Oxygen wasting effect of inotropy – is there a need for a new evaluation?
An experimental large animal study using dobutamine and levosimendan

Short title: Müller - Oxygen wasting effect of inotropy reassessed
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Abstract

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 most 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, 0.04 μg/kg/min infusion) or an equipotent dose of dobutamine (1.25 μg/kg/min). 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 (TTI), pressure-volume area (PVA) and total mechanical energy (TME). Analysis of covariance 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/min and 48 μg/kg loading with 0.2 μg/kg/min 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 using dobutamine, p=0.007 levosimendan assessed by PVA).

Conclusion

Therapeutic levels of neither dobutamine nor levosimendan demonstrate inotropic oxygen wasting in this in vivo pig model. Thus, relevant hemodynamic responses can be achieved with an adrenergic inotrope without surplus oxygen consumption.
Key words

Stunning, myocardial – inotropic agents – metabolism - oxygen
Introduction

The oxygen wasting effect of inotropic agents has been established as an energetic principle in the studies of contractility enhancing drugs (1-2). Particularly, adrenergic compounds have been shown to increase the oxygen consumption of the myocardium disproportionately, possibly due to increased energy requirements related to the intracellular calcium handling (2). This oxygen cost of contractility (3) has been regarded as detrimental in ischemic and failing myocardium (4). The theoretically unwanted side effect of these drugs has led to the search for alternatives with better pharmacodynamic profiles. Thus, the calcium-sensitizers, acting through enhancing the calcium effect on the myofilaments, in theory should contribute to an increased contractility with relatively less energy consumption. Using these drugs, a more efficient actinomyosin coupling can be induced with less calcium handling (5).

Levosimendan is a calcium sensitizer that has been advanced to clinical use, and initial clinical trials indicated an improved survival in acute heart failure patients treated with this drug compared to an established alternative, namely dobutamine (6, 7). However, although a few studies have assessed the oxygen consuming effects of levosimendan (8-12), no studies have adequately addressed the energetic profile of this drug in clinical 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 to dobutamine (13).

There are a number of uncertainties in this line of arguments. First, whether an oxygen wasting effect is truly an effect of inotropic drugs is uncertain as it can be partly explained by the particular mechanical index used for the assessment. An energetic cost
can be calculated without excessive oxygen consumption using for instance the pressure-work index proposed by Rooke and Feigl (14) or the total mechanical energy model developed by Elbeery and coworkers (15). Second, most of these studies have been conducted in isolated hearts and not in vivo. Therefore, this phenomenon could for a large part be restricted to the isolated heart models (15). Finally, the doses of inotropes needed to demonstrate such a wasting of oxygen in vivo have been excessive, inducing profound tachycardia and blood pressures exceeding clinical goals (16, 17).

In the present 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 postischemic 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 an equipotent dose of dobutamine.
Methods

Experimental animals

The experimental protocol was approved by the local steering committee of the National Animal Research Authority (NARA) located at the Faculty of Medicine, University of Tromsø, Norway. Twenty-two castrated male domestic pigs weighing 33 ±1 kg were adapted to the animal department for 5–7 days and fasted overnight prior to 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 (Nycomed Pharma, Norway). Anesthesia was induced by intravenous injection of 10 mg/kg pentobarbital-sodium (Abbott, Sweden) and 0.01 mg/kg fentanyl (Hameln Pharmaceuticals, Germany), and the animals where normoventilated after tracheostomy. A central venous catheter was placed through the left internal jugular vein, and anesthesia was maintained throughout the experiment by a continuous infusion of 4.0 mg/kg/h pentobarbital-sodium, 0.02 mg/kg/h fentanyl and 0.3 mg/kg/h midazolam (B. Braun, Germany). The circulating volume was maintained by a 20 ml/kg/h 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 (18). Briefly, a 7 Fr balloon catheter was introduced to the inferior caval vein for preload reduction, and another 7 Fr, 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 artery pressure (MPAP).

**Experimental protocol**

We used our previously established open-chest ischemia-reperfusion model (18) to assess the hemodynamic and energetic effects of levosimendan and dobutamine. This protocol employs 20 min of accumulated ischemia affecting approximately 82% of the left ventricle, and induces a reproducible acute impairment of left ventricular function that remains stable for several hours. The two initial occlusions lasted 1 min to adapt the left ventricle to latter occlusions, and thus to minimize ischemia-induced arrhythmias. Subsequently, a sequence of nine 2-min left coronary artery occlusions were performed, giving a total ischemic time of 20 min. Reperfusion times between occlusions were 60 – 120 sec, steered by the time needed to reestablish preocclusion mean arterial pressure levels.

