Levosimendan (OR-1259), a Myofilament Calcium Sensitizer, Enhances Myocardial Contractility but Does Not Alter Isovolumic Relaxation in Conscious and Anesthetized Dogs

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Background: Levosimendan is a myofilament calcium sensitizer with phosphodiesterase III inhibiting properties which increases contractile state in vitro by stabilizing calcium-induced changes in troponin C. This latter effect may produce positive inotropic actions but may also cause deleterious negative lusitropic effects. This investigation examined the effects of levosimendan on systemic and coronary hemodynamics and left ventricular systolic and diastolic function in conscious and anesthetized dogs.

Methods: Because autonomic nervous system activity may influence the actions of levosimendan and volatile anesthetics in vivo, experiments were conducted in the presence of pharmacologic blockade of the autonomic nervous system. A total of 24 experiments were performed in eight dogs chronically instrumented for measurement of aortic and left ventricular pressure, the peak rate of increase and decrease of left ventricular pressure, subendocardial segment length, diastolic coronary blood flow velocity, and cardiac output. The slope of the regional preload recruitable stroke work relation was used to assess myocardial contractility. Diastolic function was evaluated by the peak rate of decrease of left ventricular pressure, a time constant of isovolumic relaxation, maximum segment lengthening velocity during rapid ventricular filling, and a regional chamber stiffness constant. Systemic and coronary hemodynamics and left ventricular pressure-segment length diagrams and waveforms were recorded after 10 min equili-

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A new class of positive inotropic agents, the myofilament calcium (Ca²⁺) sensitizers, have been the subject
of intense experimental and clinical research in recent years. Myofilament Ca\textsuperscript{2+} sensitizers, including pimobendan and sulmazole, are imidazopyridine derivatives which enhance myocardial contractility via direct actions on the contractile apparatus.\textsuperscript{1,2} This class of compounds increases the sensitivity of the myofilaments to Ca\textsuperscript{2+} by augmenting Ca\textsuperscript{2+} binding to the Ca\textsuperscript{2+}-specific regulatory site of cardiac troponin C, thereby stabilizing Ca\textsuperscript{2+}-induced conformational changes in this protein in a highly stereospecific manner.\textsuperscript{3–6} These agents also produce partial inhibition of cardiac phosphodiesterase III (PDE-III),\textsuperscript{1,3,5} an effect which may serve to enhance dissociation of Ca\textsuperscript{2+} from the contractile apparatus during diastole and lead to shortened isovolumic relaxation in vivo despite concomitant augmentation of Ca\textsuperscript{2+} binding during systole. Myofilament Ca\textsuperscript{2+} sensitizers have been shown to improve many of the hemodynamic derangements associated with congestive heart failure in humans\textsuperscript{7–11} and may represent another clinically important therapeutic modality in the acute and chronic management of end-stage heart failure resulting from ischemic heart disease, left ventricular hypertrophy, or idiopathic dilated cardiomyopathy.\textsuperscript{1,18}

The functional interaction between drugs of the myofilament Ca\textsuperscript{2+}-sensitizer class and volatile anesthetics have yet to described. Levosimendan [(R)-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitril (OR-1259) is a novel myofilament Ca\textsuperscript{2+} sensitizer with cardiac PDE-III–inhibiting properties (fig. 1). Preliminary studies have suggested that levosimendan causes cardiovascular effects\textsuperscript{16–25} which are similar to those produced by pimobendan\textsuperscript{7–15} and sulmazole.\textsuperscript{16,17}

The current investigation examined and compared the effects of levosimendan on systemic and coronary hemodynamics and left ventricular systolic and diastolic function in conscious and anesthetized chronically instrumented dogs. These experiments tested the following hypotheses. (1) Levosimendan augments myocardial contractility and improves several indices of diastolic function, including assays of isovolumic relaxation, in conscious dogs in a dose-dependent manner via enhancement of Ca\textsuperscript{2+} affinity for and PDE-III–induced Ca\textsuperscript{2+} release from the contractile apparatus, respectively. (2) Levosimendan reverses depression of contractile function caused by isoflurane and halothane by overcoming the functional impairments of the voltage-dependent Ca\textsuperscript{2+} channel\textsuperscript{24–27} and the sarcoplasmic reticulum\textsuperscript{28} induced by volatile anesthetics. (3) The PDE-III inhibitory activity and positive inotropic effects of levosimendan reverse abnormalities in diastolic mechanics caused by volatile anesthetics despite direct increases in Ca\textsuperscript{2+} affinity for the myofilaments. Experiments were conducted in the presence of pharmacological blockade of the autonomic nervous system to avoid changes in systemic and coronary hemodynamics mediated by autonomic nervous system reflexes during administration of levosimendan or volatile anesthetics.\textsuperscript{29} Thus, the effects of levosimendan on left ventricular systolic and diastolic function were studied in conscious and anesthetized dogs independent of changes in autonomic nervous system tone.

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 Physiologic Society and were performed in accordance with the Guide for the Care and Use of Laboratory Animals.\textsuperscript{#}

General Preparation

The implantation of instruments has been previously described in detail.\textsuperscript{30,31} In brief, during general anesthesia and in sterile surgical conditions, mongrel dogs (n = 8; 25.3 ± 0.6 kg, mean ± SEM) underwent a left thoracotomy for placement of instruments for mea-

![Fig. 1. Chemical structure of levosimendan.](attachment:image.png)
measurement of aortic and left ventricular pressure, peak rates of positive and negative change in left ventricular pressure (+\(\text{dP/}dt_{\text{max}}\) and −\(\text{dP/}dt_{\text{min}}\), respectively), subendocardial segment length, intrathoracic pressure, diastolic coronary blood flow velocity, and cardiac output (fig. 2). A hydraulic vascular occluder was positioned around the inferior vena cava for control of left ventricular preload. All instrumentation was firmly secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube.

