Ca\textsuperscript{2+} sensitizer superior to catecholamine during myocardial stunning?\textsuperscript{a,}\textsuperscript{b}

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Abstract

Background: After open-chest cardiac surgery, ventricular function remains depressed (myocardial stunning). Catecholamines (epinephrine) improve ventricular function by increasing the intracellular Ca\textsuperscript{2+} concentration. In parallel, the oxygen consumption is increased, so that the hitherto intact myocardium can be jeopardized. In the very insufficient ventricle, epinephrine can even become ineffective. Since Ca\textsuperscript{2+} efficiency was increased by 212% (\textit{p} = 0.0002), stroke volume SV (44%, \textit{p} = 0.0004), maximal pressure increase \(\frac{dP}{dt_{\text{max}}}\) (133%, \textit{p} = 0.0009) and MVO\textsubscript{2}/beat (+171%, \textit{p} = 0.03), external efficiency \(\eta\) was increased by 92% (\textit{p} = 0.02). Levosimendan in postischemic hearts increased HR (32%, \textit{p} = 0.009) and improved hemodynamics in terms of CO (62%, \textit{p} = 0.0006). It increased SV (115%, \textit{p} = 0.004), \(\frac{dP}{dt_{\text{max}}}\) (133%, \textit{p} = 0.009) and MVO\textsubscript{2}/beat (+36%, \textit{p} = 0.01). External efficiency \(\eta\) was increased by 117% (\textit{p} = 0.03). In five additional extremely dysfunctional rabbit hearts, epinephrine was ineffective. Additional levosimendan increased hemodynamics in terms of CO (85%, \textit{p} = 0.01), SV (44%, \textit{p} = 0.03) and CR (−17%, \textit{n.s.}, \textit{p} = 0.1). It altered hemodynamics in terms of AVDO\textsubscript{2} (+7.0%, \textit{n.s.}, \textit{p} = 0.3) and MVO\textsubscript{2} (+32%, \textit{p} = 0.007) and MVO\textsubscript{2}/beat (+2.3%; \textit{n.s.}, \textit{p} = 0.4). External efficiency was increased by 307% (\textit{p} = 0.04). In five additional extremely dysfunctional rabbit hearts, epinephrine was ineffective. Additional levosimendan increased hemodynamics in terms of AVDO\textsubscript{2} (+7.0%, \textit{n.s.}, \textit{p} = 0.3) and MVO\textsubscript{2} (+32%, \textit{p} = 0.007) and MVO\textsubscript{2}/beat (+2.3%; \textit{n.s.}, \textit{p} = 0.4). External efficiency was increased by 307% (\textit{p} = 0.04).

1. Introduction

In 2003, almost 100,000 open-chest cardiac operations were conducted in Germany. During such operations, the heart is exposed to ischemia leading to postischemic dysfunction, i.e. myocardial stunning.

Myocardial stunning is an acute derangement of contractile function of ischemic myocardium at the moment of restoration of coronary blood flow by various interventions like bypass grafting, angioplasty or thrombolysis. The pathogenesis of ischemia/reperfusion (IR) injury consists of several mechanisms. Recently, there is increasing evidence for a hypercontracture during reperfusion induced by high cytosolic Ca\textsuperscript{2+} levels or by low ATP concentrations [1]. On the other hand, the intensity of free radical generation during reperfusion, and hence reperfusion injury, was found to be proportional to the severity of the antecedent ischemia [2].

If myocardial stunning is severe, it can be reversed with several inotropic agents, such as dobutamine, epinephrine, phosphodiesterase III inhibitors, and calcium chloride. Classical inotropes seemingly improve clinical symptoms and hemodynamics. However, they are associated with...
adverse reactions and increased long-term mortality. Catecholamines like epinephrine induce Ca^{2+} overload in cardiomyocytes. This, together with the desired positive inotropic effect, induces several undesired effects like arrhythmias, cell death and both systolic and diastolic dysfunction. Another undesired effect presents the impaired relation between cardiac function and oxygen consumption, which was termed catecholamine oxygen wasting [3].

