Is calcium sensitization the best strategy to improve myocardial contractility in acute heart failure?

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The finely-tuned increases and decreases in the intracellular calcium levels in myocytes ultimately regulate the contraction and relaxation of the heart. Therapeutic agents can improve or interfere with this delicate balance. Calcium sensitizers enhance cardiac contraction by improving the use of calcium that is available, rather than by inundating the cell with excessive calcium, as is the case with traditional inotropes. With the sensitizing mechanism, the energy cost of contraction is maintained at a near-normal level, and the threat of arrhythmias and sudden death is low. Levosimendan is the first calcium sensitizer to become available for the treatment of patients with acute heart failure. In recent clinical studies, levosimendan increased cardiac output and stroke volume without significantly increasing oxygen demand. By its additional action as a vasodilator (via potassium channel opening), levosimendan also corrects the hemodynamic decompensation, thus lowering the pulmonary capillary wedge pressure and systemic vascular resistance. Furthermore, levosimendan increases the coronary circulation thus leading to an improved function of the stunned myocardium and lessened ischemia. Taken together, levosimendan’s primary calcium-sensitizing action, along with its complementary vasodilator properties, make this new drug a highly promising agent for the treatment of patients with acute heart failure.

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occurrence of fluid overload, atrial fibrillation, myocardial ischemia or infection. In acute heart failure, the depressed myocardial contractility leads to systolic dysfunction with a resultant deficiency in tissue oxygenation. An impaired ventricular relaxation leads to diastolic dysfunction with consequent congestion of the lungs (left ventricular dysfunction) and/or congestion of the liver and kidneys (right ventricular dysfunction).

The loss of cardiac contractility is associated with a sustained activation of the neurohormonal systems (the renin-angiotensin-aldosterone system and the sympathetic nervous system), thus causing vasoconstriction, volume expansion and ventricular remodeling which, in turn, worsen the conditions of the failing heart. Therefore, mechanically-driven heart failure treatments target the reduced cardiac contractility as well as the exaggerated neurohormonal responses.

Figure 1. Intracellular calcium (Ca^{2+}) handling in cardiomyocytes. Plasma membrane-associated Na+/Ca^{2+} exchangers and ion channels control the movement of Ca^{2+} in and out of the cell. Within the cell, ryanodine receptors (RyR) and the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase pump (SERCA2a) regulate the Ca^{2+} movement in and out of the SR organelle.

Figure 2. Mechanism of myocyte contractile proteins. A: cardiac contraction normally occurs when the globular heads of myosin molecules interact with the actin filaments to form chemical cross-bridges for sliding. During relaxation, regulatory troponins (TnC, TnT, TnI) and tropomyosin (TM) block the actin-myosin interaction so that the bridges do not form. B: calcium (Ca^{2+})-induced changes in the troponin/TM complex. To initiate contraction, the intracellular Ca^{2+} levels increase, and troponin C binds Ca^{2+} and consequently promotes a conformational change that ultimately facilitates actin-myosin bridging. C: levosimendan stabilizes the Ca^{2+}-induced changes in the troponin/TM complex. Levosimendan acts by binding troponin C (in a Ca^{2+}-dependent manner), in turn stabilizing its conformational change and influencing its interaction with the downstream regulator TM. These changes facilitate and prolong actin-myosin cross-bridge formation, thus increasing the force of contraction.

of binding of Ca^{2+} to troponin C (Fig. 3). For example, a traditional inotrope such as dobutamine increases the release of Ca^{2+} from the sarcoplasmic reticulum – an upstream action that facilitates contraction. Alternatively, stabilization of the troponin C-tropomyosin interaction – as mediated by the new therapeutic agent levosimendan – is a downstream action that also promotes contraction. Central regulation, by enhancing the binding of Ca^{2+} to troponin C, is another possible way of increasing contractility, although agents with this mechanism are not presently available for clinical use.

The mechanism of acute heart failure. An episode of severe cardiac dysfunction is referred to as acute heart failure. Acute heart failure may onset de novo, as in patients who have experienced myocardial infarction. Alternatively, patients with chronic heart disease can become acutely decompensated for reasons such as the occurrence of fluid overload, atrial fibrillation, myocardial ischemia or infection. In acute heart failure, the depressed myocardial contractility leads to systolic dysfunction with a resultant deficiency in tissue oxygenation. An impaired ventricular relaxation leads to diastolic dysfunction with consequent congestion of the lungs (left ventricular dysfunction) and/or congestion of the liver and kidneys (right ventricular dysfunction).
Traditional strategies for the treatment of acute heart failure. When a patient with acute heart failure arrives at the emergency department, the earliest therapy is generally directed towards treating the symptoms – edema, angina, and acute dyspnea. Positive airway pressure is usually given immediately to improve oxygen supply. Diuretics are essential to reduce fluid overload, and vasodilators (mainly nitrates) are used to reduce the filling pressures and thereby relieve dyspnea and angina.

