Oxygen-Wasting Effect of Inotropy
Is There a Need for a New Evaluation? An Experimental Large-Animal Study Using Dobutamine and Levosimendan

Stig Müller, MD, PhD; Ole-Jakob How, PhD; Øyvind Jakobsen, MD; Stig Eggen Hermansen, MD; Assami Røsner, MD; Thor Allan Stenberg, MD; Truls Myrmel, MD, PhD

Background—We addressed the hypothesis that the inotropic drugs dobutamine and levosimendan both induce surplus oxygen consumption (oxygen wasting) relative to their contractile effect in equipotent therapeutic doses, with levosimendan being energetically more efficient.

Methods and Results—Postischemically reduced left ventricular function (stunning) was created by repetitive left coronary occlusions in 22 pigs. This contractile dysfunction was reversed by infusion of either levosimendan (24 μg/kg loading and 0.04 μg·kg⁻¹·min⁻¹ infusion) or an equipotent dose of dobutamine (1.25 μg·kg⁻¹·min⁻¹). Contractility and cardiac output were normalized by both drug regimens. The energy cost of drug-induced contractility enhancement was assessed by myocardial oxygen consumption related to the mechanical indexes tension-time index, pressure-volume area, and total mechanical energy. ANCOVA did not reveal any increased oxygen cost of contractility for either drug in these doses. However, both dobutamine and levosimendan at supratherapeutic levels (10 μg·kg⁻¹·min⁻¹ and 48 μg/kg loading with 0.2 μg·kg⁻¹·min⁻¹ infusion, respectively) induced a highly significant increase in oxygen consumption related to mechanical work, compatible with the established oxygen-wasting effect of inotropy (P<0.001 for all mechanical indexes with dobutamine; P=0.007 for levosimendan as assessed by pressure-volume area).

Conclusion—Therapeutic levels of neither dobutamine nor levosimendan showed inotropic oxygen wasting in this in vivo pig model. Thus, relevant hemodynamic responses can be achieved with an adrenergic inotrope without surplus oxygen consumption. (Circ Heart Fail. 2010;3:277-285.)

Key Words: contractility ■ stunning, myocardial ■ inotropic agents ■ metabolism ■ oxygen

The oxygen-wasting effect of inotropic agents has been established as an energetic principle in the studies of contractility-enhancing drugs. In particular, adrenergic compounds have been shown to disproportionately increase the oxygen consumption of the myocardium, possibly owing to increased energy requirements related to intracellular calcium handling. This oxygen cost of contractility has been regarded as detrimental in the ischemic and failing myocardium. The theoretically unwanted side effect of these drugs has led to the search for alternatives with better pharmacodynamic profiles. Thus, the calcium sensitizers, by enhancing the calcium effect on the myofilaments, in theory should contribute to an increased contractility with relatively less energy consumption. With these drugs, a more efficient actinomyosin coupling can be induced with less calcium handling.

Clinical Perspective on p 285
Levosimendan is a calcium sensitizer that has been advanced to clinical use, and initial clinical trials indicated improved survival in patients with acute heart failure who were treated with this drug compared with an established alternative, namely, dobutamine. However, although a few studies have assessed the oxygen-consuming effects of levosimendan, no studies have adequately addressed the energetic profile of this drug in clinically relevant doses in an in vivo model. Despite this fact, a relative oxygen-sparing effect has been proposed as a possible explanation for the initially observed survival advantages compared with dobutamine.

There are a number of uncertainties in this line of argument. First, whether an oxygen-wasting effect is truly an effect of inotropic drugs is uncertain because it can be partly explained by the particular mechanical index used for the assessment. An energetic cost can be calculated without excessive oxygen consumption by using, for instance, the pressure-work index proposed by Rooke and Feigl or the total mechanical energy (TME) model developed by Elbeery et al. Second, most of these studies have been conducted in isolated hearts and not in vivo. Therefore, this phenomenon could, in large part, be
restricted to the isolated-heart models. Finally, the doses of inotropes needed to show such a wasting of oxygen in vivo have been excessive, inducing profound tachycardia and blood pressures exceeding clinical goals.