Calcium sensitizers, like levosimendan, provide inotropic support via a different mechanism. These agents sensitize troponin C to calcium in a manner dependent on calcium concentration, thereby increasing the effects of calcium on cardiac myofilaments during systole and improving contraction at low energy cost. In contrast to epinephrine, levosimendan causes no diastolic Ca^{2+} overload, impairing myocardial relaxation and increasing energy expenditure. Furthermore, levosimendan induces vasodilatation through opening K_{ATP} channels [4].

Levosimendan is administered in the advanced state of cardiac insufficiency. Long-term administration of catecholamines or heart failure per se can down-regulate the sensitivity towards these agents. During such a state of catecholamine resistance, Ca^{2+} sensitizers will likely exert beneficial effects.

In this study on isolated rabbit hearts that were perfused with an erythrocyte-enriched Krebs–Henseleit solution, the effects of epinephrine and levosimendan on hemodynamics and oxygen consumption during postsischemic reperfusion were investigated. In particular, the effectiveness of levosimendan in catecholamine-insensitive rabbit hearts with posts ischemic dysfunction was explored.

2. Methods

The experiments were performed on 27 male New Zealand white rabbits with an average weight of 3200 ± 200 g. The rabbits were handled according to the animal welfare regulations of the German federal authorities. After rapid excision, the hearts were connected to a modified Langendorff apparatus and perfused with an erythrocyte-enriched Krebs–Henseleit solution containing (in mM): NaCl 119, NaHCO3 25, KCl 4.7, CaCl2 1.8, MgCl2 1.2, EDTA 0.5 and glucose 11. The buffer was equilibrated with 72% N2, 22% O2, 6% CO2 at 37 °C, giving a pH of 7.4. Bovine erythrocytes were added to achieve a hematocrit of 30%, and 4 g/100 ml albumin was added to avoid major edema formation. The Ca^{2+} concentration was adjusted to 2.5 mM.

A water-filled latex balloon was inserted into the left ventricular (LV) cavity via the left atrium. The balloon was connected to a systemic circuit that contained two artificial valves and a windkessel. The cardiac output was measured via an ultrasonic flow probe (T 206, Transonic Systems, Ithaca, US), aortic pressure (afterload) with a pressure transducer (P 23 II, Statham, Oxnard, US). The circuit permitted changes in afterload and in preload conditions without alteration of coronary perfusion pressure. A 3 F microtip manometer (SPR-249, Millar, Houston, US), inserted into the balloon, was used to measure LV pressure.

Sonomicrometry was employed (System 6, Model 257, Triton, San Diego, US) for the measurement of the LV internal diameter using two ultrasonic crystals, glued to either side of the balloon.

Total coronary blood flow (CBF) was drained and measured with a second ultrasonic flow probe. The difference in arterio-venous O2 content (AVDO2) was continuously measured using absorption spectrophotometry (AVOX systems, Lancaster, US).

3. Experimental protocol

During preparation and instrumentation of the isolated heart, the coronary perfusion pressure (CPP) was held at 60 mmHg. After the end of instrumentation, CPP was increased to 80 mmHg and remained unchanged throughout the rest of the protocol, except for a 25 min ischemia. The temperature of the heart was maintained at 37.0 ± 0.6 °C by immersion in a temperature-controlled chamber.

Control conditions were recorded after stabilization of LV function, i.e. 20 min after the end of instrumentation. The hearts were randomized into two groups: epinephrine and levosimendan. All hearts were subjected to 25 min normothermic, no-flow ischemia followed by 20 min reperfusion. Epinephrine (0.03 μmol) or levosimendan (0.75μmol) was administered as a bolus into the system close to the isolated heart (Fig. 1). Because of the short-lasting epinephrine effect, data were recorded while LV pressure was at maximum. In the levosimendan group, data were recorded after a new hemodynamic steady state (~5 min).

The levosimendan concentration was chosen after a dose finding study in the preischemic heart, where peak LV pressure responses from 9.0 nmol to 1.0 μmol levosimendan were assessed in five hearts (data not shown). A levosimendan dose of 0.75 μmol was taken, because it clearly increased peak LV pressure (~30%) in the preischemic hearts.

