occurrence of severe congestive heart failure or requirement for intra-aortic balloon pump or cardiopulmonary resuscitation (p = 0.0081).

The main and novel findings of this report are: 1) RV involvement in TLVABS is common, transient, and, when present, portends a longer and more critical hospitalization course as compared with patients with isolated LV involvement; and 2) RV involvement, when present, follows a similar pattern of regional wall motion abnormalities as does LV involvement in this syndrome.

It is now clear that RV function is one of the most useful indicators for patient survival in ischemic heart failure (2) and in patients with congenital heart disease (3). In our study, we show for the first time that RV involvement was common in patients with TLVABS, with approximately one-third of patients presenting with detectable RV dysfunction on echocardiography. Even if we assume that all other five patients who did not have echocardiography at initial evaluation had normal RV function, at least one-quarter (8 of 30) of patients with TLVABS have RV involvement. The RV involvement was transient but had a significant impact on hospitalization length and hemodynamic instability. This effect was independent from the accompanying LV dysfunction. Clinicians should be aware of the possibility of RV dysfunction because it might have a significant impact on patient morbidity, management, and, ultimately, outcome.

The major limitation of the study lies in its retrospective nature and relatively small number of patients. The echocardiograms were obtained for clinical use and specific imaging was not performed for the assessment of RV function. In addition, although echocardiography is used to assess RV function, technical limitations to imaging exist because of the complexity of the RV anatomy (4).

In conclusion, in TLVABS, RV involvement is relatively common and is reversible. Right ventricular involvement has a negative impact on hospital stay and morbidity, and its identification can help predict hemodynamic instability. Given our findings, we propose relabeling this syndrome as “transient cardiac apical ballooning syndrome.”

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REFERENCES


Levosimendan Improves Cardiopulmonary Resuscitation and Survival by K\textsubscript{ATP} Channel Activation

To the Editor: Global myocardial ischemia during cardiac arrest accounts for post-resuscitation myocardial dysfunction (1). The new myofilament Ca\textsuperscript{++} sensitizer, levsimendan, is of potential benefit in this setting, for it improves myocardial contractility without increasing myocardial oxygen consumption (2). Experimentally, levsimendan produces dose-dependent increases in contractility without adverse effects on diastolic function (3,4).

Levsimendan is a K\textsubscript{ATP} channel opener of both plasma membranes and mitochondria (2,5). Opening of adenine triphosphate (ATP)-sensitive potassium channels in ventricular myocytes contributes to the inotropic action of levsimendan (2). Activation of the K\textsubscript{ATP} channels also mitigates myocardial ischemic injury, reminiscent of “ischemic preconditioning” during cardiopulmonary resuscitation (6), with improved survival. We therefore hypothesized that levsimendan would improve initial cardiac resuscitation, post-resuscitation myocardial function, and post-resuscitation survival resulting from K\textsubscript{ATP} channel activation.

The study was approved by the Institutional Animal Care and Use Committee of the Weil Institute. Fifteen male Sprague-Dawley rats weighing between 450 and 550 g were fasted overnight. Anesthesia followed intraperitoneal injection of pentobarbital in an amount of 45 mg kg\textsuperscript{-1}. The trachea was orally intubated. Left ventricular pressure, including both dP/dt\textsubscript{max} and negative dP/dt, right atrial pressure, and aortic pressure were measured with polyethylene catheters (PE 50, Becton-Dickinson, Sparks, Maryland) and with a high-sensitivity pressure transducer (model 42584-01, Abbott Critical Care System, North Chicago, Illinois). A thermocouple microprobe (9030-12-D-34, Columbus Instrument, Columbus, Ohio) was advanced into the descending thoracic aorta for blood temperature measurements. For cardiac output measurements, 0.2 ml of isotonic saline, maintained at 10°C, was injected into the right atrium. Thermodilution curves were computed (CO-100, Weil Institute of Critical Care Medicine, Rancho Mirage, California). A pre-curved guide wire was advanced through a 4-F catheter into the right ventricle until an endocardial electrogram was observed. Forty-five minutes before the induction of cardiac arrest, five animals were randomized to pre-treatment with a bolus injection of glibenclamide into the right atrium (6). A 60-Hz direct current, to a maximum of 3.5 mA, was delivered to the right ventricular endocardium until ventricular fibrillation (VF) was induced. Current flow was then continued for 3 min such as to prevent spontaneous defibrillation. Ventricular fibrillation was untreated for 6 min. Pre-cordial compressions at a rate of 200/min were started after 6 min, with a pneumatically driven mechanical chest compressor, and animals were mechanically ventilated with a tidal volume of 0.65 ml/100 g animal body weight, a frequency of 100/min, and FiO\textsubscript{2} of 1.0.
Depth of compressions was adjusted to secure coronary perfusion pressure (CPP) of 23 ± 1 mm Hg. Levosimendan (Orion Corp., Espoo, Finland, for Abbott Laboratories, 2.5 mg/ml) or saline placebo was injected into the right atrium after 2 min of untreated VF. Resuscitation was attempted with up to two 2-joule biphasic shocks. Restoration of spontaneous circulation (ROSC) was defined as the return of supraventricular rhythm with a mean aortic pressure of 60 mm Hg. Electrocardiographic lead II was continuously recorded. ST-segment elevation was digitally measured at baseline and at 3 min after ROSC, utilizing WINDAQ software (DATAQ Instruments, Inc., Akron, Ohio) (1,7). Mechanical ventilation with oxygen was continued for 4 h after resuscitation. Animals were then allowed to recover and all catheters were removed. Post-resuscitation survival was observed for a total of 48 h.