All dogs received systemic analgesics [Innovar-Vet (fentanyl-droperidol); Pitman-Moore, Mundelein, IL] as needed after surgery. Dogs were allowed to recover a minimum of 7 days prior to experimentation during which time all were treated with intramuscular antibiotics [cephalothin (40 mg/kg) and gentamicin (4.5 mg/kg)] and trained to stand quietly in an animal sling during hemodynamic monitoring. Coronary blood flow velocity and segment length signals were monitored by ultrasonic amplifiers (Crystal Biotech, Hopkinton, MA). End-systolic (ESL) and end-diastolic segment length (EDL) were measured at −\(\text{dP/}dt_{\text{min}}\) and immediately prior to the onset of left ventricular isovolumic contraction, respectively. The lengths were normalized according to the method of Theroux et al.\(^{32}\) Percent segment shortening (%SS) was calculated as %SS = \((\text{EDL} - \text{ESL}) \times 100 \times \text{EDL}^{-1}\). Relative diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and peak diastolic coronary blood flow velocity. The pressure work index, an estimate of myocardial oxygen consumption, was determined using the formula of Rooker and Feigl.\(^{33}\) The hemodynamic data were continuously recorded on a polygraph (7758A, Hewlett-Packard, San Francisco, CA) and digitized by a computer interfaced with an analog to digital converter. Left ventricular pressure and segment length data were also transmitted to a digital storage oscilloscope (4094, Nicolet, Madison, WI) for recording of left ventricular pressure-segment length waveforms and diagrams.

**Experimental Protocol**

Dogs were randomly assigned to receive levosimendan in the conscious or anesthetized state on separate experimental days. Each dog was fasted overnight, and fluid deficits were replaced prior to experimentation.

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Fig. 2. Continuous left ventricular pressure (LVP), rate of change of left ventricular pressure (\(\text{dP/}dt\)), aortic blood pressure (ABP), segment length (SL), coronary blood flow velocity (CBFV), and aortic blood flow (ABF) waveforms during control conditions, autonomic nervous system (ANS) blockade, halothane (HAL) anesthesia (1 MAC), and levosimendan infusions (0.5, 1.0, 2.0, and 4.0 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) in a typical experiment.
LEVOSIMENDAN AND LEFT VENTRICULAR FUNCTION

with crystalloid (500 ml 0.9% saline) which was con-
tinued at 3 ml·kg⁻¹·h⁻¹ for the duration of each ex-
periment. Pharmacological blockade of the autonomic
nervous system consisted of intravenous propranolol
hydrochloride (2 mg/kg), atropine methyl nitrate (3
mg/kg), and hexamethonium bromide (20 mg/kg).
Adequacy of autonomic nervous system blockade was
established by lack of reflex change in heart rate during
a rapid decline of venous return caused by inflation of
the inferior vena caval hydraulic occluder before, dur-
ing and after each experiment. Left ventricular pres-
sure, intrathoracic pressure, and segment length wave-
forms were recorded continuously on the digital osci-
silloscope for later off-line analysis of diastolic func-
tion. Left ventricular pressure-segment length dia-
grams used to assess contractile state were generated
by abruptly decreasing left ventricular preload. This
was accomplished by constricting the inferior vena cava
resulting in an approximately 30 mmHg decline in left
ventricular systolic pressure over 10 to 15 cardiac cy-
cles. Respiratory variation in ventricular pressure in
the conscious state was later reduced off-line by elec-
tronically zeroing out the continuous intrathoracic
pressure waveform from the left ventricular pressure
waveform via the digital oscilloscope as detailed pre-
viously. 31 During anesthesia, waveforms were recorded
at end expiration. Inferior vena caval occlusion was
released immediately after recording of the waveforms.
Abrupt alteration of preload did not cause a change in
heart rate in any experiment.

In one group of experiments, levosimendan was ad-
ministered in the conscious state after pharmacologic
blockade of the autonomic nervous system had been
completed. Control systemic and coronary hemody-
namics and left ventricular pressure-segment length
waveforms and diagrams were recorded. Intravenous
infusions of levosimendan at 0.5, 1.0, 2.0, or 4.0
µg·kg⁻¹·min⁻¹ (1.8, 3.6, 7.2, or 14.3 nmol·kg⁻¹·
min⁻¹) were then administered in a random fashion.
Hemodynamics were recorded, and left ventricular
pressure-segment length waveforms and diagrams were
obtained using the techniques described above after 10
min of equilibration at each dose of levosimendan.
The infusion rate of levosimendan was then changed,
and measurements were repeated after a similar period
of equilibration.

Levosimendan was also administered to autononi-
cally blocked dogs anesthetized with isoflurane or
halothane in two other groups of experiments on sep-
itate days. After autonomic nervous system blockade,
inhalation induction, and tracheal intubation, anes-
thesia was maintained with 1.0 MAC (end-tidal con-
centration) isoflurane or halothane in a nitrogen (75%)
and oxygen (25%) mixture via positive pressure ven-
tilation. The canine MAC values for isoflurane and
halothane used in this investigation were 1.28% and
0.86%, respectively. End-tidal concentrations of isoflu-
rane and halothane were measured using a mass spec-
trometer (Advantage 2000, Marquette, St. Louis, MO).
The mass spectrometer was calibrated using known
standards before and during experimentation. Systemic
and coronary hemodynamics were recorded, and left
ventricular pressure-segment length waveforms and
diagrams were generated and stored on the digital osci-
silloscope after a 30-min equilibration period in the
anesthetized state. Intravenous infusions of levosimen-
dan (0.5, 1.0, 2.0, or 4.0 µg·kg⁻¹·min⁻¹) were ad-
ministered in a random fashion, and data was recorded
as described above. Each dog was allowed to recover
from anesthesia and autonomic nervous system block-
ade for 3 days prior to subsequent experimentation. A
total of 24 experiments in three groups (levosimendan
administered in the conscious state and during isoflu-
rane or halothane anesthesia) were completed in which
the same eight dogs were used.