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Fig. 1. Epinephrine in postischemic/reperfused hearts (n = 16) caused significant decreases in rel. LVPed (A) and significant increases in external efficiency (η) (B) compared to reperfusion (~25 min; p < 0.05 vs control; p < 0.05 epinephrine vs levosimendan). Levosimendan (n = 11) caused significant decreases in rel. LVPed (A) and significant increase in η (B) compared to reperfusion. ( p < 0.05 vs control; p < 0.05 epinephrine vs levosimendan).
The corresponding concentration agrees in part with the literature [5]. The epinephrine dose (5.0 μg) was also chosen in accordance with the literature [6]. The mean duration of action was 121 s.

In five hearts, 0.03 μmol epinephrine did not exert any detectable effect during reperfusion. In these catecholamine-insensitive hearts, 0.75 μmol levosimendan was administered.

Preloading conditions were assessed via the intraventricular diameter. At the end of the protocol, the atria were cut to determine the wet weight of the ventricles.

4. Data acquisition

The following variables were continuously assessed via a Powerlab and Quad Bridge system (ADInstruments, BRSP, Spechbach, DE) and recorded using standard software (ADInstruments, Chart 5, Spechbach): cardiac output (CO), left ventricular pressure (LVP), coronary blood flow, AVDO2 and inner LV diameter. Heart rate (HR), LV dp/dtmax and dp/dtmin were derived from the pressure signal.

5. Calculations and statistics

Stroke volume (SV) was derived from CO and HR. Stroke work (W) was assessed from SV and LVPmax. CBF was normalized to 100 g wet weight. Myocardial oxygen consumption (MVO2) was calculated from normalized CBF and AVDO2. MVO2 was divided by HR to give MVO2/beat. Finally, external efficiency (η) was calculated as the ratio between W and MVO2/beat.

Data are expressed as mean ± SD. Because of a relatively large biological variation, data were normalized. Thus, relative values from the epinephrine group and the levosimendan group were compared by using a two-way analysis of variance (ANOVA) for repeated measures (SPSS 11.5; SPSS Inc., US). After detection of a significant overall effect in the relative values, a post-hoc test with Bonferroni correction was performed to compare single mean values. A p value of 0.05 was considered indicative of significant differences.

6. Results

The hemodynamic measures of both groups remained comparable during control. Similarly, the postschismic function was depressed to a comparable degree (Table 1). Epinephrine (epi) or levosimendan (levo) in the postschismic hearts significantly improved nearly all systolic and diastolic measures (Table 1; Fig. 2).

However, some measures exhibited different responses. While early relaxation (dp/dtmin) was improved, end-diastolic pressure after epi was significantly impaired versus levo (−26% vs −63%; Fig. 2A). On the other hand, coronary resistance exhibited different tendencies as it was increased after epi (+31%; Fig. 2B) and unaffected after levo (−17% n.s.; Fig. 2B). Although systolic function in both groups was comparable, AVDO2 was significantly increased in the epi group (63%) and unaffected in the levo group (7.0% n.s.). As a result, both MVO2 was higher in the epi group (+67%) compared with the levo group (+32%), as well as MVO2/beat (epi: +36% vs levo: +2% n.s.; Fig. 2C). Hence, both drugs improved ventricular external efficiency (η), whereas this...
increase was significantly more pronounced in the levo group (epi: 92% vs levo: 30%; Fig. 2D).

Five additional hearts exhibited considerable postischemic dysfunction (Table 2; Fig. 3) compared to hearts mentioned above. Epi administration in these hearts only insignificantly improved systolic measures (Table 2; Fig. 3) whereas subsequent levo clearly improved these measures (Table 2; Fig. 3), although not identically as if given without prior epinephrine.

Combination of epinephrine and levosimendan in the catecholamine resistant heart (res) caused a disproportional increase in systolic and diastolic measures compared to levosimendan (levo) alone: stroke work (res: 588 vs levo: 115), LVP\text{max} (168 vs 95), dP/dt\text{max} (103 vs 133), LVP\text{ed} (−98 vs −63), coronary resistance (−54 vs −17 n.s.), MVO\text{2} (132 vs 32) and MVO\text{2}/beat (164 vs 2.3 n.s.).