In this study, we investigated whether the inotropic drugs dobutamine and levosimendan have relatively increased oxygen consumption (oxygen wasting) in clinically relevant doses applied in a large-animal model of postischemically reduced left ventricular function. As such, the study also addressed the assumption that a therapeutic level of levosimendan has a more advantageous energetic profile than does an equipotent dose of dobutamine.

Methods

Experimental Animals

The experimental protocol was approved by the local steering committee of the National Animal Research Authority located at the Faculty of Medicine, University of Tromsø, Tromsø, Norway. Twenty-two castrated male domestic pigs weighing 33±1 kg were adapted to the animal department for 5 to 7 days and fasted overnight before the experiments, with free access to water.

Instrumentation

The animals were premedicated with intramuscular injections of 20 mg/kg Ketalar (Pfizer AS, Norway) and 1 mg atropine (Nynomed Pharma, Norway). Anesthesia was induced by intravenous injection of 10 mg/kg pentobarbital sodium (Abbott, Sweden) and 0.01 mg/kg fentanyl (Hanel Pharmaceutical, Germany), and the animals were normoventilated after tracheostomy. A central venous catheter was placed through the left jugular vein, and anesthesia was maintained throughout the experiment by a continuous infusion of 4.0 mg·kg⁻¹·h⁻¹ pentobarbital sodium, 0.02 mg·kg⁻¹·h⁻¹ fentanyl, and 0.3 mg·kg⁻¹·h⁻¹ midazolam (B. Braun, Germany). The circulating volume was maintained by a 20 mL·kg⁻¹·h⁻¹ continuous infusion of 0.9% NaCl supplemented with 1.25 g/L glucose. The animals received 2500 IU heparin and 5 mg/kg amiodarone (Sanofi-Synthelabo, Sweden) to avoid blood clotting of catheters and cardiac arrhythmias.

The surgical instrumentation of the animals has been described in detail previously. In brief, a 7F balloon catheter was introduced to the inferior caval vein for preload reduction, and another 7F, dual-field, combined pressure-conductance catheter (CD Leycom, the Netherlands) was inserted into the left ventricular cavity via the left carotid artery for measurements of left ventricular pressure and volume. Transit-time flow probes (Medi-stim, Norway) were placed on the coronary arteries and pulmonary trunk to measure coronary blood flow and cardiac output, respectively, and myocardial venous blood was drawn from a catheter placed in the great cardiac vein via the coronary sinus (after ligating the hemiazygos vein). A catheter was inserted into the main pulmonary trunk through the right ventricular wall for measurement of mean pulmonary arterial pressure.

Experimental Protocol

We used our previously established open-chest ischemia-reperfusion model to assess the hemodynamic and energetic effects of levosimendan and dobutamine. This protocol uses 20 minutes of accumulated ischemia affecting ~82% of the left ventricle and induces a reproducible acute impairment of left ventricular function that remains stable for several hours. The 2 initial occlusions lasted 1 minute to adapt the left ventricle to latter occlusions and thus to minimize ischemia-induced arrhythmias. Subsequently, a sequence of nine 2-minute left coronary artery occlusions were performed, giving a total ischemic time of 20 minutes. Reperfusion times between occlusions were 60 to 120 seconds, allowed by the time needed to reestablish preclosure mean arterial pressure levels. Levosimendan was given in a clinically recommended dosage with an initial bolus of 24 μg/kg intravenously. Compared with this clinical protocol, however, the continuous infusion of levosimendan was reduced in the main protocol (0.04 μg·kg⁻¹·min⁻¹), because this dosage normalized hemodynamics to preischemic levels. Subsequently, a dose-response curve of dobutamine (0.25 to 12.5 μg·kg⁻¹·min⁻¹) was obtained in separate animals to determine the dose necessary to achieve equipotent hemodynamic effects compared with levosimendan (dose response presented in the online-only Data Supplement). After the pilot series, the first series of experiments presented in this article (n=16) were conducted randomly with either levosimendan (dosage as stated earlier) or dobutamine (1.25 μg·kg⁻¹·min⁻¹) after completing the ischemia-reperfusion protocol. The animals in the dobutamine group were also given a supratherapeutic dose of dobutamine (10 μg·kg⁻¹·min⁻¹) to assess the mechanoenergetic effect of this drug in such a high dose. Finally, to assess the energetic effects of a supratherapeutic dose of levosimendan, a final group of pigs (n=6) was given a high dose of levosimendan (48 μg/kg loading and an infusion of 0.2 μg·kg⁻¹·min⁻¹). The experimental protocol is outlined in Figure 1.