Levosimendan was given in a clinically recommended dosage (7) with an initial bolus of 24μg/kg intravenously. Compared to this clinical protocol however, the continuous infusion of levosimendan was reduced in the main protocol (0.04 μg/kg/min),
as this dosage normalized hemodynamics to preischemic levels. Subsequently, a dose response curve of dobutamine (0.25 – 12.5 μg/kg/min) was obtained using separate animals to determine the dose necessary to achieve equipotent hemodynamic effects compared to levosimendan (dose-response presented as Supplementary data). After the pilot series, the first series of experiments presented in this paper (n=16) were conducted randomly using either levosimendan (dosage above) or dobutamine (1.25 μg/kg/min) after completing the ischemia-reperfusion protocol. The animals in the dobutamine group were also given a supratherapeutic dose of dobutamine (10 μg/kg/min) in order to assess the mechanoenergetic effect of this drug in such a high dose. Finally, in order to assess the energetic effects of a supratherapeutic dose of levosimendan, a final group of pigs (n=6) were given a high dose of levosimendan (48 μg/kg loading and an infusion of 0.2 μg/kg/min). The experimental protocol is outlined in figure 1.

Calculation of hemodynamic and energetic indexes

Left ventricular conductance and pressure signals were sampled and digitized at 250 Hz during 10-12 seconds runs (Conduct 2000, CD Leycom, The Netherlands), and analyzed 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 (see figure 1) five to seven recordings of varying steady state ventricular mechanical work levels, hemodynamic parameters, coronary flow and blood sampling from the coronary sinus 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) (2), as the tension-time index (TTI) (19) and the total mechanical energy (TME) (15). Briefly, PVA consists of the area bounded by the pressure-volume loop (external work, SW) and the area limited by the line of the end-systolic and end-diastolic pressure-volume relationships (potential energy, PE). PVA was calculated by the formula:

$$PVA = SW + [ESP \cdot (ESV - V_0)/2] - [EDP \cdot (ESV - V_0)/2]$$ (20)

where SW is calculated from integrated pressure-volume data; ESP and ESV are end-systolic pressure and volume, respectively. $V_0$ is the interpolated x-intercept of quadratic fitted end-systolic pressure-volume relationship during steady state recordings, and EDP is end-diastolic pressure.

The tension-time index (TTI) was calculated by the formula

$$TTI = \int P \cdot dt$$ (19)

which is the area under the systolic ventricular pressure curve during one steady state beat.

Total mechanical energy (TME) was calculated by the formula

$$TME = [(MEP \cdot EDV/k) + SW]$$

where MEP is mean ejection pressure (21) and k equals 2.28, a factor correcting for the omission of Vw (x-intercept of SW-EDV relationship) and using a constant parallel conductance volume Vp (15, 22).

Left coronary blood flow was estimated by the formula:

$$LVCBF = CBF/W \cdot LVW$$
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 by:

\[ MVO_2 = \frac{(LVCBF \cdot avdO_2 \cdot Hb \times 1.39)}{HR \cdot 20.2} \]

where \( MVO_2 \) is left ventricular myocardial oxygen consumption, \( avdO_2 \) the difference between aortic and myocardial venous oxygen saturation, Hb hemoglobin in g/l, 1.39 is a constant (in ml O₂/g Hb) and HR is heart rate. In order to convert \( MVO_2 \) 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 using 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 one-way repeated measure ANOVA, followed by a Bonferroni corrected t-test, was used to determine hemodynamic differences between postischemic, low-dose and high-dose dobutamine values. Myocardial energetics (\( MVO_2/ \) mechanical work index) obtained postischemically, during low-dose levosimendan and the two doses of dobutamine infusions were compared by ANCOVA (23, 24) and post hoc tests (SPSS 15.0, Chicago, Ill, USA). High-dose levosimendan was added in a supplementary experimental group and was compared to the postischemic hemodynamic and energetic data in this particular group (t-test, paired and ANCOVA for \( MVO_2/ \)mechanical work). Differences between means were regarded as statistically significant when \( p \)-values were less than 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 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/dt\_max and preload recruitable stroke work, PRSW), a small but non-significant fall in the mean arterial pressure (MAP), concomitant with an increased MPAP (mean pulmonary arterial pressure). The postischemic left ventricle had a relatively increased oxygen consumption (not shown; details of this model can be found in reference 18). The two 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/dt\_max and PRSW (table 1). This dose of levosimendan induced a significant peripheral vasodilation and thus increased cardiac output compared to the postischemic state. The matching level of dobutamine was well balanced to the levosimendan group and induced a comparable hemodynamic effect (table 2). Contrary to this, high dose dobutamine induced an approximately 30% increase in heart rate, a doubling of contractility indexes and a 74% increase in cardiac output. The excessive dose of levosimendan (48 \(\mu\)g/kg loading followed by 0.2 \(\mu\)g/kg/min infusion) gave tachycardia and vasodilation, but contrary to
dobutamine, only a marginal increase in the contractility indexes \( \frac{dP}{dt_{\text{max}}} \) and PRSW with a resulting hypotension (table 3). Representative pressure-volume loops from these drug interventions are demonstrated in figure 2.