Drugs that increase contraction (positive inotropes) have been used as the next level of therapy for patients with systolic dysfunction. Unfortunately, traditional inotropes (beta-agonists and phosphodiesterase inhibitors) are now recognized as having the serious drawback of decreasing the long-term survival. These inotropes act through the common mechanism of raising the levels of cyclic adenosine monophosphate (cAMP) in cardiac myocytes. In turn, the elevated cAMP levels promote the release of calcium from the sarcoplasmic reticulum for a consequent rise in cytosolic Ca²⁺ – an action that ultimately generates the contractile force. Beta-agonists such as dobutamine increase cAMP production, while phosphodiesterase inhibitors such as milrinone prevent cAMP breakdown. It is now understood that such therapeutic agents increase the risk of death because a sustained elevation of intracellular Ca²⁺ increases oxygen demand, impairs relaxation, and exacerbates ischemia and arrhythmias.

Altogether, the adverse outcomes with traditional inotropes clearly call for an alternative strategy for the treatment of patients with acute heart failure. When acute heart failure occurs, it is important to consider the long-term outcomes as well as the short-term contractile and hemodynamic needs.

Calcium sensitization: rational therapy to increase cardiac contractility

Calcium sensitizers work by improving the use of Ca²⁺ that is available in the cell, rather than by inundating the cell with excessive Ca²⁺. Consequently, the energy cost of contraction is maintained at a near-normal level, thus lowering the threat of arrhythmias and sudden death. Although a number of drugs can now be categorized as calcium sensitizers, levosimendan has evolved as one of the more promising representatives of this group. In fact, levosimendan is about 100 times more potent as a calcium sensitizer than pimobendan and other agents, and it also appears to provide long-term survival advantages.

Levosimendan is a safe and effective calcium sensitizer. Levosimendan selectively binds to cardiac troponin C that is Ca²⁺-saturated as a result of the normal calcium transient. Such binding stabilizes and prolongs a specific conformation of troponin C that ultimately mediates myofibril contraction. Through a cascade of changes in troponins I and T and in tropomyosin, bridges between the actin and myosin filaments form, thus producing force-generation with a prolonged contraction.

While levosimendan improves contractility, it does not impair relaxation. Levosimendan binds optimally to...
troponin C at normal calcium peak levels, but dissociates from this protein during the decay of the intracellular Ca\textsuperscript{2+} transient preceding the relaxation phase\textsuperscript{9,29}.

Myocyte traces can be used to measure contraction (percentage of cell shortening) and the amount of released Ca\textsuperscript{2+} to promote the contraction ([Ca\textsuperscript{2+}]i transient expressed as indo-1 fluorescence ratio), as illustrated in figure 4\textsuperscript{22}. While levosimendan generates a contractile trace with an amplitude similar to that of the traditional inotropes dobutamine and milrinone (Fig. 4, upper), these latter agents elicit a substantially higher level of calcium to achieve this contraction (Fig. 4, lower). Following contraction, the elevated intracellular Ca\textsuperscript{2+} levels fall off normally with the calcium sensitizer levosimendan, but are sustained longer with the traditional inotropes, thus impairing relaxation. With levosimendan, the intracellular Ca\textsuperscript{2+} levels do not rise above normal, and the sarcoplasmic reticulum is unlikely to get overloaded with Ca\textsuperscript{2+}; hence, arrhythmias due to inappropriate Ca\textsuperscript{2+} dumping are also unlikely. In fact, electrocardiographic recordings of the effects of intravenous levosimendan on patients with severe heart failure showed no evidence of a life-threatening proarrhythmic potential\textsuperscript{30}. In another study, dynamic positron emission tomography with [11C]acetate was used to assess myocardial oxygen consumption in patients hospitalized with heart failure and treated with levosimendan\textsuperscript{31}. The results showed that levosimendan enhanced cardiac output without oxygen wasting, particularly by improving the efficiency in the right ventricle\textsuperscript{31}.

**Beyond calcium sensitization: additional benefits of levosimendan.** In another cellular action, levosimendan promotes vasodilation by opening the ATP-sensitive potassium channels\textsuperscript{32,33}. The resultant venous and arteriolar dilation reduces cardiac preload and afterload, improves oxygen supply to the myocardium (Fig. 5), and enhances the renal blood flow\textsuperscript{32,34-37}. Such vasodilation by levosimendan is also thought to underlie the reductions in infarct size and myocardial ischemia (Fig. 6), as well as to afford anti-stunning benefits (Fig. 7)\textsuperscript{38-41}.