Drugs

Propranolol hydrochloride, atropine methyl nitrate,
and hexamethonium bromide were purchased from
Sigma Chemical Company, St Louis, MO and were dis-
solved in 0.9% normal saline. Levosimendan was gen-
erously donated by Orion-Farmos Pharmaceuticals,
Espoo, Finland. The drug vehicle for levosimendan con-
sisted of 25% ethanol (95%), 25% polyethylene glycol
(5%), and 50% normal saline. No hemodynamic effects
were produced the drug vehicle as previously de-
scribed. 34

Calculation of Indices of Systolic and Diastolic
Left Ventricular Function

The slope of the regional preload recruitable stroke
work relation (Mₜ₀) was used to determine myocardial
contractility. 35 A series of left ventricular pressure-seg-
ment length diagrams were obtained by transient con-
striction of the inferior vena cava in the conscious or
anesthetized state and during each dose of levosimen-
dan. The area of each diagram, corresponding to seg-
mental stroke work, was plotted against the corre-
sponding EDL for each loop, and linear regression anal-
ysis was used to determine Mₜ₀ and the length intercept

Anesthesiology, V 81, No 4, Oct 1994
Table 1. Hemodynamic Effects of Levosimendan in Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Conscious Control</th>
<th>ANS Blockade</th>
<th>Levosimendan Infusion (µg · kg⁻¹ · min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>8</td>
<td>74 ± 6*</td>
<td>116 ± 4</td>
<td>120 ± 4</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>8</td>
<td>97 ± 4*</td>
<td>79 ± 5</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>RPP (mmHg · bpm · 10⁶)</td>
<td>8</td>
<td>9.8 ± 0.5</td>
<td>10.8 ± 0.4</td>
<td>11.1 ± 0.8</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>8</td>
<td>126 ± 5*</td>
<td>96 ± 4</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>8</td>
<td>10 ± 2</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>DCBFV (Hz · 10⁶)</td>
<td>7</td>
<td>54 ± 5</td>
<td>56 ± 5</td>
<td>61 ± 6</td>
</tr>
<tr>
<td>DCVR (mmHg · Hz⁻¹ · 10⁻⁹)</td>
<td>7</td>
<td>1.61 ± 0.19*</td>
<td>1.33 ± 0.18</td>
<td>1.16 ± 0.14</td>
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<tr>
<td>EDL (mm)</td>
<td>8</td>
<td>14.8 ± 0.7</td>
<td>14.6 ± 0.7</td>
<td>14.4 ± 0.6</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>8</td>
<td>11.7 ± 0.5</td>
<td>11.7 ± 0.6</td>
<td>11.5 ± 0.5</td>
</tr>
<tr>
<td>SS (%)</td>
<td>8</td>
<td>20.9 ± 2.0</td>
<td>20.0 ± 1.7</td>
<td>19.9 ± 1.6</td>
</tr>
<tr>
<td>CO (l · min⁻¹)</td>
<td>7</td>
<td>2.5 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>2.9 ± 0.2</td>
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<tr>
<td>SVR (dyne · s · cm⁻²)</td>
<td>7</td>
<td>3,150 ± 220*</td>
<td>2,160 ± 130</td>
<td>2,080 ± 170</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>7</td>
<td>35 ± 4*</td>
<td>25 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>PWI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>7</td>
<td>8.8 ± 0.6</td>
<td>9.2 ± 0.6</td>
<td>9.2 ± 0.7</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

HR = heart rate; MBP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; ANS = autonomic nervous system; PWI = pressure work index.

* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from 0.5 µg · kg⁻¹ · min⁻¹ levosimendan infusion.
§ Significantly (P < 0.05) different from 1.0 µg · kg⁻¹ · min⁻¹ levosimendan infusion.
‡ Significantly (P < 0.05) different from 2.0 µg · kg⁻¹ · min⁻¹ levosimendan infusion.

of the preload recruitable stroke work relation (Lwₐ): segmental stroke work = Mw · (EDL − Lw). The time constant of isovolumic relaxation (τ) was determined assuming a nonzero asymptote of left ventricular pressure decay. The maximum segment lengthening velocity during rapid ventricular filling (dL/dtₐₚₚ) was determined by differentiation of the continuous segment length waveform. The regional chamber stiffness constant (Kₕ) was derived from left ventricular pressure-segment length data between minimum ventricular pressure and the beginning of atrial systole using a monoexponential relation assuming a simple elastic model.

**Statistical Analysis**

Statistical analysis of the data within and between groups in the conscious state with and without blockade of the autonomic nervous system, during anesthetic interventions, and during multiple doses of levosimendan was performed by multiple analysis of variance (MANOVA) with repeated measures, followed by use of the student's t test with Bonferroni's correction. Changes were considered to be statistically significant when the probability (P) value was < 0.05. All data are expressed as mean ± SEM.

**Results**

Autonomic nervous system blockade caused significant (P < 0.05) increases in heart rate and decreases in mean arterial pressure, left ventricular systolic pressure, systemic vascular resistance, diastolic coronary vascular resistance and stroke volume. No changes in left ventricular end-diastolic pressure, cardiac output, diastolic coronary blood flow velocity, rate pressure product, or pressure-work index were observed (tables 1–3). There were no differences in baseline systemic or coronary hemodynamics with or without autonomic nervous system blockade among groups.