**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 3-6. Figures 3a and b illustrate how the data were obtained by gradually reducing the mechanical work through preload reductions. After obtaining steady-state mechanical work at each preload level (approximately 20-30 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 (TTI) or a volume-assessing index accounting for close to all energy consumption (TME).

Figure 4 presents all data points used in the statistical analysis to calculate the effects of the three different drug-regimens included in the randomized protocol on the relation between mechanical work and oxygen consumption i.e. levosimendan in the therapeutic dose and dobutamine in low and high doses. Only the MVO\textsubscript{2}-TTI relation is shown, since this index has been consistently presented as the most sensitive to a surplus oxygen-consumption by drug addition (14). In principle, an equal relationship between mechanical work and oxygen consumption was found for pressure-volume area (PVA) and total mechanical energy (TME). ANCOVA with MVO\textsubscript{2} as dependent variable,
mechanical work as covariate and drug as group variable, found the regression model highly descriptive for the data. A post hoc Sidak test revealed 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 by levosimendan or low-dose dobutamine.

Figure 5 shows the mean covariation lines for the three mechanical work indexes and left ventricular oxygen consumption (MVO2) observed in the first randomized part of the protocol (see figure 1). The figure illustrates the influence of the three drug regimens on this relation. For all three indexes, only the high dose regimen of dobutamine demonstrated the oxygen wasting effect of inotropy; a relatively increased oxygen consumption related to the mechanical work (p<0.001). No surplus oxygen consumption could be observed for either levosimendan or the equipotent level of low-dose dobutamine on any of the three 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). In spite of this, high-dose levosimendan induced a surplus oxygen consumption in postischemic hearts and thus an energetic inefficiency (ANCOVA with post hoc Sidak test p=0.007 compared to 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. As 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, two 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 do not demonstrate a worse energetic profile compared to levosimendan 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, reveals that a relatively increased oxygen consumption has mainly been observed in isolated hearts (2). Furthermore, the few studies resembling clinical application and concomitantly addressing the topic using in vivo models, document an increased oxygen consumption with adrenergic drug doses inducing hypertension and tachycardia (16, 17). This oxygen wasting effect of somewhat excessive doses could also be documented in our model, as a surplus oxygen consumption could be induced by increasing the level of both infused dobutamine and levosimendan. These doses, however, lead to tachycardia and vasodilation. Dobutamine in such a high dose demonstrated a prominent increase in
the contractility index preload recruitable stroke work (PRSW), while the high dose of levosimendan had only a minor effect on contractility thus leading 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 are not resembling clinical applications (1, 2, 19) and by hemodynamic responses that at times are in excess of clinically desired effects (16, 17). An evaluation of energetic effects of inotropic drugs thus not only demands 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 tension-time index (TTI) (2, 14, 19). Using this index, oxygen consumption has been related to the pressure development in the left ventricle (19), and the index has proven to be the most sensitive in picking up surplus oxygen consumption (4, 14). 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 as no volume alterations are assessed. Importantly, even when using the TTI in the present model no oxygen wasting was observed in the therapeutic levels of both inotropic drugs. Likewise, no excessive oxygen consumption was observed using indexes including both the volume work and potential or metabolic energy in the equation (TME and PVA).
Are the present doses relevant to previous clinical observations?