Figure 1. The outline of the experimental protocol. The first 16 pigs had a common step of transient ischemia and were subsequently randomly allocated to either low-dose (LD) and high-dose (HD) dobutamine or low-dose (LD) levosimendan treatment. The last group of 6 pigs was given HD levosimendan only. The dotted lines encircle the time points of data collection. The complete duration of the protocol was ~3 hours for each experimental animal.

Calculation of Hemodynamic and Energetic Indexes

Left ventricular conductance and pressure signals were sampled, digitized at 250 Hz during 10- to 12-second runs (Conduct 2000; CD Leycom, the Netherlands), and analyzed by using CircLab (GTX Medical Software; Zoetermeer, the Netherlands) to obtain various indexes of ventricular function. Systemic and pulmonary vascular resistances were calculated as the respective pressure drops divided by cardiac output.

At each analysis point throughout the experiment (Figure 1), 5 to 7 recordings of varying steady-state ventricular mechanical work levels, hemodynamic parameters, coronary flow, and blood sampling from the coronary sinuses were performed. After each recording, preload was reduced stepwise by inflating the balloon catheter in the caval vein to obtain these alterations in mechanical work and corresponding oxygen consumption. Total left ventricular mechanical work was calculated as the pressure-volume area (PVA), the tension-time index (TTI), and the TME. In brief, PVA consists of the area bounded by the pressure-volume loop (external work [stroke work; SW]) and the area limited by the line of the end-systolic and end-diastolic pressure-volume relations (potential energy). PVA was calculated from the formula PVA = SW + [ESP · (ESV−V₀)/2]−[EDP · (ESV−V₀)]/2, where SW is calculated from the pressure-volume data, and ESP and ESV are end-systolic pressure and volume, respectively. V₀ is the interpolated x intercept of the quadratic fitted end-systolic pressure-volume relation during steady-state recordings, and EDP is end-diastolic pressure.
The TTI was calculated from the formula TTI = f/Pdtt,19 which is the area under the systolic ventricular pressure curve during 1 steady-state beat.

TME was calculated from the formula TME = ([(MEP · EDV/k) + SW]); where MEP is mean ejection pressure21 and k equals 2.28, a factor correcting for the omission of Vw (the intercept of the SW-EDV relation) and a constant parallel conductance volume Vp.15,22

Left coronary blood flow was estimated from the formula LVCBF = CBF/W · LVW; where LVCBF and CBF are left ventricular and total coronary blood flow, respectively. W and LVW are total and left ventricular myocardial weight, respectively. Left ventricular oxygen consumption was calculated from the formula MVO2 = (LVCBF · avO2 · Hb · 1.39)/HR · 20.2; where MVO2 is left ventricular myocardial oxygen consumption, avO2 is the difference between aortic and myocardial venous oxygen saturations, Hb is hemoglobin in grams per liter, 1.39 is a constant (in mL O2/g Hb), and HR is heart rate. To convert MVO2 to mechanical energy equivalents, the factor 20.2 J/mL O2 was used.