Administration of levosimendan to conscious dogs produced significant and dose-related increases in heart rate and diastolic coronary blood flow velocity and decreases in diastolic coronary vascular resistance, ESL, and EDL (table 1). Significant increases in cardiac output, rate-pressure product, pressure-
Table 2. Hemodynamic Effects of Levosimendan in Isoflurane-Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Conscious Control</th>
<th>ANS Blockade</th>
<th>Isoflurane (1.0 MAC)</th>
<th>Levosimendan Infusion (µg·kg⁻¹·min⁻¹)</th>
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<td></td>
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<td>1.0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>8</td>
<td>82 ± 5⁺</td>
<td>108 ± 4</td>
<td>90 ± 5⁺</td>
<td>89 ± 4⁺</td>
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<tr>
<td></td>
<td>8</td>
<td>100 ± 5</td>
<td>77 ± 2</td>
<td>63 ± 3⁺</td>
<td>65 ± 3⁺</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>10.3 ± 0.8</td>
<td>9.9 ± 0.4</td>
<td>6.8 ± 0.5⁺</td>
<td>6.9 ± 0.5⁺</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>127 ± 5⁺</td>
<td>93 ± 3</td>
<td>77 ± 3</td>
<td>78 ± 3⁺</td>
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<tr>
<td></td>
<td>8</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
<td>7 ± 1</td>
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<tr>
<td></td>
<td>8</td>
<td>53 ± 3</td>
<td>52 ± 4</td>
<td>36 ± 4</td>
<td>56 ± 4</td>
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<tr>
<td>DCBFV (mL·min⁻¹·10⁻³)</td>
<td>7</td>
<td>1.55 ± 0.15⁺</td>
<td>1.37 ± 0.11</td>
<td>1.01 ± 0.07⁺</td>
<td>1.04 ± 0.06⁺</td>
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<tr>
<td></td>
<td>7</td>
<td>13.9 ± 0.4</td>
<td>13.5 ± 0.4</td>
<td>13.0 ± 0.4</td>
<td>12.8 ± 0.4</td>
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<tr>
<td></td>
<td>8</td>
<td>11.1 ± 0.4</td>
<td>11.0 ± 0.5</td>
<td>10.6 ± 0.4</td>
<td>10.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>20.1 ± 2.0</td>
<td>19.0 ± 1.9</td>
<td>18.1 ± 1.7</td>
<td>18.8 ± 2.1</td>
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<td>2.8 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>2.0 ± 0.2⁺</td>
<td>2.0 ± 0.2⁺</td>
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<tr>
<td></td>
<td>7</td>
<td>2,900 ± 120⁺</td>
<td>2,410 ± 170</td>
<td>2,680 ± 260</td>
<td>2,750 ± 200</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>32 ± 2⁺</td>
<td>24 ± 2</td>
<td>22 ± 2</td>
<td>22 ± 2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>9.1 ± 0.8</td>
<td>8.5 ± 0.3</td>
<td>6.2 ± 0.4⁺</td>
<td>6.2 ± 0.4⁺</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>1.30 ± 0.01</td>
<td>1.30 ± 0.01</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

HR = heart rate; MBP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = diastolic coronary blood flow velocity; DCFV = diastolic coronary vascular resistance; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; ANS = autonomic nervous system; PwI = pressure-work index; ET = end-tidal isoflurane concentration.

* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from isoflurane alone.
§ Significantly (P < 0.05) different from 0.5 µg·kg⁻¹·min⁻¹ levosimendan infusion.
‡ Significantly (P < 0.05) different from 1.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.

work index, and %SS and decreases in left ventricular systolic pressure, left ventricular end-diastolic pressure, and systemic vascular resistance were observed at the 4.0 µg·kg⁻¹·min⁻¹ dose of levosimendan. No changes in mean arterial pressure or stroke volume were observed. Levosimendan increased myocardial contractility in a dose-dependent manner (Mw 65 ± 6 during control to 139 ± 9 mmHg at 4.0 µg·kg⁻¹·min⁻¹) in conscious dogs (table 4). No significant change in Lw occurred. Concomitant increases in +dP/dtmax were also observed (1929 ± 84 during control to 2865 ± 205 mmHg·s⁻¹ at 4.0 µg·kg⁻¹·min⁻¹). No alterations in τ (38 ± 1 during control to 35 ± 2 ms at 4.0 µg·kg⁻¹·min⁻¹) and −dP/dtmin (−1838 ± 90 during control to −1667 ± 76 mmHg·s⁻¹ at 4.0 µg·kg⁻¹·min⁻¹) were observed, indicating that this phase of diastole was unaltered by administration of levosimendan. Dose-related increases in dI/dtmax (34 ± 3 during control to 47 ± 5 mm·s⁻¹ at 4.0 µg·kg⁻¹·min⁻¹) occurred, consistent with enhanced early ventricular filling. Kp was unchanged by levosimendan, suggesting that chamber compliance was not affected by the myofilament Ca²⁺ sensitizer in conscious dogs (table 4).