We primarily employed an identical levosimendan loading dose as used in the LIDO trial (7). However, our experimental continuous infusion-dose needed to restore contractile dysfunction, was approximately half of the dose used in this trial, but identical to doses used in a contemporary registry (25). Importantly, the hemodynamic responses to the employed dose is compatible with the effect in the LIDO (7) and SURVIVE (26, 27) studies inducing a similar increase in cardiac output compared to the clinical trials. Also compared to these trials, a lower dose of dobutamine was necessary to reverse and exceed the hemodynamic status in the posts ischemic pigs. A possible explanation for these observations could be that these relatively young and healthy animals have no chronic failure-induced desensitization of the beta-receptors, and no preischemic chronic beta-blocker treatment hampering the inotropic effects. Our model of acute coronary occlusions and reperfusion in the pig differs from the remodeled human failing hearts both in hemodynamic responses and subcellular functions, but the model has proven sensitive to surplus oxygen consumption (18, 22) and can thus act as a model system for drug efficiencies and metabolism. It should be mentioned that the small amount amiodarone used in pigs are 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 (28).

Energetic effects of levosimendan

Several previous studies have addressed the issue of a relatively energy-conserving effect of levosimendan in experimental models of posts ischemic stunning and heart failure.
Pagel and coworkers (10) 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 clinical relevant dose of levosimendan in these dogs. However, in this study the control group had an excessive increase in these indexes, possibly marking the different vascular loading conditions in the two groups. In addition, the actual oxygen consumption was not assessed in these hearts.

Todaka et al. (11) assessed the oxygen consumption related to levosimendan infusions in isolated rat and failing dog hearts by calculating the mechanical work in the pressure-volume area model. In their study, the oxygen wasting effect of inotropy was observed from levosimendan infusions compatible with a previously described phosphodiesterase III effect of the drug (5). However, the doses chosen in this study were complicated by the non-physiological isolated heart model revealed by the excessive tachycardia induced by the drug (exceeding 140 beats per min). The study does 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. (8) compared the energetic effects of high-dose dobutamine and levosimendan in isolated rabbit hearts after transient ischemia with principally the same findings; a surplus oxygen waste can be induced by levosimendan in excessive doses parallel to the effect of the adrenergic dobutamine.

In the present study the effect of a supratherapeutic dose of levosimendan was assessed in a separate group of pigs. Due to the long half life of the drug (t_{1/2} of 81 hours for the active metabolite OR-1896) and long acting duration from an injection (24 hours)
(29), a comparison of different drug doses in the same animals is impractical. Data from these experiments did demonstrate the known tachycardia and hypotension following excessive doses of levosimendan, and also confirmed the oxygen wasting effect of these high and non-therapeutic 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 (UCP) and reactive oxygen species (30) 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 (2). Our study suggests that in low doses, an adrenergic inotrope like dobutamine will convert the mobilized calcium to active actinomyosin crosslinking without excessive metabolic demands.

Levosimendan in high doses possibly induce an increased oxygen metabolism through the phosphodiesterase III effect and thereby also increased handling of calcium (5).

**Conclusion**

The present study demonstrates that neither dobutamine nor levosimendan induce surplus oxygen in clinically relevant doses in the stunned pig heart. This observation is compatible with the equal survival effects of the two drugs in the large randomized studies on acute heart failure (26, 27), and the possibility of such an energetically neutral effect of inotropic drugs should influence the planning and interpretation of clinical trials employing inotropes.
Funding

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Disclosures

None declared
References


Legends to figures

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

Figure 2
Representative pressure-volume loops during vena cava occlusions. Each panel demonstrates the loops in postischemic hearts and during subsequent treatment with levosimendan low (LD) or high dose (HD) or corresponding dobutamine (low dose LD, high dose HD).

Figure 3a
One experiment demonstrating the relation between mechanical work and oxygen consumption during levosimendan LD infusion as the mechanical work was gradually reduced by preload reductions. PVA; pressure volume area, TTI; tension-time index, TME; total mechanical energy.

Figure 3b
One experiment demonstrating the relation between mechanical work and oxygen consumption during low (LD) and high dose (HD) dobutamine infusions as the mechanical work was gradually reduced by preload reductions. The mechanical indexes are defined in fig 3a.

Figure 4.

All observed relations between mechanical work and oxygen consumption in the 16 pigs from the first randomized part of the protocol (levosomendan LD and dobutamin LD and HD). The curves are shown for the tension-time index (TTI) only since this index has been proven to be the most sensitive to detect surplus oxygen consumption. Significantly increased MVO₂/TTI compared to postischemic values was observed only for the high dose of dobutamine.

