

## VIEWPOINT

# Post-Myocardial Infarction Cardiogenic Shock Is a Systemic Illness in Need of Systemic Treatment

## Is Therapeutic Hypothermia One Possibility?

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Early observations of cardiogenic shock as a systemic clinical syndrome were first described in 1942. Today, cardiogenic shock remains the leading cause of death among patients hospitalized for myocardial infarction (MI). Mortality rates in post-MI cardiogenic shock approach 50% despite rapid revascularization, optimal medical care, and use of mechanical support. New therapeutic strategies with global systemic effects may offer advances in treatment and outcome in post-MI cardiogenic shock. Therapeutic hypothermia for post-MI cardiogenic shock has multiple potentially beneficial physiologic effects, including the potential to improve post-ischemic cardiac function and hemodynamics, decrease myocardial damage, and reduce end-organ injury from prolonged hypoperfusion. Available data in animal models of post-MI cardiogenic shock and ischemia/reperfusion injury and small case series of human patients with cardiogenic shock suggest its promise as a potential therapeutic strategy for cardiogenic shock in the post-MI setting. We hypothesize that systemic therapeutic hypothermia could decrease morbidity and mortality in post-MI patients with cardiogenic shock and warrants study a new treatment that could be widely available at hospitals worldwide. (J Am Coll Cardiol 2012;59:644-7)

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In 1942, Stead and Ebert published their seminal observations of the manifestations of shock resulting from failure of the heart, “characterized clinically by the signs of a marked decrease in cardiac output and tissue anoxia. . .,” as a disease with broad-ranging systemic effects (1). Today, nearly 70 years later, cardiogenic shock remains the major killer of patients hospitalized for acute myocardial infarction (MI), with mortality approaching 50% despite urgent reperfusion therapy, optimal medical care, and intra-aortic balloon pumping (2).

Cardiogenic shock is generally defined by cardiac index  $<2.2$  l/min/m<sup>2</sup>, hypotension, elevated pulmonary capillary wedge pressure, and end-organ hypoperfusion. Cardiogenic shock affects approximately 5% to 7% of patients with MI and is the leading cause of death among hospitalized patients with MI (2). Unfortunately, there have been few recent advances in the treatment of cardiogenic shock in the setting of MI. A small study of advanced mechanical support using left ventricular (LV) assist devices revealed

improvement in hemodynamic parameters, but mortality benefit from use of such devices in the setting of acute MI has not been demonstrated (3). These mechanical treatments also require highly specialized care at large medical centers, which could significantly limit availability to many patients with acute MI with cardiogenic shock who are initially treated in community centers. Therapeutic hypothermia is widely available and has become a standard component of treatment for out-of-hospital ventricular tachycardia/ventricular fibrillation arrest (4). It also has wide-ranging systemic effects that might be particularly advantageous when considering the systemic manifestations of cardiogenic shock in the post-MI setting. We hypothesized the following: first, the properties of therapeutic hypothermia that protect the brain and promote recovery after cardiac arrest will have similar effects on other vital organs; and second, therapeutic hypothermia merits further study as a potential novel treatment for post-MI cardiogenic shock and could represent the next measurable advance in survival after MI.

### Animal Models, Molecular Profiles, and Early Human Studies of Hypothermia

Hypoperfusion in the setting of post-MI cardiogenic shock leads to multiple end-organ damage and dysfunction that contributes to morbidity and mortality after MI. Hypothermia

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decreases metabolic rate 5% to 7% per degree reduction of body temperature, and it decreases oxygen consumption, carbon dioxide production, and glucose consumption (5). In addition, hypothermia affects the cardiovascular system in multiple ways, many of which could be potentially beneficial in cardiogenic shock, especially in a post-MI setting. In dogs, reduction of body temperature to 34°C in conjunction with vasodilator therapy results in increased contractility and external work of the left ventricle without increasing myocardial oxygen consumption (6). In a dog model of post-MI cardiogenic shock, treatment with hypothermia to 32°C reduced heart rate, LV end-diastolic pressure, systemic oxygen consumption, and estimated myocardial oxygen consumption while maintaining cardiac output and improving survival (7). This study was validated recently in a porcine model of post-MI cardiogenic shock showing that animals treated with hypothermia had increased mean arterial pressure, stroke volume, pH, and mixed venous oxygen saturation with decreased heart rate (8). Mortality was also improved in the hypothermia group (0% mortality in the hypothermia group vs. 63% in the control group). The inotropic effects of hypothermia seem to be at least partially related to an increase in action potential duration, calcium transients, sarcoplasmic reticulum calcium stores, and the fractional release of calcium in individual cardiac myocytes (9).

