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/m², 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
Therapeutic Hypothermia for Cardiogenic Shock

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JACC Vol. 59, No. 7, 2012
February 14, 2012:644–7

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.

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 ± 0.3 to 2.2 ± 0.3), mixed venous saturation (55 ± 7% to 64 ± 6%), and urine output (2.1 ± 1.1 ml/kg/h to 3.4 ± 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 ± 0.26 to 2.3 ± 0.371. In addition, heart rate decreased among cardiogenic shock
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.