Isoflurane anesthesia (1.0 MAC) caused decreases in heart rate, mean arterial pressure, left ventricular systolic pressure, diastolic coronary vascular resistance, cardiac output, rate-pressure product, and pressure-work index in the presence of autonomic nervous system blockade. No changes in left ventricular end-diastolic pressure, diastolic coronary blood flow velocity, systemic vascular resistance, %SS, or stroke volume were observed (table 2). The hemodynamic effects of halothane were similar to those produced by isoflurane (table 3). In contrast to isoflurane, however, 1.0 MAC halothane caused a significant decrease in %SS. Isoflurane and halothane depressed myocardial contractility (decreases in Mw and +dP/dtmax), prolonged isovolumic relaxation (increase in τ and decrease in the magnitude of −dP/dtmin), and impaired rapid ventricular filling (decrease in dI/dtmax) without alteration in Kp (tables 5 and 6, respectively). No changes in Lw were observed during anesthesia. Halothane caused significantly greater negative inotropic effects than isoflurane at 1.0 MAC (Mw of 38 ± 3 for halothane compared to 57 ± 4 mmHg for isoflurane); however, no differences in indices of diastolic function were noted during halothane and isoflurane anesthesia.
Table 3. Hemodynamic Effects of Levosimendan in Halothane-Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>Conscious Control</th>
<th>ANS Blockade</th>
<th>Halothane (1.0 MAC)</th>
<th>Levosimendan Infusion (µg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>8</td>
<td>83 ± 5*</td>
<td>107 ± 5</td>
<td>89 ± 5*</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>8</td>
<td>102 ± 4*</td>
<td>77 ± 3</td>
<td>63 ± 4*</td>
</tr>
<tr>
<td>RPP (mmHg·bpm⁻¹·10⁶)</td>
<td>8</td>
<td>10.6 ± 0.7</td>
<td>9.7 ± 0.5</td>
<td>6.7 ± 0.6*</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>8</td>
<td>128 ± 5*</td>
<td>94 ± 5</td>
<td>76 ± 4*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>8</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>DCBVF (Hz·10⁻²)</td>
<td>7</td>
<td>53 ± 5</td>
<td>54 ± 5</td>
<td>51 ± 5</td>
</tr>
<tr>
<td>DCVR (mmHg·H⁻¹·10⁻⁶)</td>
<td>7</td>
<td>1.67 ± 0.15*</td>
<td>1.31 ± 0.13</td>
<td>1.16 ± 0.13</td>
</tr>
<tr>
<td>EDL (mm)</td>
<td>8</td>
<td>14.6 ± 0.7</td>
<td>14.4 ± 0.6</td>
<td>14.0 ± 0.7</td>
</tr>
<tr>
<td>ESL (mm)</td>
<td>8</td>
<td>11.5 ± 0.7</td>
<td>11.7 ± 0.5</td>
<td>11.8 ± 0.6</td>
</tr>
<tr>
<td>SS(%)</td>
<td>8</td>
<td>20.7 ± 1.3</td>
<td>18.7 ± 1.1</td>
<td>15.7 ± 1.0*</td>
</tr>
<tr>
<td>CO (l·min⁻¹)</td>
<td>7</td>
<td>2.7 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td>2.0 ± 0.3*</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻¹)</td>
<td>7</td>
<td>3,020 ± 240*</td>
<td>2,180 ± 220</td>
<td>2,680 ± 330</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>7</td>
<td>35 ± 6*</td>
<td>27 ± 3</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>PVRI (ml·m⁻¹·100·g⁻¹)</td>
<td>7</td>
<td>9.6 ± 0.5</td>
<td>8.5 ± 0.5</td>
<td>6.0 ± 0.6*</td>
</tr>
<tr>
<td>ET (%)</td>
<td>8</td>
<td>—</td>
<td>0.89 ± 0.01</td>
<td>0.89 ± 0.01</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

HR = heart rate; MBP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; EDL and ESL = end-diastolic and end-systolic segment length, respectively; SS = segment shortening; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; ANS = autonomic nervous system; PWI = pressure work index; ET = end-tidal halothane concentration.

* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from halothane alone.
‡ Significant (P < 0.05) different from 0.5 µg·kg⁻¹·min⁻¹ levosimendan infusion.
§ Significant (P < 0.05) different from 1.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.
‖ Significant (P < 0.05) different from 2.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.

Levosimendan caused changes in systemic and coronary hemodynamics during isoflurane and halothane anesthesia which were qualitatively similar to those observed in the conscious state (tables 2 and 3, respectively). Levosimendan decreased diastolic coronary and systemic vascular resistances, left ventricular end-diastolic pressure, EDL, and ESL and increased diastolic coronary blood flow velocity and %SS in isoflurane-

Table 4. Effects of Levosimendan on Indices of Left Ventricular Function in Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>ANS Blockade</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>65 ± 6</td>
<td>67 ± 3</td>
<td>80 ± 5*</td>
<td>102 ± 9†§</td>
</tr>
<tr>
<td>Lw (mm)</td>
<td></td>
<td>10.4 ± 0.6</td>
<td>10.3 ± 0.6</td>
<td>10.8 ± 0.6</td>
<td>10.7 ± 0.6</td>
</tr>
<tr>
<td>+dP/dtmax (mmHg·s⁻¹)</td>
<td></td>
<td>1,929 ± 84</td>
<td>1,933 ± 88</td>
<td>2,059 ± 106</td>
<td>2,432 ± 148†§</td>
</tr>
<tr>
<td>τ (ms)</td>
<td></td>
<td>-1,808 ± 90</td>
<td>-1,810 ± 112</td>
<td>-1,912 ± 114</td>
<td>-1,825 ± 139</td>
</tr>
<tr>
<td>Kp (mm⁻¹)</td>
<td></td>
<td>0.36 ± 0.03</td>
<td>0.32 ± 0.03</td>
<td>0.32 ± 0.03</td>
<td>0.31 ± 0.04</td>
</tr>
<tr>
<td>dL/dtmax (mm·s⁻¹)</td>
<td></td>
<td>34 ± 3</td>
<td>37 ± 5</td>
<td>38 ± 4</td>
<td>44 ± 5*</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; n = 8.

Lw and Lw = preload recruitable stroke work slope and length intercept, respectively; SS = segment shortening; τ = time constant of isovolumic relaxation; k = regional chamber stiffness; ANS = autonomic nervous system.

* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from 0.5 µg·kg⁻¹·min⁻¹ levosimendan infusion.
‡ Significant (P < 0.05) different from 1.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.
§ Significant (P < 0.05) different from 2.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.