Results of animal models further suggest that therapeutic hypothermia may reduce ischemia/reperfusion injury after urgent revascularization for acute MI. In dogs, hypothermia beginning 30 min after left anterior descending coronary artery occlusion and continued through reperfusion 3 hours later improved cardiac function during occlusion, blunted hemodynamic derangements during reperfusion, and reduced infarct size at 7 days (10). In sheep, in addition to greater immediate myocardial salvage, LV systolic function was improved at 8 weeks in animals treated with therapeutic hypothermia (11). One study in humans showed decreased infarct size among patients with anterior infarcts treated with therapeutic hypothermia who reached a temperature of <35°C at time of reperfusion (12). More recently, a pilot study of 20 patients with acute MI undergoing endovascular cooling and cold saline infusion to ensure body temperature of <35°C at time of reperfusion demonstrated a significant decrease in infarct size and biomarker elevation without increasing door-to-balloon time (13). To the best of our knowledge, there have been no randomized human studies of therapeutic hypothermia in post-MI cardiogenic shock.

Hypothermia has additional outcomes outside its direct cardiovascular effects that may benefit patients with post-MI cardiogenic shock. Accumulation of oxygen free radicals and an intense inflammatory response are hallmarks of myocardial ischemia and systemic hypoperfusion in post-MI cardiogenic shock (14,15). Hypothermia impairs neutrophil and macrophage phagocytic function and production of many proinflammatory cytokines (5). Therefore, therapeutic hypothermia could decrease the severity of myocardial injury and dysfunction associated with MI.

Furthermore, hypothermia attenuates ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis and systemic oxidative stress (16,17). Hypothermia also increases urine output, likely via reduction in fluid resorption beyond the mid-distal tubule in the kidney (18), an effect that could prove beneficial in post-MI cardiogenic shock patients with difficult-to-manage volume status. Figure 1 identifies potential pathways leading to or mediating the systemic effects of cardiogenic shock and where preclinical data suggest therapeutic hypothermia may modulate these effects.