In recent clinical studies, the dual-mechanism levosimendan increased cardiac output and stroke volume, while concomitantly decreasing the pulmonary capillary wedge pressure and systemic vascular resistance\textsuperscript{25-28}. Importantly, the symptoms of dyspnea and fatigue were significantly lessened in levosimendan-treated patients\textsuperscript{26}. Furthermore, due to its unique sensitizing mechanism and low-energy cost to the heart, levosimendan appeared to provide long-term survival benefits for patients who experienced acute heart failure after myocardial infarction as well as for those who were hospitalized with acutely decompensated chronic heart failure\textsuperscript{27,28}.

**Figure 4.** Typical myocyte traces showing the percentage of cell shortening (a measure of contraction) and the [Ca\textsuperscript{2+}]i transient expressed as the indo-1 fluorescence ratio (a measure of the Ca\textsuperscript{2+} released to promote contraction). While levosimendan elicits a contraction with an amplitude similar to that generated by a traditional inotrope such as dobutamine (upper), the latter necessitates a substantially higher level of calcium to achieve this contraction (lower). Following contraction, the elevated intracellular Ca\textsuperscript{2+} levels fall off normally with the calcium sensitizer levosimendan (dotted arrows), but are sustained longer with the traditional inotrope, thus impairing relaxation (black arrows). Adapted from Lancaster and Cook\textsuperscript{22}.

**Figure 5.** Levosimendan tends to increase coronary blood flow. For this study, 23 low-risk patients undergoing coronary artery bypass graft surgery were enrolled. Patients were randomized to receive placebo or levosimendan at the indicated doses as a 5-min infusion. The average increase in coronary blood flow was 35 ml/min, with a p value of 0.039 when both levosimendan doses were combined in the analysis. Adapted from Lilleberg et al.\textsuperscript{34}.
Practical use of levosimendan today. Levosimendan is indicated for the short-term treatment of acutely decompensated severe chronic heart failure. Levosimendan is administered in hospitalized patients by peripheral- or central-intravenous infusion. Treatment is usually initiated as a loading dose (12 to 24 µg/kg infused over 10 min) followed by a continuous infusion (0.1 µg/kg/min) up to 24 hours.

There are as yet no definitive data regarding the benefits of intermittent levosimendan infusions, but with the hemodynamic effects of 24-hour infusions lasting up to 1 week, levosimendan may prove an ideal agent for pulsed intravenous therapy, particularly in patients with poor symptom control.

Future clinical uses for calcium sensitization by levosimendan

Although levosimendan’s full clinical utility continues to evolve, there appears to be considerable potential for its use beyond the treatment of acutely decompensated chronic heart failure. Levosimendan is also expected to be effective for the treatment of patients with acute post-infarction heart failure, for patients with diastolic heart failure, for those with a low cardiac output following coronary artery bypass grafting and for circulatory failure due to septic shock. In addition, levosimendan has the potential for supporting cardiac function during the start-up of beta-blocker therapy, for weaning patients from cardiopulmonary bypass, for individuals with valvular abnormalities and for those with myocarditis.

Summary

Calcium sensitizers enhance cardiac contraction by improving the use of the Ca²⁺ that is normally available. With this mechanism, the energy cost of contraction is maintained at a near-normal level, and the threat of arrhythmias and sudden death is low. Levosimendan is the first calcium sensitizer to become available for the treatment of patients with acute heart failure. In recent clinical studies, levosimendan increased cardiac output and stroke volume without significantly increasing oxygen demand. The vasodilator properties of levosimendan (via potassium-channel opening) also contribute to the correction of the hemodynamic decompensation by lowering the pulmonary capillary wedge pressure and systemic vascular resistance. Furthermore, levosimendan increases the coronary circulation leading to an improved function of the stunned myocardium and lessened ischemia. Taken together, levosimendan’s primary calcium-sensitizing action, along with its complementary vasodilator properties, make this new drug a highly promising agent for the treatment of patients with acute heart failure (Table I).

Table I. Summary of the clinical benefits of levosimendan.

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<th>Calcium-sensitizing effects</th>
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<tr>
<td>Enhanced cardiac output</td>
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<td>Increased stroke volume</td>
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<td>No significant increase in oxygen demand</td>
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<tr>
<th>Potassium-channel opening (vasodilator) effects</th>
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<tr>
<td>Reduction in preload and afterload</td>
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<td>Increased coronary blood flow</td>
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<td>Anti-ischemic effect</td>
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