How can you mend a broken heart?*

Inotropic agents are the cornerstone in the management of low-output states in critically ill patients. Different agents are available, and although different mechanisms of action and effects on e.g., splanchic blood flow or acid-base balance are recognized, evidence for relevant differences on short-term mortality between compounds are scarce. For instance, there is no evidence that epinephrine is better or worse than norepinephrine plus dobutamine (1), but recent data indicate that the use of dopamine is associated with an increase in arrhythmias and possibly a higher intensive care unit mortality (2).

Calcium sensitizers are a relatively new group of inotropic agents, characterized by the ability to improve sensitivity of cardiac troponin C for calcium (3). Accordingly, higher levels of force are generated for a similar cytosolic calcium concentration. Since reuptake of calcium in the sarcoplasmic reticulum is an energy-consuming process, calcium sensitizers improve cardiac muscle contractile efficiency. From a physiologic point of view, this mechanism of action is highly appropriate, since it does not increase energy expenditure in a stressed muscle. Today, levosimendan is the only calcium sensitizer approved for use in humans. Interestingly, experimental data have shown that levosimendan improves contractile efficiency of the respiratory muscles as well (4, 5). In addition to calcium sensitizing, levosimendan has vasodilating and anti-ischemic properties, which can be attributed to the activation of potassium and mitochondria. Previous meta-analyses of the effects of levosimendan have shown a beneficial effect on infant size and mortality (6), but a more detailed analysis was missing. In this issue of Critical Care Medicine, a new, comprehensive meta-analysis by Landoni and colleagues (7) is published that not only describes the impact of levosimendan on mortality and hospital stay, but also includes an interesting range of subanalyses. The present meta-analysis included >2,000 additional patients compared to the last one, including all large clinical trials. In addition, the results of blinded and open-label studies are now reported separately and levosimendan is compared to placebo as well as to dobutamine. Comparisons between levosimendan-treated patients and control groups for the rate of myocardial infarction, cardiac arrhythmias, and hypotension/use of norepinephrine are informative. To know whether the beneficial effects of levosimendan on mortality are dose dependent, analysis of studies with study drug infusion rate equal or inferior to 0.1 µg/kg/min, and studies with study drug infusion rate higher than 0.1 µg/kg/min with and without bolus administration are now reported. In addition, the authors determined the relation between follow-up time and mortality rates to find out if the beneficial effect of levosimendan is sustained or not. In summary, the results suggest that survival is better, compared to both placebo and dobutamine. With the exception of hypotension, there was no higher rate of adverse events (including arrhythmias) with the use of levosimendan. Using the low-dose levosimendan, without a loading dose, appears to be superior, or at least not inferior, to a higher dose or use of a loading dose in terms of mortality rate. Since the latter is associated with a higher rate of hypotension, it suggests that physicians should avoid the loading dose and not routinely use a high dose of levosimendan. Furthermore, mortality rates favor levosimendan compared to the control group for a follow-up of 30, 90, and 180 days, suggesting a sustained beneficial effect of levosimendan.

With all these beneficial effects, should levosimendan be considered a first-line therapy for critically ill patients with low cardiac output states? That question is still difficult to answer. The studies compiled in any meta-analysis are frequently so different in terms of goals, population, and outcome assessment that one should cautiously look at the net results. Limitations of the present meta-analysis include the fact that it mainly consists of cardiac surgery/severe heart failure patients. Beneficial effects of levosimendan in critically ill patients suffering from, e.g., sepsis-associated myocardial dysfunction, did not reach statistical significance simply because statistical power was not adequate. Although levosimendan is becoming more and more available worldwide, and its prescription is increasing (approximately 500,000 vials sold in total, of which 75,000 were in 2010), levosimendan has not been submitted by its manufacturer to the Food and Drug Administration for approval in the United States, possibly related to the lack of a large clinical trial in critically ill patients and less positive results of the SURVIVE and REVIVE II trials (8, 9). Importantly, a search in clinicaltrials.gov indicates that such a trial in critically ill patients is not in the pipeline. So, while patients in the United States are not being treated with levosimendan, in Europe, levosimendan is authorized in various countries and the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 formulated a Class IIb recommendation at level of evidence B for levosimendan (similar to dobutamine) (10).

Although the beneficial effects described in the present meta-analysis sound very promising, it is clear that we need to evaluate for which critically ill patients levosimendan may have beneficial effects over conventional inotropes, and consequently perform a well-designed and powered phase III trial. If positive results of levosimendan persist, another continent of patients deserves their optimal cardiovascular treatment to mend their broken heart.

*See also p. 634.