Statistical Analysis
The data are expressed as mean±SD. Hemodynamic parameters at baseline and postischemically were compared with a paired t test. The effects of low-dose levosimendan on hemodynamic parameters in postischemic left ventricles were also determined by a paired t test. A 1-way repeated-measure ANOVA, followed by a Bonferroni post hoc tests (SPSS 15.0, Chicago, Ill), High-dose levosimendan was added in a supplementary experimental group and was compared with the postischemic hemodynamic and energetic data in this particular group (t test, paired and ANCOVA for MVO2/mechanical work). Differences between means were regarded as statistically significant when P values were <0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Hemodynamic and Energetic Effects of Repetitive Ischemia
Hemodynamic effects of the ischemia-reperfusion protocol are shown in Table 1 for the therapeutic-level levosimendan group and in Table 2 for the dobutamine group. The effects of the accumulated 20 minutes of ischemia are compatible with postischemic left ventricular stunning with normal to increased coronary blood flow, reduced contractile function (dP/dtmax and preload recruitable SW), a small but nonsignificant fall in the mean arterial pressure, and a concomitant increased mean pulmonary arterial pressure. The postischemic left ventricle had a relatively increased oxygen consumption (not shown; details of this model can be found in Korvald et al19). The 2 groups were well balanced in their response to the ischemia-reperfusion protocol.

Hemodynamic Effects of Levosimendan and Dobutamine
As stated, levosimendan was first infused in recommended doses to induce a hemodynamic effect reversing the left ventricular stunning measured as dP/dtmax and preload recruitable SW (Table 1). This dose of levosimendan induced a significant peripheral vasodilation and thus increased cardiac output compared with the postischemic state. The matching level of dobutamine was well balanced with the levosimendan group and induced a comparable hemodynamic effect (Table 2). Contrary to this, high-dose dobutamine induced an ≈30% increase in heart rate, a doubling of contractility indexes, and a 74% increase in cardiac output. The excessive dose of levosimendan (48 μg/kg loading followed by 0.2 μg · kg⁻¹ · min⁻¹ infusion) resulted in tachycardia and vaso-
The Hemodynamic Effects of Repetitive Ischemia in Pig Left Ventricles and the Effects of Dobutamine on Postischemic Circulatory Function

**Table 2.** The Hemodynamic Effects of Repetitive Ischemia in Pig Left Ventricles and the Effects of Dobutamine on Postischemic Circulatory Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean ± SD</th>
<th>Postischemic Mean ± SD</th>
<th>Dobutamine, 1.25 μg·kg⁻¹·min⁻¹ Mean ± SD</th>
<th>Dobutamine, 10 μg·kg⁻¹·min⁻¹ Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P vs Baseline 0.061</td>
<td>P vs Postischemic 0.043</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>97 ± 14</td>
<td>89 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, 1/min</td>
<td>82 ± 18</td>
<td>95 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>18 ± 3</td>
<td>23 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.83 ± 0.4</td>
<td>2.73 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR, dynes·s/cm²</td>
<td>2625 ± 417</td>
<td>2531 ± 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, dynes·s/cm²</td>
<td>388 ± 53</td>
<td>523 ± 129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dPdtmax, mm Hg/s</td>
<td>1441 ± 154</td>
<td>1148 ± 87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dPdtmin, mm Hg/s</td>
<td>−1834 ± 250</td>
<td>−1560 ± 183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES, mm Hg/mL</td>
<td>2.0 ± 0.5</td>
<td>2.7 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRSW, mm Hg</td>
<td>51 ± 13</td>
<td>49 ± 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVCBF, mL/min</td>
<td>74 ± 15</td>
<td>88 ± 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV, mL</td>
<td>35 ± 5</td>
<td>30 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>18 ± 6</td>
<td>19 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>τ, ms</td>
<td>48 ± 9</td>
<td>46 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW, mL·mm Hg</td>
<td>3195 ± 788</td>
<td>2357 ± 717</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; EES, end-systolic elastance; PRSW, preload recruitable stroke work; LVCBF, left ventricular coronary blood flow; SV, stroke volume; EDP, end-diastolic pressure; τ, asymptotic pressure decay in the left ventricle; SW, stroke work.

dilation, but contrary to dobutamine, only a marginal increase in the contractility indexes, dP/dt max, and preload recruitable SW with resulting hypotension (Table 3). Representative pressure-volume loops from these drug interventions are shown in Figure 2.