#### Abbreviation and Acronym

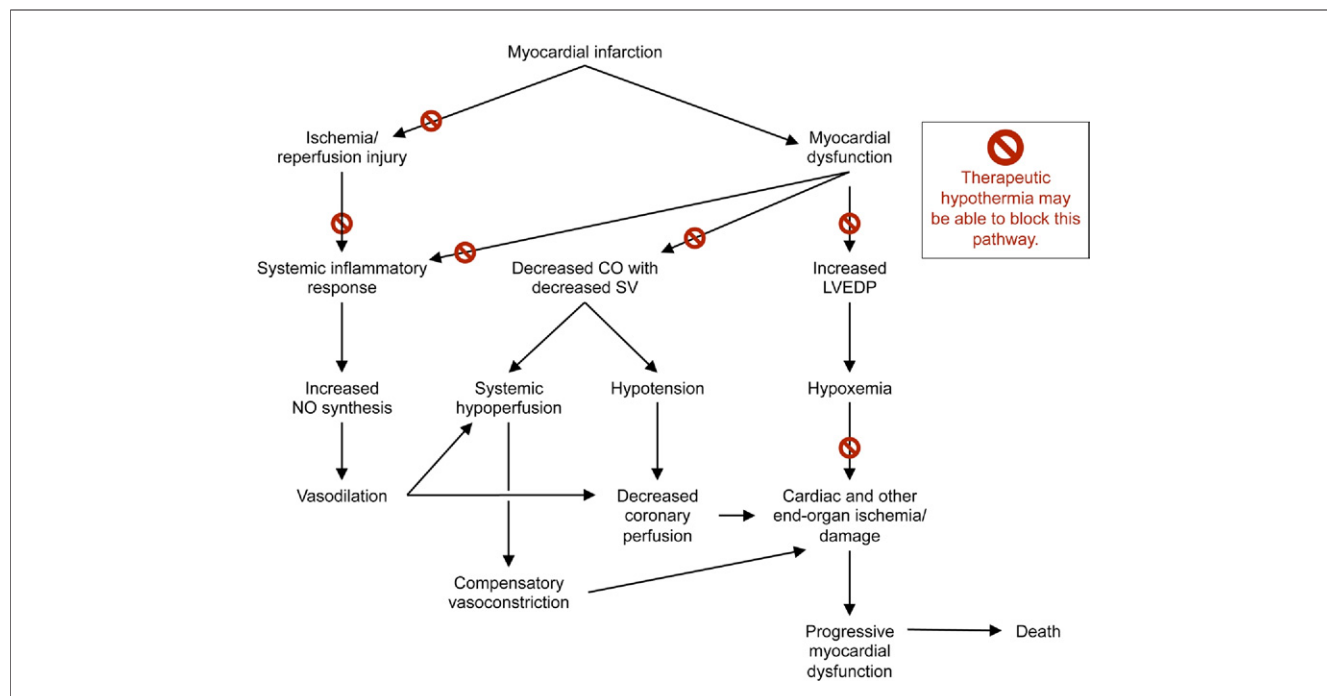
LV = left ventricular

MI = myocardial infarction

### Human Studies of Hypothermia in Cardiogenic Shock

There are only a few case reports and case series of hypothermia in patients with cardiogenic shock, mostly limited to pediatric and adult cardiac surgery patients whose postoperative courses were complicated by cardiogenic shock (19–21); none were from patients with cardiogenic shock in the acute MI setting. It is also important to recognize that these are reports of highly selected cases in which treatment was nonrandomized and concurrent therapy was uncontrolled. Only a well-designed randomized clinical trial can provide evidence sufficient to support clinical practice in post-MI patients. In general, whether in infants or children, when hypothermia is added to conventional therapy in patients with refractory shock after cardiothoracic surgery, it resulted in decreases in heart rate and increases in mean arterial pressure and urine output with improved clinical stability (19,20). Therapeutic hypothermia has been reported in only one case series in adult patients with refractory heart failure (21). In this report, 10 adult patients experienced post-cardiac surgery cardiogenic shock that was refractory to medical therapy, including multiple vasopressors and intra-aortic balloon pumping; the use of external cooling along with cold gastric lavage to a temperature of 34.5°C resulted in improved cardiac index ( $1.9 \pm 0.3$  to  $2.2 \pm 0.3$ ), mixed venous saturation ( $55 \pm 7\%$  to  $64 \pm 6\%$ ), and urine output ( $2.1 \pm 1.1$  ml/kg/h to  $3.4 \pm 2.2$  ml/kg/h) without changes in mean arterial pressure, heart rate, systemic vascular resistance, or pH. Eight of 10 patients survived to discharge.

Patients with signs of cardiogenic shock after cardiac arrest who underwent cooling provide another possible source of information, although little is currently available. In one study, 28 of 56 patients who were cooled after cardiac arrest also had cardiogenic shock, although it was not reported how many of these patients had acute MI concurrent with the cardiac arrest (22). Among the cardiogenic shock patients, after 24 to 48 h of therapeutic hypothermia, cardiac index increased from  $1.5 \pm 0.26$  to  $2.3 \pm 0.371$ . In addition, heart rate decreased among cardiogenic shock



**Figure 1** Pathways Potentially Affected by Therapeutic Hypothermia

Graphic summarizes ways in which therapeutic hypothermia may block certain pathways involved in cardiogenic shock. CO = cardiac output; LVEDP = left ventricular end-diastolic pressure; NO = nitric oxide; SV = stroke volume.

patients but to a lesser extent than among patients without shock; mean arterial pressure increased in patients with cardiogenic shock whereas it decreased in patients without initial signs of shock.

### Potentially Detrimental Effects of Therapeutic Hypothermia

Induction of hypothermia has been associated with alterations in normal physiology that could prove detrimental and may create challenges for future clinical trials of therapeutic hypothermia in post-MI cardiogenic shock. For example, therapeutic cooling to core temperatures of 32°C to 34°C results in shivering, which is both uncomfortable for the patient and increases systemic oxygen consumption (5). Shivering is best controlled with sedation and paralysis during cooling that necessitates intubation and mechanical ventilation. In general practice, 85% of patients with cardiogenic shock in the setting of acute MI require mechanical ventilation during their treatment, but the risks of such treatment in the patients who otherwise would not have required it must be explored (23). Furthermore, hypothermia reportedly increases the risk of infection (especially pneumonia), coagulopathy, electrolyte abnormalities, and arrhythmias, although these risks have not translated to worsened clinical outcomes in cardiac arrest patients (5,24). These potential adverse effects must also be understood in balance with potential benefits in the post-MI cardiogenic shock setting.

### Conclusions

Rapid reperfusion to treat coronary obstruction is a major advance in treating patients with acute MI presenting with cardiogenic shock. Unfortunately, mortality remains high in patients who have cardiogenic shock that persists after reperfusion. Now, 70 years after the seminal description of the systemic manifestations of cardiogenic shock, it is time to draw on those observations to direct development of new approaches that address the systemic consequences of post-MI cardiogenic shock and protect end organs during stabilization. Therapeutic hypothermia has many physiologic effects that could be beneficial to patients with post-MI shock. Among these, the potential to improve cardiac function and hemodynamics and reduce end-organ damage from prolonged hypoperfusion may be the most relevant. Favorable effects of therapeutic hypothermia have been demonstrated in animal studies and small case series of patients with non-MI cardiogenic shock. Therefore, therapeutic hypothermia warrants further investigation as a potential treatment strategy for post-MI cardiogenic shock to address the multitude of clinical effects that characterize the downward spiral that so frequently defines this fatal complication of MI.

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**Key Words:** acute myocardial infarction ■ cardiogenic shock ■ therapeutic hypothermia ■ treatment.