### Table 2
After reperfusion, systolic measures were drastically decreased in five additional hearts

<table>
<thead>
<tr>
<th>Reperfusion</th>
<th>Resistive versus non-resistive</th>
<th>Epinephrine (0.03 µmol)</th>
<th>Levosimendan (0.75 µmol)</th>
<th>Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>123 ± 85 versus n.s. 125 ± 45</td>
<td>123 ± 85 versus n.s. 123 ± 92</td>
<td>123 ± 92 versus n.s. 125 ± 49</td>
<td>+56 ± 94 n.s.</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>2.3 ± 2.0 versus 4.3 ± 3.3</td>
<td>2.3 ± 2.0 versus n.s. 1.2 ± 0.5</td>
<td>1.2 ± 0.5 versus 3.6 ± 2.2</td>
<td>+159 ± 126</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>0.03 ± 0.02 versus 0.06 ± 0.05</td>
<td>0.03 ± 0.02 versus n.s. 0.02 ± 0.02</td>
<td>0.02 ± 0.02 versus 0.03 ± 0.02</td>
<td>+89 ± 100</td>
</tr>
<tr>
<td>W (mmHg ml)</td>
<td>0.4 ± 0.3 versus 2.1 ± 2.0</td>
<td>0.4 ± 0.3 versus n.s. 0.4 ± 0.2</td>
<td>0.4 ± 0.2 versus 2.6 ± 2.6</td>
<td>+588 ± 470</td>
</tr>
<tr>
<td>LVP\text{max} (mmHg)</td>
<td>30 ± 14 versus 39 ± 34</td>
<td>30 ± 14 versus n.s. 29 ± 10</td>
<td>29 ± 10 versus 73 ± 39</td>
<td>+168 ± 146</td>
</tr>
<tr>
<td>dP/dt\text{max} (mmHg/s)</td>
<td>750 ± 169 versus n.s. 824 ± 531</td>
<td>750 ± 169 versus n.s. 715 ± 240</td>
<td>715 ± 240 versus 1498 ± 817</td>
<td>+103 ± 50</td>
</tr>
<tr>
<td>dP/dt\text{min} (mmHg/s)</td>
<td>−685 ± 323 versus n.s. −593 ± 357</td>
<td>−685 ± 323 versus n.s. −673 ± 349</td>
<td>−673 ± 349 versus −1205 ± 702</td>
<td>+84 ± 42</td>
</tr>
<tr>
<td>LV\text{ed} (mmHg)</td>
<td>0.7 ± 0.4 versus 4.1 ± 3.2</td>
<td>0.7 ± 0.4 versus n.s. 0.9 ± 0.6</td>
<td>0.9 ± 0.6 versus 0.03 ± 0.02</td>
<td>−98 ± 1.9</td>
</tr>
<tr>
<td>CR (mmHg/ml/min/100 g)</td>
<td>5.3 ± 4.4 versus 1.4 ± 0.8</td>
<td>5.3 ± 4.4 versus n.s. 4.8 ± 4.4</td>
<td>4.8 ± 4.4 versus 1.7 ± 1.2</td>
<td>−54 ± 29</td>
</tr>
<tr>
<td>AVDO\text{2} (ml O2/100 ml blood)</td>
<td>9.6 ± 1.0 versus n.s. 9.1 ± 2.7</td>
<td>9.6 ± 1.0 versus n.s. 10.1 ± 1.4</td>
<td>10 ± 1.4 versus n.s. 9.0 ± 1.0</td>
<td>−11 ± 12 n.s.</td>
</tr>
<tr>
<td>MVO\text{2} (ml/min/100 g)</td>
<td>63 ± 60 versus n.s. 76 ± 40</td>
<td>63 ± 60 versus n.s. 54 ± 26</td>
<td>54 ± 26 versus 90 ± 73</td>
<td>+132 ± 106</td>
</tr>
<tr>
<td>MVO\text{2}/beat (ml/beat/100 g)</td>
<td>0.4 ± 0.2 versus n.s. 0.6 ± 0.2</td>
<td>0.4 ± 0.2 versus n.s. 0.3 ± 0.2</td>
<td>0.3 ± 0.2 versus 0.8 ± 0.7</td>
<td>+164 ± 140</td>
</tr>
<tr>
<td>External efficiency (%)</td>
<td>1.5 ± 1.2 versus 3.4 ± 3.1</td>
<td>1.5 ± 1.2 versus n.s. 1.2 ± 0.8</td>
<td>1.2 ± 0.8 versus 4.1 ± 2.7</td>
<td>+212 ± 161</td>
</tr>
<tr>
<td>q\text{ad} (mm)</td>
<td>8.0 ± 2.9 versus n.s. 7.8 ± 1.9</td>
<td>8.0 ± 2.9 versus n.s. 8.0 ± 2.6</td>
<td>8.0 ± 2.6 versus n.s. 8.5 ± 1.4</td>
<td>−9 ± 32 n.s.</td>
</tr>
</tbody>
</table>