Table 3. The Hemodynamic Effects of Repetitive Ischemia in Pig Left Ventricles and the Effect of a Supratherapeutic Dose of Levosimendan on Postischemic Circulatory Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean ± SD</th>
<th>Postischemic Mean ± SD</th>
<th>Levosimendan, 48 μg/kg Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P vs Baseline 0.006</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>94 ± 21</td>
<td>81 ± 19</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>HR, 1/min</td>
<td>82 ± 20</td>
<td>105 ± 44</td>
<td>120 ± 45</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>20 ± 3</td>
<td>23 ± 2</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>2.92 ± 0.8</td>
<td>2.62 ± 0.7</td>
<td>3.03 ± 1</td>
</tr>
<tr>
<td>SVR, dynes·s/cm²</td>
<td>2418 ± 567</td>
<td>2252 ± 670</td>
<td>1807 ± 343</td>
</tr>
<tr>
<td>PVR, dynes·s/cm²</td>
<td>336 ± 63</td>
<td>462 ± 150</td>
<td>401 ± 117</td>
</tr>
<tr>
<td>dPdtmax, mm Hg/s</td>
<td>1622 ± 364</td>
<td>1230 ± 273</td>
<td>1408 ± 355</td>
</tr>
<tr>
<td>dPdtmin, mm Hg/s</td>
<td>−1919 ± 460</td>
<td>−1536 ± 391</td>
<td>−1531 ± 468</td>
</tr>
<tr>
<td>EES, mm Hg/mL</td>
<td>3.2 ± 0.6</td>
<td>3.0 ± 1.6</td>
<td>3.9 ± 1.5</td>
</tr>
<tr>
<td>PRSW, mm Hg</td>
<td>49 ± 13</td>
<td>35 ± 12</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>LVCBF, mL/min</td>
<td>82 ± 24</td>
<td>85 ± 23</td>
<td>103 ± 37</td>
</tr>
<tr>
<td>SV, mL</td>
<td>35 ± 3</td>
<td>27 ± 8</td>
<td>27 ± 8</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>14 ± 4</td>
<td>14 ± 4</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>τ, ms</td>
<td>42 ± 8</td>
<td>44 ± 6</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>SW, mL·mm Hg</td>
<td>2672 ± 807</td>
<td>1910 ± 711</td>
<td>2014 ± 830</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; EES, end-systolic elastance; PRSW, preload recruitable stroke work; LVCBF, left ventricular coronary blood flow; SV, stroke volume; EDP, end-diastolic pressure; τ, asymptotic pressure decay in the left ventricle; SW, stroke work.

Energetic Effects of Levosimendan and Dobutamine

The drug-induced effects on the relation between mechanical work and oxygen consumption in the left ventricle are shown in Figures 3 through 6. Figure 3a and 3b illustrates how the...
data were obtained by gradually reducing the mechanical work through preload reductions. After obtaining steady-state mechanical work at each preload level (≈20 to 30 seconds needed), the pressure and volume data used to calculate the mechanical indexes were obtained concomitantly with oxygen consumption in the left ventricle. In principle, the same relation between mechanical work and oxygen consumption was obtained whether the mechanical work was calculated with an energy-convertible index (PVA), a predominately pressure-assessing index (TTI), or a volume-assessing index accounting for almost all energy consumption (TME).

Figure 4 presents all data points used in the statistical analysis to calculate the effects of the 3 different drug regimens included in the randomized protocol on the relation between mechanical work and oxygen consumption, ie, levosimendan in the therapeutic dose and dobutamine in low and high doses. Only the MVO₂-TTI relation is shown, because this index has been consistently presented as the most sensitive to a surplus oxygen consumption by drug addition. In principle, an equal relation between mechanical work and oxygen consumption was found for PVA and TME. ANCOVA with MVO₂ as a dependent variable, mechanical work as a covariate, and drug as a group variable found the regression model highly descriptive for the data. A post hoc Sidak test showed that the only drug effect on the postischemic MVO₂-TTI relation was the effect of the high-dose dobutamine (P<0.001) and that no effect could be observed for either levosimendan or the equipotent level of low-dose dobutamine on any of the 3 indexes.