Anesthesiology, V 81, No 4, Oct 1994
LEVOSIMENDAN AND LEFT VENTRICULAR FUNCTION

Table 5. Effects of Levosimendan on Indices of Left Ventricular Function in Isoflurane-anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>ANS Blockade</th>
<th>Isoflurane (1.0 MAC)</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mw (mmHg)</strong></td>
<td>72 ± 5</td>
<td>57 ± 4*</td>
<td>66 ± 5</td>
<td>77 ± 6†</td>
<td>96 ± 7†‡§</td>
<td>116 ± 12†‡§</td>
</tr>
<tr>
<td>Lw (mm)</td>
<td>10.2 ± 0.6</td>
<td>10.1 ± 0.5</td>
<td>8.9 ± 1.2</td>
<td>10.2 ± 0.5</td>
<td>10.1 ± 0.5</td>
<td>10.1 ± 0.8</td>
</tr>
<tr>
<td>+dP/dtmax (mmHg·s⁻¹)</td>
<td>1,935 ± 67</td>
<td>1,637 ± 76*</td>
<td>1,671 ± 55*</td>
<td>1,770 ± 54</td>
<td>2,040 ± 84§</td>
<td>2,317 ± 160†‡§</td>
</tr>
<tr>
<td>-dP/dtmin (mmHg·s⁻¹)</td>
<td>-1,837 ± 62</td>
<td>-1,317 ± 80*</td>
<td>-1,327 ± 63*</td>
<td>-1,278 ± 80*</td>
<td>-1,254 ± 91*</td>
<td>-1,208 ± 81*</td>
</tr>
<tr>
<td>τ (ms)</td>
<td>38 ± 1</td>
<td>44 ± 2*</td>
<td>45 ± 1*</td>
<td>44 ± 2*</td>
<td>43 ± 2*</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>Kp (mm⁻¹)</td>
<td>0.45 ± 0.06</td>
<td>0.41 ± 0.07</td>
<td>0.39 ± 0.05</td>
<td>0.37 ± 0.06</td>
<td>0.30 ± 0.05</td>
<td>0.29 ± 0.05</td>
</tr>
<tr>
<td>dL/dtmax (mm·s⁻¹)</td>
<td>34 ± 2</td>
<td>27 ± 3*</td>
<td>28 ± 3*</td>
<td>29 ± 3</td>
<td>33 ± 3</td>
<td>34 ± 3‡§</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; n = 8.
Mw and Lw = preload recruitable stroke work slope and length intercept, respectively; SS = segment shortening; τ = time constant of isovolumic relaxation; Kp = regional chamber stiffness constant; ANS = autonomic nervous system.
* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from isoflurane.
§ Significantly (P < 0.05) different from 0.5 µg·kg⁻¹·min⁻¹ levosimendan infusion.
‡ Significantly (P < 0.05) different from 1.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.

halothane-anesthetized dogs. Levosimendan significantly increased heart rate in the presence of isoflurane but not halothane. In contrast to the findings in the conscious state, levosimendan decreased mean arterial pressure and did not change calculated estimates of myocardial oxygen consumption (rate-pressure product and pressure-work index) in anesthetized dogs. Levosimendan enhanced myocardial contractility in a dose-related manner during anesthesia (Mw 57 ± 4 and 38 ± 3 during isoflurane and halothane alone to 116 ± 12 and 92 ± 8 mmHg at 4.0 µg·kg⁻¹·min⁻¹, respectively; tables 5 and 6). No changes in Lw were observed. Differences in contractile state between isoflurane and halothane groups were maintained during levosimendan infusions; however, relative increases in Mw produced by levosimendan were similar in both conscious and anesthetized dogs (fig. 3). No alterations in τ or -dP/dtmin were produced by levosimendan during isoflurane or halothane anesthesia. Despite the lack of change in indices of isovolumic relaxation, levosimendan enhanced rapid ventricular filling (e.g., 27 ± 3 during isoflurane alone to 34 ± 3 mm·s⁻¹ at 4.0

Table 6. Effects of Levosimendan on Indices of Left Ventricular Function in Halothane-anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>ANS Blockade</th>
<th>Halothane (1.0 MAC)</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mw (mmHg)</strong></td>
<td>66 ± 7</td>
<td>38 ± 3*</td>
<td>47 ± 6*</td>
<td>56 ± 6†</td>
<td>75 ± 7†‡§</td>
<td>92 ± 8†‡§</td>
</tr>
<tr>
<td>Lw (mm)</td>
<td>10.5 ± 0.6</td>
<td>10.4 ± 0.7</td>
<td>10.8 ± 0.7</td>
<td>10.7 ± 0.7</td>
<td>10.8 ± 0.7</td>
<td>10.7 ± 0.7</td>
</tr>
<tr>
<td>+dP/dtmax (mmHg·s⁻¹)</td>
<td>1,828 ± 79</td>
<td>1,211 ± 76*</td>
<td>1,246 ± 80*</td>
<td>1,312 ± 90*</td>
<td>1,514 ± 106§</td>
<td>1,734 ± 145†‡§</td>
</tr>
<tr>
<td>-dP/dtmin (mmHg·s⁻¹)</td>
<td>-1,758 ± 96</td>
<td>-1,240 ± 97*</td>
<td>-1,246 ± 92*</td>
<td>-1,252 ± 98*</td>
<td>-1,272 ± 105*</td>
<td>-1,198 ± 107*</td>
</tr>
<tr>
<td>τ (ms)</td>
<td>38 ± 1</td>
<td>48 ± 2</td>
<td>47 ± 2*</td>
<td>45 ± 2*</td>
<td>43 ± 2</td>
<td>43 ± 2</td>
</tr>
<tr>
<td>Kp (mm⁻¹)</td>
<td>0.47 ± 0.09</td>
<td>0.45 ± 0.06</td>
<td>0.46 ± 0.07</td>
<td>0.40 ± 0.05</td>
<td>0.34 ± 0.05</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td>dL/dtmax (mm·s⁻¹)</td>
<td>32 ± 2</td>
<td>24 ± 1*</td>
<td>25 ± 1*</td>
<td>28 ± 1*</td>
<td>28 ± 2*</td>
<td>33 ± 2†‡§</td>
</tr>
</tbody>
</table>

Data are mean ± SEM; n = 8.
Mw and Lw = preload recruitable stroke work slope and length intercept, respectively; SS = segment shortening; τ = time constant of isovolumic relaxation; Kp = regional chamber stiffness constant; ANS = autonomic nervous system.
* Significantly (P < 0.05) different from ANS blockade.
† Significantly (P < 0.05) different from halothane.
§ Significantly (P < 0.05) different from 0.5 µg·kg⁻¹·min⁻¹ levosimendan infusion.
‡ Significantly (P < 0.05) different from 1.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.
†† Significantly (P < 0.05) different from 2.0 µg·kg⁻¹·min⁻¹ levosimendan infusion.