For measurements between groups, analysis of variance (ANOVA) and Scheffe’s multicomparison techniques were employed. Comparisons between time-based measurements within each group were performed with ANOVA repeated measurement. Categorical variables were analyzed with the Fisher exact test. Measurements are reported as mean ± SD. Values of p < 0.05 were considered significant.

Baseline hemodynamic and blood analysis did not differ significantly among the groups. Pre-cordial compression increased CPP to an average of 23 ± 1 mm Hg. Each animal, excepting only one pre-treated with glibenclamide, was resuscitated. A significantly lesser number of electrical shocks were required before resuscitation in levosimendan-treated animals (Table 1). Three minutes after levosimendan, each animal survived for more than 48 h. This contrasted with animals pre-treated with glibenclamide, a K<sub>ATP</sub>-channel-blocking agent, in which duration of survival approximated placebo controls (27 ± 7 h and 28 ± 8 h, respectively).

Moderation of ischemic injury by K<sup>+</sup>-channel opening after levosimendan resulted in lesser myocardial dysfunction and prolonged the duration of survival. Pre-treatment with a non-selective K<sup>+</sup>-channel blocker abolished these benefits.

The capability of minimizing myocardial ischemic injury during cardiac arrest, like pre-conditioning, is possibly explained by its K<sub>ATP</sub>-channel agonist effects. Lesser post-resuscitation ST-segment elevations provide additional evidence of levosimendan’s capability to minimize ischemic injury and thereby improve post-resuscitation myocardial function. Each of these effects would explain, at least in part, improvement in post-resuscitation myocardial function and outcomes.

We recognize limitations in the interpretation of our findings. The studies were performed on animals without cardiovascular disease. Accordingly, direct applicability to human patients remains to be proven. We conclude that the administration of levosimendan in experimental settings of VF facilitates resuscitation, significantly lessens post-resuscitation myocardial dysfunction, and improves post-resuscitation survival.

Table 1. Effects of Blocking K<sub>ATP</sub> Channel Action of Levosimendan

<table>
<thead>
<tr>
<th></th>
<th>Resuscitated/ Total</th>
<th>Number of Shocks</th>
<th>Duration of CPR (s)</th>
<th>ST-Segment Elevation (μV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan</td>
<td>5/5</td>
<td>3.8 ± 2.7†</td>
<td>407 ± 48†</td>
<td>75 ± 39*</td>
</tr>
<tr>
<td>Glibenclamide + levosimendan</td>
<td>4/5</td>
<td>7.0 ± 2.1</td>
<td>476 ± 43</td>
<td>168 ± 10</td>
</tr>
<tr>
<td>Placebo</td>
<td>5/5</td>
<td>9.0 ± 3.0</td>
<td>487 ± 61</td>
<td>167 ± 36</td>
</tr>
</tbody>
</table>

*p ≤ 0.01 vs. placebo and glibenclamide + levosimendan. †p < 0.05 vs. placebo.

