11). Previous studies have demonstrated that levosimendan enhances myocardial contractility, improves indices of diastolic function, and causes venous and arterial dilation in conscious and anesthetized dogs (20, 35, 36) and produces favorable hemodynamic alterations in humans with normal (27, 50) and abnormal left ventricular function (28).

Optimal transfer of stroke volume from the left ventricle to the arterial circulation requires appropriate matching of these mechanical systems. Left ventricular-arterial coupling has been shown to be conveniently studied in pressure-volume phase space by characterizing the elastances of the left ventricle (E\(_{es}\)) and the arterial vasculature (E\(_{a}\)) using left ventricular end-systolic pressure-volume and end-systolic arterial pressure-stroke volume relations, respectively (9, 48, 49). The ratio of E\(_{es}\) to E\(_{a}\) defines mechanical coupling between the left ventricle and the arterial circulation (48, 49) and provides a useful technique for assessment of the actions of pharmacological agents, including vasoactive drugs, on overall cardiovascular performance in vivo (24, 29, 43). In addition, the analysis of the pressure-volume plane creates a framework for the study of left ventricular mechanical efficiency defined by the ratio of stroke work (SW) to pressure-volume area (PVA) (45). This investigation was designed to compare the actions of levosimendan, pimobendan, and milrinone, a PDE inhibitor without myofilament Ca\(^{2+}\) sensitizing activity, on left ventricular-arterial coupling and mechanical efficiency in barbiturate-anesthetized dogs.

**Materials and methods**
All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All procedures conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were performed in accordance with the Guide for the Care and Use of Laboratory Animals [DHEW(DHHS) publication (NIH) no. 85-23, revised 1985].

**Implantation of instruments**
Conditioned mongrel dogs (n = 23) of either sex weighing between 25 and 30 kg were fasted overnight and anesthetized with sodium pentobarbital (25 mg·kg\(^{-1}\)) and sodium barbital (200 mg·kg\(^{-1}\)). Fluid deficits were replaced prior to experimentation with 0.9 % saline (500 ml), which was continued at 3 ml·kg\(^{-1}·hr\(^{-1}\)) for the duration of each experiment. After tracheal intubation, the dogs were ventilated via positive pressure with a mixture (1 L·min\(^{-1}\)) of oxygen (90 %) and air (10 %). Respiratory rate and tidal volume were adjusted to maintain acid-base status (pH = 7.35 – 7.40) and carbon dioxide partial pressure (PCO\(_2\) = 30 – 35 mmHg) within physiologic limits. The right femoral vein was isolated through a small incision and a catheter was placed in this vessel for fluid and drug administration. A 7F, dual micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted through the left carotid artery and positioned across the aortic valve with the distal transducer in the left ventricle and the proximal transducer in the ascending thoracic aorta for measurement of continuous left ventricular and arterial pressures, respectively. The peak rate