These (resistive) hearts did almost not react towards epinephrine, but effectively responded towards levosimendan. 1. Column: n.s., not significantly different versus the corresponding reperfusion value in the non-resistant group (paired t-test), p < 0.05. 2. Column: n.s., not significantly different versus the corresponding reperfusion value in the same group (paired t-test), p < 0.05. 3. Column: n.s., not significantly different versus the corresponding epinephrine value in the same group. Changes in % do not result from the values in the preceding columns but represent the averages of the various number of changes (paired t-test), p < 0.05.

### 7. Discussion
The main findings of this experimental study are that both epinephrine and levosimendan improve systolic and diastolic ventricular function of postischemic hearts. Because ventricular function is more increased than myocardial oxygen consumption, external efficiency is significantly improved after both drugs. However, this beneficial effect was significantly more pronounced in the levosimendan group. In drastically dysfunctional hearts, epinephrine was ineffective. Additional levosimendan improved both systolic and diastolic function. Under this condition, oxygen consumption for the functional improvement was clearly higher compared with less dysfunctional hearts. Nevertheless external efficiency was clearly improved.
7.1. Inotropic stimulation of stunned myocardium

Myocardial stunning, no matter how severe or prolonged, is a fully reversible abnormality. It is not caused by a primary deficit of postischemic perfusion [2]. In the stunned myocardium, an inotropic reserve can be recruited [7], e.g. by using inotropic agents [8].

However, stimulating the β-adrenoceptor pathway with catecholamines will finally increase the Ca\(^{2+}\) concentration in the cardiomyocyte [9]. In the stunned myocardium, the Ca\(^{2+}\) homeostasis is already disturbed [10]. Thus, further increasing the Ca\(^{2+}\) concentration will likely cause cardiac arrhythmias, myocardial cell injury and, ultimately, cell death [11].

Levosimendan increases Ca\(^{2+}\)-sensitivity of myofilaments by a molecular mechanism that appears to involve direct binding to the N-lobe of Ca\(^{2+}\)-saturated cardiac troponin C (cTNC). This accounts for this drug's ability to increase tension, because physiological levels of Ca\(^{2+}\) generally do not saturate the myofilaments [12]. In the stunned myocardium, myofilament responsiveness is decreased [13]. Thus, drugs increasing the responsiveness to calcium leaving the cytosolic Ca\(^{2+}\) concentration unchanged, would seemingly present a causal therapy.

7.2. Systolic and diastolic function

In spite of the different modes of action, almost all systolic measures were markedly and comparably increased after both epinephrine and levosimendan. Likewise, early diastolic function (dP/dt\(_{min}\)) was considerably improved. In the epinephrine hearts, late diastolic function was moderately improved by decreasing LVP\(_{ed}\), whereas it was significantly improved after levosimendan, although the heart rate was somewhat increased after both drugs.

Leverosimendan reportedly improves diastolic function in experimental animals [14] and in patients with severe heart failure [15]. In this study, the decrease in LVP\(_{ed}\) after levosimendan was accompanied by an increase in the LV end-diastolic diameter, indicating a right and downward shift of the pressure volume curve, i.e. ventricular compliance was increased. Such a change was not observed in the epinephrine hearts.

7.3. Energetics

This aspect will be elucidated in more detail. Beside the oxygen costs for the contractile machinery [16], additional oxygen is consumed for the increased Ca\(^{2+}\) handling. The costs for this excitation–contraction coupling can become surprisingly high for catecholamines [16]. Because of this, the term catecholamine-induced oxygen wasting was introduced [3].