In Figure 6, the energetic effect of high-dose levosimendan is illustrated. As stated and shown in Figure 1, this group (n=6) was added as an extra group to determine the energetic effect of a supratherapeutic dose of levosimendan. Such a high dose of the drug induced hypotension and only a minimal effect on myocardial contractility (Table 3). Despite this limited contractile effect, levosimendan induced surplus oxygen consumption in postischemic hearts and thus an energetic inefficiency (ANCOVA with post hoc Sidak test; P=0.007 compared with the postischemic level).

**Discussion**

The most important observation in this study was the lack of surplus oxygen consumption in postischemic hearts during infusion of therapeutically relevant doses of both levosimendan and dobutamine. Transient ischemia in this model induces a state of myocardial stunning with reduced contractility and systemic blood pressure. Because contractility was restored and there was a significant increase in cardiac output by both drugs in the given doses, these doses are relevant to desired drug effects in a clinical setting. From this core observation, 2 important conclusions can be drawn: (1) inotropic drugs do not necessarily “waste” oxygen when used to correct hemodynamic deficiencies in hearts altered by pathological processes and (2) dobutamine does not show a worse energetic profile compared with levosimendan when used in vivo in therapeutically relevant doses of both drugs.

**Oxygen-Wasting Effects of Inotropic Drugs**

An analysis of previously published pathophysiological studies addressing this issue shows that a relatively increased oxygen consumption has mainly been observed in isolated hearts. Furthermore, the few studies resembling clinical application and concomitantly addressing the topic in vivo
models document an increased oxygen consumption with adrenergic drug doses inducing hypertension and tachycardia.\textsuperscript{16,17} This oxygen-wasting effect of somewhat excessive doses could also be documented in our model, because a surplus oxygen consumption could be induced by increasing the level of both infused dobutamine and levosimendan. However, these doses led to tachycardia and vasodilation. Dobutamine in such a high dose showed a prominent increase in the contractility index preload recruitable SW, whereas the high dose of levosimendan had only a minor

---

**Figure 3.** a. One experiment showing the relation between mechanical work and oxygen consumption during levosimendan low-dose (LD) infusion as the mechanical work was gradually reduced by preload reductions. b. One experiment showing the relation between mechanical work and oxygen consumption during LD and high-dose (HD) dobutamine infusions as the mechanical work was gradually reduced by preload reductions. PVA indicates pressure volume area; TTI, tension-time index; TME, total mechanical energy.

**Figure 4.** All observed relations between mechanical work and oxygen consumption in the 16 pigs from the first randomized part of the protocol (levosimendan, LD, and dobutamine, LD and HD). The curves are shown for the TTI only because this index has been proven to be the most sensitive for detecting surplus oxygen consumption. Significantly increased MVO\textsubscript{2}/TTI compared with postischemic values was observed only for the high dose of dobutamine. LD dobutamine is 1.25 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), HD dobutamine is 10 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), and LD levosimendan is 24 \(\mu\text{g/kg bolus in addition to 0.04 \mu g \cdot kg^{-1} \cdot min^{-1}}\).
effect on contractility and thus led to an overall hypotension. These observations are of paramount importance when one is to evaluate the energetic effects of such drugs. Oxygen wasting can be induced in models that do not resemble clinical applications and by hemodynamic responses that at times are in excess of clinically desired effects. An evaluation of energetic effects of inotropic drugs thus demands not only a clinically relevant model but also a careful selection of doses with relevant hemodynamic responses.