![Figure 1](https://example.com/image1.png)

Figure 1. Increases in mean arterial pressure and end-tidal CO₂ (ETCO₂) after levosimendan (L, solid circles) in comparison with saline placebo (P, open squares) and glibenclamide (G + L, open triangles). Values represent mean and bars represent ± SD. *p ≤ 0.05, **p ≤ 0.01 vs. placebo, †p ≤ 0.05, ††p ≤ 0.01 vs. glibenclamide. BL = baseline; DF = defibrillation; PC = pre-cordial compression; VF = ventricular fibrillation.

REFERENCES


A Protective Anti-Inflammatory Phenotype in High-Risk Individuals Who Do Not Develop Coronary Artery Disease

To the Editor: Patients with hypercholesterolemia, even with additional risk factors, may not during a lifetime develop coronary artery disease (CAD) (1). These observations suggest that protective mechanisms may balance those directly related to hypercholesterolemia and delay, or even abolish, the atherosclerotic process in otherwise high-risk individuals. To further elucidate these issues, we examined endothelial function as well as soluble markers of endothelial cell activation and inflammation in selected patients referred to coronary angiography with low or high levels of plasma low-density lipoprotein (LDL) cholesterol.

We consecutively screened all individuals attending to our coronary care unit for clinically indicated diagnostic coronary angiography in order to identify high-risk patients (LDL cholesterol >4.5 mmol/l; high-cholesterol group) and low-risk patients (LDL cholesterol <2.7 mmol/l; low-cholesterol group) with and without CAD, resulting in four different study groups: 1) Low LDL without CAD (n = 26), 2) low LDL with CAD (n = 21), 3) high LDL without CAD (n = 22), and 4) high LDL with CAD (n = 24). Significant CAD was predefined as at least two diseased vessels (>70% narrowing of luminal diameter). The exclusion criteria included previous or current statin treatment, previous episodes of acute coronary syndrome (myocardial infarction or unstable angina), signs of left ventricular dysfunction (left ventricular ejection fraction <50%), plasma homocysteine >14 mmol/l, smoking or other known risk factor for development of CAD, extensive use of alcohol, and signs of any acute inflammatory condition. All individuals were receiving aspirin (160 mg/day) and 72% were receiving beta-blocker therapy. The study was approved by the regional ethical committee. Signed informed consent was obtained from each individual.

The determination of endothelium-dependent and -independent vasodilatation in the forearm skin microcirculation was performed by iontophoresis of acetylcholine (Ach) and sodium nitroprusside (SNP) with laser-Doppler perfusion measurements (2). Plasma levels of soluble markers of endothelial cell activation and inflammation were measured by enzyme immunoassays (2–4).

For comparisons of two groups of individuals, the Mann-Whitney rank-sum test was used. When comparing four groups of individuals, the Kruskal-Wallis test was used. Probability values of p < 0.05 (two-sided) were considered statistically significant.

With the exception of plasma lipid levels, there were no significant differences in clinical variables between the four groups of individuals. Within the low- and the high-cholesterol groups, the lipid levels were comparable between those with and without CAD.

The vasodilatory response to Ach, but not the endothelial-independent response to SNP, was significantly lower in both groups of CAD patients compared to those with similar LDL levels and normal coronary angiograms (Fig. 1). Coronary artery disease patients in both the high- and the low-LDL groups had markedly elevated plasma levels of von Willebrand factor when compared to those with normal angiograms, but with similar LDL levels, showing a similar pattern as the endothelial-dependent Ach response (Fig. 1).

The highest plasma levels of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor (TNF)-alpha were found in those with CAD, regardless of cholesterol levels (Fig. 2). In contrast, the prototypical anti-inflammatory cytokine interleukin (IL)-10 showed a different pattern with raised levels in those with hypercholesterolemia and normal coronary angiogram comparing to the other groups (Fig. 2). This “high-risk” cholesterol group without CAD was also characterized by a low TNF-alpha/IL-10 ratio, suggesting anti-inflammatory net effects in these individuals compared with the other groups (Fig. 2).

Similarly to markers of endothelial cell activation and systemic inflammation, those with CAD had enhanced plasma levels of soluble CD40 ligand (sCD40L) compared with those with normal angiograms, regardless of cholesterol levels, suggesting enhanced...