To assess changes in energetics, the external efficiency (η = cardiac work/myocardial oxygen consumption) proved to be useful [17]. For example, an increased η denotes that the same stroke work is generated with less oxygen expenditure. Oxygen consumption in this experimental model was not increased out of proportion after epinephrine. Thus, energetics, in terms of external efficiency, were improved in these postischemic hearts. On the other hand, the improved systolic function after levosimendan was achieved at almost maintained oxygen consumption. This finding is in agreement with other, earlier reports describing that myosin ATPase is not directly activated and intracellular Ca\(^{2+}\) handling is not increased with this Ca\(^{2+}\) sensitizer [18]. Thus, η after levosimendan was substantially more increased compared with η after epinephrine.

7.4. Coronary resistance

In spite of the increased cardiac work, the coronary resistance was increased after epinephrine. This flow reduction, however, was compensated by an increased arterio-venous oxygen difference. Hence, the α\(_1\)- and α\(_2\)-adrenoceptor-mediated vasoconstriction predominated over a metabolism-induced vasodilation in our model.

In turn, the coronary resistance was decreased after levosimendan, which is in concert with the notion of the drug being an inodilator [4]. This vasodilation originates from a reduced Ca\(^{2+}\) sensitivity of contractile proteins in the vascular smooth muscle, which is the opposite to its Ca\(^{2+}\) sensitization in the cardiac muscle. The vasodilatory action of levosimendan through Ca\(^{2+}\) desensitization occurs without a proportionate decrease in intracellular Ca\(^{2+}\) and may be due to a direct action on contractile proteins or due to hyperpolarization [19].

7.5. Drug administration

A continuous increase in cardiac energy expenditure is supposed to lead to earlier exhaustion of myocardial cells. Thus, continuous administration may have energetic disadvantages due to Ca\(^{2+}\) overload and metabolic effects leading to apoptosis and arrhythmias [11].

Because the half-life of levosimendan is about 1 h, its effects were always long-lasting, i.e. until the end of the protocol. The relatively long half-life (70–80 h; [20]) of the active metabolite OR-1896 facilitates handling in the clinical setting. Nevertheless, levosimendan infusion of 24 h is common [21].

7.6. Epinephrine resistance

Cardiac surgery requiring cardiopulmonary bypass can result in acute desensitization of β-adrenoceptors [22]. Hence the response towards catecholamines is attenuated or even lost. Such a catecholamine resistance might also develop chronically, e.g. in patients on catecholamine treatment [23].

In some of our hearts, the function remained markedly depressed upon reperfusion; here, epinephrine was ineffective. We suggest that in these hearts, the functional responsiveness of β-adrenergic receptors was acutely reduced after myocardial ischemia. Ventricular function was drastically improved, likely due to the different mode of action of this drug. Levosimendan directly binds to the N-lobe of Ca\(^{2+}\)-saturated cardiac cTNC without requiring functional β-adrenergic receptors.

This finding is in agreement with the clinical situation in which patients experience clinical deterioration or do not respond to a single inotropic drug. Increasing evidence
suggests the use of levosimendan in combination with dobutamine in patients with decompensated heart failure that is refractory to dobutamine alone [24]. Combining levosimendan with epinephrine rendered the catecholamine more potent as an inotrope, and adding epinephrine increased the potency as well as the efficacy of levosimendan [25].

Unfortunately, the external efficiency was decreased compared with just levosimendan alone, indicating a disproportionate increase in oxygen consumption in these very dysfunctional rabbit hearts. Because we did not assess Ca2+ concentration in myocytes, it is difficult to judge whether or not Ca2+-overload was responsible for this increase. In fact, the increase in potency of epinephrine with the addition of levosimendan appeared to be largely independent of cAMP [25]. Whether or not the same is true for the catecholamine resistant hearts is still to be examined.

7.7. In summary

Both epinephrine and levosimendan caused positive inotropic and chronotropic effects in postsischemic/reperfused hearts. Due to the different modes of action, the energetic costs in terms of the external efficiency are different: The increased intracellular Ca2+ concentration was associated with a disproportionate increase in oxygen consumption, whereas the increase in Ca2+ responsiveness was not. In parallel, the coronary resistance was increased after epinephrine but was reduced after levosimendan, supporting the latter’s denomination as an inodilator.

In some postsischemic hearts, depressed ventricular function cannot be improved by using catecholamines, likely owing to catecholamine resistance. In these hearts, levsimendan on top of epinephrine was effective, demonstrating the usefulness of a Ca2+ sensitizer in this very adverse condition.

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