A further aspect of importance when evaluating the energetic effects of various drugs is the index of energetics used to assess the relation between mechanical work and oxygen consumption. The apparent oxygen-wasting effect of inotropic drugs is particularly pronounced when applying the TTI. With this index, oxygen consumption has been related to pressure development in the left ventricle, and the index has proven to be the most sensitive in detecting surplus oxygen consumption. This is explained by the fact that the duration of systole becomes briefer with increasing contractility and heart rate. However, the TTI model has certain limitations in calculating mechanical energy levels because no volume alterations are assessed. Importantly, even with the use of TTI in the present model, no oxygen wasting was observed in the therapeutic levels of both inotropic drugs. Similarly, no excessive oxygen consumption was observed when we used indexes that included both volume work and potential or metabolic energy in the equation (TME and PVA).

**Are the Present Doses Relevant to Previous Clinical Observations?**

We primarily used an identical levosimendan loading dose as used in the LIDO trial [Levosimendan Infusion versus Dobutamine trial]. However, our experimental continuous-infusion dose needed to restore contractile dysfunction was approximately half of the dose used in that trial but was identical to doses used in a contemporary registry. Importantly, the hemodynamic responses to the used dose are compatible with the effect in the LIDO and SURVIVE [Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support] studies, as they induced a similar increase in cardiac output compared with the clinical trials. Furthermore, compared with these trials, a lower dose of dobutamine was necessary to reverse and exceed the hemodynamic status in the postischemic pigs. A possible explanation for these observations could be that these relatively young and healthy animals had no chronic failure-induced desensitization of the β-adrenergic receptors and no preischemic chronic β-blocker treatment that might have

---

**Figure 5.** The curves represent the mean covariant regression lines for the posts ischemic mechanoenergetic relation and the effects of the 3 drug regimens shown in Figure 4. All 3 mechanical indexes (PVA, TME, and TTI) show the principally same result: an increased oxygen consumption related to mechanical work was only observed for the high dose (10 µg · kg⁻¹ · min⁻¹) of dobutamine (P<0.001).

**Figure 6.** All observed relations between mechanical work and oxygen consumption in the 6 pigs treated with high-dose (HD) levosimendan (48 µg/kg bolus in addition to 0.2 µg · kg⁻¹ · min⁻¹). There was a significantly increased MVO₂/mechanical index compared with posts ischemic values for all 3 mechanical indexes (PVA, P=0.007; TTI, P=0.025; TME, P<0.0001).
hampered the inotropic effects. Our model of acute coronary occlusions and reperfusion in the pig differs from the remodeled human failing heart, both in hemodynamic responses and subcellular functions, but the model has proven sensitive to surplus oxygen consumption and can thus act as a model system for drug efficiencies and metabolism. It should be mentioned that the small amount of amiodarone used in the pigs was dissolved in polysorbate 80, and this compound has been shown to induce a slight reduction of myocardial oxygen consumption in dogs, parallel to a small reduction in aortic pressure.

Energetic Effects of Levosimendan

Several previous studies have addressed the issue of a relatively energy-conserving effect of levosimendan in experimental models of postischemic stunning and heart failure. Pagel et al calculated mechanical indexes known to determine myocardial oxygen consumption in dogs with pacing-induced heart failure. As opposed to the control group, heart rate, rate-pressure products, and the pressure-work index were not altered by a clinically relevant dose of levosimendan in these dogs. However, in that study, the control group had an excessive increase in these indexes, possibly marking the different vascular loading conditions in the 2 groups. In addition, the actual oxygen consumption was not assessed in those hearts.

Todaka et al assessed the oxygen consumption related to levosimendan infusions in isolated rat and failing dog hearts by calculating the mechanical work in the PVA model. In their study, the oxygen-wasting effect of inotropes was observed with levosimendan infusions compatible with a previously described phosphodiesterase III effect of the drug. However, the doses chosen in that study were complicated by the nonphysiological isolated-heart model, revealed by the excessive tachycardia induced by the drug (exceeding 140 beats per minute). The study did show, however, that a potentially dose-related oxygen wasting can be induced by levosimendan in parallel with the effect of high-dose dobutamine or other adrenergic drugs. Finally, Meyer et al compared the energetic effects of high-dose dobutamine and levosimendan in isolated rabbit hearts after transient ischemia with principally the same findings; ie, surplus oxygen wasting can be induced by levosimendan in excessive doses parallel to the effect of the adrenergic dobutamine.