Key Words: heart failure; inotropic agents; intensive care; levosimendan; meta-analysis

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The big chill: Cooling sickle cells with caution*

The use of therapeutic hypothermia (TH) in the adjunctive treatment of patients who have experienced a cardiac arrest has been shown to improve neurologic outcome in both adults and neonates, while efficacy in pediatric patients is unclear (1–5). For adult patients, TH for 12 to 24 hrs after resuscitation from cardiac arrest resulting from ventricular fibrillation is currently recommended by the American Heart Association. While the value of TH following resuscitation from cardiac arrest caused by other arrhythmias or by asphyxia is not clear, there are data to suggest that time from arrest rather than the specific causative arrhythmia may be the critical element in determining efficacy (6). Even with the uncertainty in identifying the patients most likely to benefit from TH, this therapy is often incorporated as a routine element of postcardiac resuscitation care in many hospitals. Documented adverse events associated with TH include metabolic disturbances (especially hyperglycemia), seizures, bleeding, and infections (7, 8). While many of these may, in fact, be secondary to the arrest, or associated with the cause for the arrest, rather than the TH, a decision to employ this treatment modality to all postcardiac arrest resuscitation patients may be premature. Consequently, it may still be prudent to critically evaluate the potential risks of TH for all patients before initiating this treatment.

In this issue of Critical Care Medicine, Metske and colleagues (9) report a single patient with double-heterozygous hemoglobin (Hb) Sβ₀ thalassemia sickle cell disease who was treated with TH following a prolonged resuscitation from cardiac arrest. In addition to TH and standard cardiac arrest resuscitation measures, the authors performed two exchange transfusions before the patient was placed on TH, lowering his Hbs to <10% of total Hb (the first exchange before the arrest and the second post resuscitation before TH). The second exchange was performed to minimize the known risk for inducing intravascular red blood cell (RBC) sickle transformation with consequent vaso-occlusion that hypothermia presents to an individual with sickle cell disease. While the second exchange transfusion before initiation of TH was appropriate and prudent, the decision to employ TH in this patient took a fair amount of intestinal fortitude on the part of his treating physicians since there is no precedent in the literature for this therapy in patients with sickle cell anemia. However, there are scattered reports of hypothermic cardiac surgery with cardiopulmonary bypass preceded by exchange transfusion in patients with sickle cell disease without the induction of acute sickling crises (10–13). Hypothermia results in a shifting of the Hb-oxygen dissociation curve to the left (i.e., increased Hb affinity for oxygen [increased Hb-oxygen saturation] at low P0₂), which would ordinarily protect against sickle transformation of RBCs. However, this increased Hb-oxygen affinity results in decreased oxygen delivery to the tissues, with the result being oxygen debt and initiation of anaerobic glycolysis with a local decrease in pH. In turn, the local acidosis decreases Hb-oxygen affinity thereby enhancing oxygen unloading (the so-called Bohr effect). The increase in deoxygenated Hb increases the risk of sickle cell disease without the induction of acute sickling crises (10–13). Hypothermia results in a shifting of the Hb-oxygen dissociation curve to the left (i.e., increased Hb affinity for oxygen [increased Hb-oxygen saturation] at low P0₂), which would ordinarily protect against sickle transformation of RBCs. However, this increased Hb-oxygen affinity results in decreased oxygen delivery to the tissues, with the result being oxygen debt and initiation of anaerobic glycolysis with a local decrease in pH. In turn, the local acidosis decreases Hb-oxygen affinity thereby enhancing oxygen unloading (the so-called Bohr effect). The increase in deoxygenated Hb increases the risk of sickle cell disease without the induction of acute sickling crises (10–13). Hypothermia results in a shifting of the Hb-oxygen dissociation curve to the left (i.e., increased Hb affinity for oxygen [increased Hb-oxygen saturation] at low P0₂), which would ordinarily protect against sickle transformation of RBCs. However, this increased Hb-oxygen affinity results in decreased oxygen delivery to the tissues, with the result being oxygen debt and initiation of anaerobic glycolysis with a local decrease in pH. In turn, the local acidosis decreases Hb-oxygen affinity thereby enhancing oxygen unloading (the so-called Bohr effect). The increase in deoxygenated Hb increases the risk of sickle cell disease without the induction of acute sickling crises (10–13). Hypothermia results in a shifting of the Hb-oxygen dissociation curve to the left (i.e., increased Hb affinity for oxygen [increased Hb-oxygen saturation] at low P0₂), which would ordinarily protect against sickle transformation of RBCs. However, this increased Hb-oxygen affinity results in decreased oxygen delivery to the tissues, with the result being oxygen debt and initiation of anaerobic glycolysis with a local decrease in pH. In turn, the local acidosis decreases Hb-oxygen affinity thereby enhancing oxygen unloading (the so-called Bohr effect). The increase in deoxygenated Hb increases the risk of sickle cell disease without the induction of acute sickling crises (10–13).

*See also p. 651.

Key Words: cardiac arrest; exchange transfusion; sickle cell anemia; therapeutic cooling

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