Dobutamine LD is 1.25 µg/kg/min, dobutamine HD is 10µg/kg/min and levosimendan LD is 24 µg/kg bolus in addition to 0.04 µg/kg/min.

Figure 5

The curves represent the mean covariant regression lines for the postischemic mechanoenergetic relation and the effects of the three drug regimens shown in figure 4. All three 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/min) 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/min). There was a significantly increased MVO2/mechanical index compared to postischemic values for all the three mechanical indexes (PVA; p=0.007, TTI; p=0.025, TME; p<0.0001)
Table 1: The hemodynamic effects of repetitive ischemia in pig left ventricles and the effect of a therapeutic dose of levosimendan on postischemic circulatory function.

<table>
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<tr>
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<th>Baseline Mean ±SD</th>
<th>Postischemic Mean ±SD</th>
<th>Levosimendan 24 μg/kg Mean ±SD</th>
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<td>MAP [mmHg]</td>
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<td>PVR [dynes·sec/cm²]</td>
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</table>

MAP; 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 blood flow, SV; stroke volume, EDP; end-diastolic pressure, Tau; asymptotic pressure decay in the left ventricle, SW; stroke work
Table 2 The hemodynamic effect of repetitive ischemia in pig left ventricles and the effect of dobutamine on postischemic circulatory function.