In our study, the effect of a supratherapeutic dose of levosimendan was assessed in a separate group of pigs. Because of the long half-life of the drug (t1/2 of 81 hours for the active metabolite OR-1896) and long-acting duration from an injection (24 hours), a comparison of different drug doses in the same animals is impractical. Data from these experiments did show the known tachycardia and hypotension after excessive doses of levosimendan and confirmed the oxygen-wasting effect of these high and nontherapeutic doses of the drug.

What are the possible mechanisms for an increased relative oxygen consumption in hearts treated with high doses of inotropic drugs? Per se, ischemia and reperfusion induce an increased activity of uncoupling proteins and reactive oxygen species that possibly can increase the oxygen consumption in the mitochondria. However, the relative increase in oxygen consumption induced by high levels of adrenergic drugs has been linked to the handling of excessive calcium in the cells. Our study suggests that in low doses, an adrenergic inotrope such as dobutamine will convert the mobilized calcium to active actinomyosin crosslinking without excessive metabolic demands. Levosimendan in high doses possibly induces an increased oxygen metabolism through the phosphodiesterase III effect and thereby also increased handling of calcium.

Conclusion

This study shows that neither dobutamine nor levosimendan in clinically relevant doses induces surplus oxygen in the stunned pig heart. This observation is compatible with the equal survival effects of the 2 drugs in the large randomized studies on acute heart failure, and the possibility of such an energetically neutral effect of inotropic drugs should influence the planning and interpretation of clinical trials of inotropes.

Sources of Funding

This work was supported by the health authorities of North Norway.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

A disproportionate increase in myocardial oxygen consumption induced by inotropic drugs, particularly adrenergic compounds, has been observed in a number of experimental studies. However, most of these data are from isolated heart studies or from studies with high doses of inotropes. In this study, we examined the relation between myocardial oxygen consumption and mechanical work in an intact pig model of postischemic ventricular dysfunction. We assessed both dobutamine and levosimendan in doses titrated to reverse ventricular dysfunction and in supratherapeutic doses. In the therapeutic doses of both drugs, no excessive myocardial oxygen consumption could be observed. In supratherapeutic doses, however, an excessive or oxygen-wasting effect of these drugs was found. These results challenge the traditional concept of a mandatory oxygen-wasting effect of inotropic drugs. These data are potentially important in planning clinical studies of inotropes.
Oxygen-Wasting Effect of Inotropy: Is There a Need for a New Evaluation? An Experimental Large-Animal Study Using Dobutamine and Levosimendan
Stig Müller, Ole-Jakob How, Øyvind Jakobsen, Stig Eggen Hermansen, Assami Røsner, Thor Allan Stenberg and Truls Myrmel

*Circ Heart Fail.* 2010;3:277-285; originally published online December 16, 2009; doi: 10.1161/CIRCHEARTFAILURE.109.865519
*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/2/277

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2010/01/26/CIRCHEARTFAILURE.109.865519.DC1

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Heart Failure* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Circulation: Heart Failure* is online at:
http://circheartfailure.ahajournals.org//subscriptions/
Dose-Response relationship of dobutamine mediated increase in cardiac output. Data are obtained in pigs (n=7, mean ± SEM) with left ventricular ischemia. The dotted line indicates pre ischemic levels, before left anterior descending (LAD) arterial flow was reduced to 20% by a rubber band tourniquet. This relationship was used to select the appropriate therapeutic (LD dobutamine, 1.25 µg/kg/min) as well as the supratherapeutic (HD dobutamine, 10 µg/kg/min) dobutamine dose used in the main study, as indicated by the arrows.