Anesthesiology, V 81, No 4, Oct 1994
inhibition of sarcolemmal Na\(^{+}\)-K\(^{+}\) adenosine triphosphatase activity, receptor-mediated stimulation of the adenylate cyclase–cyclic adenosine monophosphate (cAMP) pathway, and blockade of cAMP degradation, respectively. In contrast, drugs in the myofilament Ca\(^{2+}\)-sensitizing class directly augment contractile force by increasing the affinity of the regulatory site of troponin C for Ca\(^{2+}\) in a highly stereospecific manner. 3-6,59 This effect stabilizes Ca\(^{2+}\)-induced conformational changes in troponin C and allows for prolonged systolic interaction of actin and myosin filaments. 5,6 Thus, these cardiotonic drugs enhance contractile performance by modulating the response of the myofilament regulatory proteins 1-6,59 or the contractile elements 50 to Ca\(^{2+}\) without specifically altering the intracellular concentration of this ion.

Myofilament Ca\(^{2+}\)-sensitizing agents may also possess PDE-III–inhibiting activity which contribute 5,59 but do not entirely account for the positive inotropic effects of these compounds via cAMP-induced, protein kinase A–mediated phosphorylation of the voltage-dependent Ca\(^{2+}\) channel. Inhibition of PDE-III by myofilament Ca\(^{2+}\) sensitizers may also result in positive lusitropic (relaxation) effects through direct intracellular mechanisms, including PDE-III–mediated, protein kinase A–induced promotion of Ca\(^{2+}\) dissociation from troponin C and increased sarcoplasmic reticular Ca\(^{2+}\)–adenosine triphosphatase function via phosphorylation of troponin I and phospholamban, respectively. Positive lusitropic actions induced by these agents may also be mediated by indirect systemic hemodynamic effects resulting from improved left ventricular loading conditions via PDE-III–induced venodilation and vasodilation. 1,18,41-43 Thus, shortened isovolumic relaxation may occur with myofilament Ca\(^{2+}\) sensitizers with PDE-III activity despite the primary increases in Ca\(^{2+}\) binding to troponin C resulting from these agents. These positive lusitropic effects may be particularly important because impaired left ventricular relaxation frequently occurs in end-stage heart failure, resulting from delayed Ca\(^{2+}\) clearance from the sarcoplasm and, subsequently, diminished restoration of submicromolar Ca\(^{2+}\) concentrations during diastole. 1,44,45

The effects of myofilament Ca\(^{2+}\) sensitizers, including pimobendan and sulmazole, on systemic and coronary hemodynamics, myocardial oxygen consumption, and left ventricular pump performance have been examined in experimental animals and humans. Several investigators have described increases in cardiac index, \(+\Delta\rho/\Delta t_{\text{max}}\), and ejection fraction with concomitant decreases
in left ventricular preload (end-diastolic pressure or wall stress) and afterload (calculated systemic vascular resistance or end-systolic wall stress) after administration of pimobendan to patients with severe congestive heart failure resulting from chronic ischemia or idiopathic dilated cardiomyopathy. \textsuperscript{7–15,46,47} These effects were often accompanied by decreases in myocardial oxygen consumption and increases in exercise duration and capacity, peak oxygen uptake, and the ratio of myocardial oxygen supply to demand.\textsuperscript{10,11,13,44} Favorable improvements in myocardial energetics presumably resulted from reductions in left ventricular preload and afterload. Decreases in circulating endogenous catecholamines and an enhanced response to $\beta$-adrenoceptor stimulation have also been observed with chronic pimobendan treatment.\textsuperscript{5,9,48} Findings which suggest that pimobendan may indirectly reverse $\beta$-receptor down regulation associated with congestive heart failure. Pimobendan increased the magnitude of $-dP/dt_{\text{min}}$ in patients with left ventricular dysfunction consistent with a positive lusitropic effect.\textsuperscript{12} This improvement in $-dP/dt_{\text{min}}$ may have occurred because of the direct PDE-III–inhibiting effects of pimobendan or may have been caused by indirect actions of the drug on ventricular loading conditions, enhanced $\beta$-adrenoceptor responsiveness to circulating catecholamines, or reflex effects mediated by intact autonomic nervous system function, however. Another myofilament $Ca^{2+}$ sensitizer which has been less extensively studied, sulmazole, has been reported to cause systemic hemodynamic effects and left ventricular mechanical actions in patients with coronary artery disease which are similar to those produced by pimobendan.\textsuperscript{16,17} The current investigation is the first to examine the interactions between a drug in the myofilament $Ca^{2+}$-sensitizing class of positive inotropic agents and volatile anesthetics. The results indicate that levsimendan causes systemic and coronary hemodynamic effects in the absence of autonomic nervous system tone which are qualitatively similar to those produced by pimobendan and sulmazole in patients with congestive heart failure. A dose-related increase in heart rate was observed during administration of levsimendan to conscious dogs with blockade of the autonomic nervous system, indicating that levsimendan may cause direct increases in heart rate independent of autonomic reflexes. Kitzen \textit{et al.} observed increases in heart rate with pimobendan which resulted from direct increases in atrioventricular nodal conduction and decreases in effective ventricular refractory period in barbiturate-anesthetized, acutely instrumented dogs.\textsuperscript{60} Pimobendan-induced tachycardia has also been reported in open-chest pigs with and without pretreatment with propranolol, excluding activity at the $\beta$-adrenoceptor as a potential mechanism for the increases in heart rate.\textsuperscript{48} Levsimendan-induced increases in heart rate were also observed during isoflurane but not halothane anesthesia in the current study, suggesting that the direct negative chronotropic effects of halothane\textsuperscript{50} may differentially antagonize the positive chronotropic actions of levsimendan.