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean ± SD</th>
<th>Postischemic Mean ± SD</th>
<th>P vs baseline</th>
<th>Dobutamine 1.25 μg/kg/min Mean ± SD</th>
<th>P vs Postischemic</th>
<th>Dobutamine 10 μg/kg/min Mean ± SD</th>
<th>P vs Dobutamine 1.25 μg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP [mmHg]</td>
<td>97 ±14</td>
<td>89 ±11</td>
<td>0.061</td>
<td>96 ±12</td>
<td>0.043</td>
<td>92 ±13</td>
<td>0.683</td>
</tr>
<tr>
<td>HR [1/min]</td>
<td>82 ±18</td>
<td>95 ±28</td>
<td>0.105</td>
<td>100 ±27</td>
<td>0.791</td>
<td>132 ±28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPAP [mmHg]</td>
<td>23 ±3</td>
<td>23 ±4</td>
<td>0.002</td>
<td>23 ±5</td>
<td>1.000</td>
<td>26 ±5</td>
<td>0.039</td>
</tr>
<tr>
<td>CO [l/min]</td>
<td>2.83 ±0.4</td>
<td>2.73 ±0.6</td>
<td>0.493</td>
<td>3.16 ±0.6</td>
<td>0.002</td>
<td>4.76 ±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR [dynes·sec/cm²]</td>
<td>2625 ±417</td>
<td>2531 ±570</td>
<td>0.425</td>
<td>2317 ±376</td>
<td>0.310</td>
<td>1485 ±205</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR [dynes·sec/cm²]</td>
<td>388 ±53</td>
<td>523 ±129</td>
<td>0.006</td>
<td>443 ±144</td>
<td>0.025</td>
<td>369 ±102</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dPdmtmax [mmHg/s]</td>
<td>1441 ±154</td>
<td>1148 ±87</td>
<td>&lt;0.001</td>
<td>1679 ±108</td>
<td>&lt;0.001</td>
<td>3721 ±746</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dPdmin [mmHg/s]</td>
<td>-1834 ±250</td>
<td>-1560 ±183</td>
<td>0.010</td>
<td>-1932 ±282</td>
<td>0.018</td>
<td>-2740 ±535</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ees [mmHg/ml]</td>
<td>2.0 ±0.5</td>
<td>2.7 ±1.8</td>
<td>0.256</td>
<td>3.1 ±2.2</td>
<td>1.000</td>
<td>5.9 ±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRSW [mmHg]</td>
<td>51 ±13</td>
<td>49 ±13</td>
<td>0.667</td>
<td>62 ±19</td>
<td>0.014</td>
<td>105 ±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVCBF [ml/min]</td>
<td>74 ±15</td>
<td>88 ±24</td>
<td>0.172</td>
<td>106 ±18</td>
<td>0.077</td>
<td>165 ±29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV [ml]</td>
<td>35 ±5</td>
<td>30 ±7</td>
<td>0.018</td>
<td>33 ±8</td>
<td>0.284</td>
<td>37 ±8</td>
<td>0.001</td>
</tr>
<tr>
<td>EDP [mmHg]</td>
<td>18 ±6</td>
<td>19 ±4</td>
<td>0.695</td>
<td>16 ±3</td>
<td>0.125</td>
<td>18 ±9</td>
<td>0.796</td>
</tr>
<tr>
<td>Tau [msec]</td>
<td>48 ±9</td>
<td>46 ±7</td>
<td>0.264</td>
<td>40 ±5</td>
<td>0.002</td>
<td>26 ±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SW [ml·mmHg]</td>
<td>3195 ±788</td>
<td>2357 ±717</td>
<td>0.005</td>
<td>3110 ±1090</td>
<td>0.125</td>
<td>3562 ±1179</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Abbreviations; see table 1.
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>Baseline Mean ±SD</th>
<th>Levosimendan 48 μg/kg Mean ±SD</th>
<th>Levosimendan 48 μg/kg Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P vs. baseline</td>
<td>P vs. postischemic</td>
<td>P vs. postischemic</td>
</tr>
<tr>
<td>MAP [mmHg]</td>
<td>94 ±21</td>
<td>81 ±19</td>
<td>0.006</td>
<td>74 ±13</td>
</tr>
<tr>
<td>HR [1/min]</td>
<td>82 ±20</td>
<td>105 ±44</td>
<td>0.156</td>
<td>120 ±45</td>
</tr>
<tr>
<td>MPAP [mmHg]</td>
<td>20 ±3</td>
<td>23 ±2</td>
<td>0.055</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>0.037</td>
<td>3.03 ±1</td>
</tr>
<tr>
<td>SVR [dynes·sec/cm²]</td>
<td>2418 ±567</td>
<td>2252 ±670</td>
<td>0.112</td>
<td>1807 ±343</td>
</tr>
<tr>
<td>PVR [dynes·sec/cm²]</td>
<td>336 ±63</td>
<td>462 ±150</td>
<td>0.041</td>
<td>401 ±117</td>
</tr>
<tr>
<td>dPdmax [mmHg/s]</td>
<td>1622 ±364</td>
<td>1230 ±273</td>
<td>0.001</td>
<td>1408 ±355</td>
</tr>
<tr>
<td>dPdmin [mmHg/s]</td>
<td>-1919 ±460</td>
<td>-1536 ±391</td>
<td>0.003</td>
<td>-1531 ±468</td>
</tr>
<tr>
<td>Ees [mmHg/ml]</td>
<td>3.2 ±0.6</td>
<td>3.0 ±1.6</td>
<td>0.748</td>
<td>3.9 ±1.5</td>
</tr>
<tr>
<td>PRSW [mmHg]</td>
<td>49 ±13</td>
<td>53 ±12</td>
<td>0.109</td>
<td>50 ±8</td>
</tr>
<tr>
<td>LVCBF [ml/min]</td>
<td>82 ±24</td>
<td>85 ±23</td>
<td>0.480</td>
<td>103 ±37</td>
</tr>
<tr>
<td>SV [ml]</td>
<td>35 ±3</td>
<td>27 ±8</td>
<td>0.01</td>
<td>27 ±8</td>
</tr>
<tr>
<td>EDP [mmHg]</td>
<td>14 ±4</td>
<td>14 ±4</td>
<td>0.641</td>
<td>11 ±3</td>
</tr>
<tr>
<td>Tau [msec]</td>
<td>42 ±8</td>
<td>44 ±6</td>
<td>0.342</td>
<td>39 ±5</td>
</tr>
<tr>
<td>SW [ml·mmHg]</td>
<td>2672 ±807</td>
<td>1910 ±711</td>
<td>0.050</td>
<td>2014 ±830</td>
</tr>
</tbody>
</table>

Abbreviations; see table 1.
Figure 1

[Diagram showing the experimental protocol for treatments involving Dobutamine and Levosimendan at different concentrations and durations.]
Figure 2
Figure 4
Figure 5

Graph showing the relationship between MVO2 (J/b/100g LV) and PVA (J/b/100g LV), TTI (mmHg*s), and TME (J/b/100g LV) for different conditions:
- Postischemic
- Dobutamine LD
- Dobutamine HD
- Levosimendan

Legend indicates significance level with an asterisk (*) for certain conditions.
Figure 6

Three scatter plots showing the relationship between MVO2 (J/b/100g LV) and PVA (J/b/100g LV), TTI (mmHg*s), and TME (J/b/100g LV). The plots compare Postischemic and Levosimendan HD conditions.
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

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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.