Levsimendan caused decreases in left ventricular systolic and end-diastolic pressures in conscious and anesthetized dogs. Concomitant declines in ESL and calculated systemic vascular resistance, and decreases in EDL also occurred, suggesting that the myofilament $Ca^{2+}$ sensitizer causes a reduction in left ventricular preload and afterload, respectively, via dilatation of the venous and arterial vasculature. The current findings in autonomicomically blocked dogs are similar to the results of several previous studies which reported decreases in left ventricular end-systolic and end-diastolic pressure, volume and wall stress with administration of pimobendan\textsuperscript{7–12,14,46,47} or sulmazole\textsuperscript{16,17} to patients with congestive heart failure, observations which have been attributed to the PDE-III–inhibiting activity of these agents.

The rate-pressure product and pressure-work index increased only at the highest dose of levsimendan in conscious dogs and did not change during isoflurane and halothane anesthesia, indicating that levsimendan has little, if any, direct effect on calculated estimates of myocardial oxygen consumption. These results probably occurred because levsimendan-induced increases in heart rate and myocardial contractility were offset by concomitant declines in left ventricular preload and afterload. The current findings in autonomicomically blocked dogs are consistent with the relative maintenance or modest reduction of myocardial oxygen consumption observed in response to pimobendan in humans with compromised left ventricular function.\textsuperscript{10,11,13,47} Levsimendan caused declines in diastolic coronary vascular resistance and concomitant increases in peak diastolic coronary blood flow velocity at higher doses in conscious and anesthetized dogs. These alterations in coronary hemodynamics occurred without parallel changes in calculated myocardial oxygen consumption, suggesting that levsimendan may also produce direct coronary vasodilation. Although the pressure-work index has been shown to accurately reflect

\textit{Anesthesiology, V 81, No 4, Oct 1994}
alterations in measured myocardial oxygen consumption over a wide range of heart rates, ventricular loading conditions, and contractile states, coronary sinus oxygen tension and myocardial oxygen consumption were not specifically measured in the current investigation. Similar increases in coronary blood flow, measured using an electromagnetic flow probe or with the radioactive microsphere technique, without changes in myocardial oxygen consumption have been previously reported for pimobedan in acutely instrumented dogs and pigs, respectively.

The results of the current investigation indicate that levosimendan has important functional actions on left ventricular systolic and diastolic mechanical performance. Levosimendan caused dose-dependent increases in myocardial contractility in the conscious and anesthetized states as assessed using Mw, derived from a series of left ventricular pressure-segment length diagrams, an easily quantified and relatively heart rate- and load-independent index of contractility in vivo. No changes in Lw occurred with any intervention, indicating that changes in myocardial contractility were reflected solely by changes in Mw. Levosimendan did not alter measures of isovolumic relaxation including τ and \[-dP/dt_{\min}\], indicating that levosimendan did not affect this phase of diastole. Increases in the dL/dt}_{max} were observed during administration of levosimendan to conscious and anesthetized dogs, demonstrating an improvement in rapid ventricular filling. No changes in Kp were observed during the conscious or anesthetized states, suggesting that levosimendan does not alter regional ventricular compliance.

The current results contrast with those observed with amrinone, a specific cardiac PDE-III inhibitor without myofilament Ca\(^{2+}\)-sensitizing activity, was administered in a previous investigation from this laboratory using the identical canine model. Amrinone produced dose-related increases in Mw and decreases in τ in conscious and anesthetized dogs. The positive inotropic effects of amrinone, resulting from increases in total cytosolic Ca\(^{2+}\) during systole via increased voltage-dependent Ca\(^{2+}\) channel conductance, did not lead to simultaneous alterations in Ca\(^{2+}\) clearance during diastole because amrinone also stimulated Ca\(^{2+}\) dissociation from the contractile apparatus and facilitated Ca\(^{2+}\) uptake into the sarcoplasmic reticulum via cAMP-mediated mechanisms. In contrast, increases in Mw caused by levosimendan were not accompanied by similar reductions in τ in either the conscious or anesthetized states. A lack of change in τ during the administration of le-
in this gradient caused by levosimendan or volatile anesthetics may have influenced the observed changes in dI/dt\text{max}. Passive ventricular elastic properties may have also been influenced by alterations in ventricular loading conditions and contractile state produced by levosimendan or anesthetics and may have contributed to the lack of changes in K\text{m} observed during the administration of these agents.54

In summary, the results of this investigation indicate that levosimendan, a new myofilament Ca\textsuperscript{2+} sensitizer, produces direct positive inotropic effects as evaluated using regional M\text{w}, in conscious and anesthetized, chronically instrumented dogs. Levosimendan also improved rapid ventricular filling in a dose-related fashion as indicated by dI/dt\text{max}. Despite causing increases in myocardial contractility and rapid ventricular filling, however, levosimendan did not alter indices of left ventricular isovolumetric relaxation. This finding indicates that levosimendan selectivity enhances contractile state and filling without affecting diastolic relaxation (lusitropic state). The current results are in contrast to the findings obtained with amrinone,\textsuperscript{52} an inhibitor of cardiac PDE-III without myofilament Ca\textsuperscript{2+}-sensitization characteristics, suggesting that the enhanced affinity of troponin C for Ca\textsuperscript{2+} caused by levosimendan was contributing to a relative delay in Ca\textsuperscript{2+} dissociation from the contractile apparatus during early diastole that could not be completely overcome by the PDE-III-inhibiting activity of the drug.

The authors thank John Tessmer and David Schwabe for excellent technical assistance and Lasse Lehtonen, M.D., Ph.D., L.M.M., and Heimo Haikala, Ph.D., of Orion-Farmos Pharmaceuticals for the generous supply of levosimendan.

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Anesthesiology, V 81, No 4, Oct 1994
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