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Successful Re-Initiation of Therapeutic Hypothermia as Adjunctive Salvage Therapy in a Case of Refractory Cardiogenic Shock Due to Acute Myocardial Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 37
Final Diagnosis: Acute myocardial infarction
Symptoms: Retrosternal chest pain
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Unusual setting of medical care

Background: Acute myocardial infarction (AMI) complicated by cardiogenic shock has a high mortality rate, despite prompt revascularization, advanced medical therapy and the use of mechanical circulatory support devices. Therapeutic hypothermia is associated with physiological cellular changes in the ischemic myocardium, and a trend towards improved hemodynamics in patients with AMI and cardiogenic shock, but is currently not considered to be a therapeutic modality. A case is presented that supports the role of therapeutic hypothermia as salvage therapy in patients with cardiogenic shock following AMI.

Case Report: A 37-year-old man who presented with cardiac arrest following an anterior wall AMI due to occlusion of the left anterior descending coronary artery complicated by cardiogenic shock, underwent emergent percutaneous revascularization with placement of a stent, a percutaneous left ventricular-assist device (LVAD), and a pulmonary artery catheter. Therapeutic hypothermia was initiated to achieve a target core body temperature of between 32–34°C for 24 hours, followed by slow re-warming. However, after rewarming, the patient developed refractory cardiogenic shock, despite revascularization, pharmacological and mechanical circulatory support. A second cycle of therapeutic hypothermia was initiated as salvage therapy, leading to clinical improvement. The patient had a favorable outcome, was discharged from hospital and was able to return to work.

Conclusions: The first successful case is described in which therapeutic hypothermia was re-initiated as salvage therapy for cardiogenic shock where no other hemodynamic support resources were available.

MeSH Keywords: Hypothermia, Induced • Myocardial Infarction • Out-of-Hospital Cardiac Arrest • Shock, Cardiogenic

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Background

Cardiogenic shock results from acute myocardial infarction (AMI) in 6–7% of patients [1], and is associated with an in-hospital mortality rate of approximately 60% despite early revascularization and medical therapy [2]. Mild therapeutic hypothermia is recommended in comatose patients with ventricular fibrillation (VF) and in cardiac arrest in non-hospitalized patients to improve neurological outcome [3].

Therapeutic hypothermia has been reported to be associated with enhanced cardiac performance and myocardial perfusion, decreased heart rate, lower metabolic demands, and reduced myocardial cell apoptosis post-reperfusion in the setting of myocardial ischemia [4,5]. Whether these potentially favorable physiologic effects of therapeutic hypothermia can translate into an improved clinical outcome in the setting of cardiogenic shock has not been well studied.

The first case is described in which therapeutic hypothermia was re-initiated as a successful adjunctive or salvage therapy for cardiogenic shock in a patient with an anterior wall AMI complicated by cardiac arrest where no other hemodynamic support resources alone were successful.

Case Report

A 37-year-old man with no significant past medical history developed sudden and severe retrosternal chest pain while jogging on his treadmill. He was taking no medications and denied alcohol, tobacco, or recreational drug use. He recently started an exercise program, having previously been sedentary. His father suffered a myocardial infarction at the age of 62 years. The patient drove himself to the emergency center and while parking his car he lost consciousness and his vehicle collided against the emergency room entrance. He was promptly removed from his vehicle and was found to be in ventricular fibrillation (VF).

The emergency department staff initiated cardiopulmonary resuscitation (CPR) and defibrillation, with the restoration of spontaneous circulation after a downtime of 15 minutes. The patient remained poorly responsive, requiring endotracheal intubation and mechanical ventilation. Following resuscitation, an initial electrocardiogram (ECG) showed an anterior wall acute myocardial infarction (AMI) (Figure 1). Hypothermia with cold saline infusion and ice packs was commenced, and the patient was airlifted to our facility. Due to the trauma resulting from the motor vehicle accident, thrombolytic therapy and anticoagulation were contraindicated, and only aspirin treatment was given in the field. The patient required defibrillation twice on his transfer to the hospital and required two rounds of cardiopulmonary resuscitation (CPR).

He arrived at our facility within 45 minutes. On arrival, he was in cardiogenic shock with pulmonary edema requiring treatment with vasopressors and positive-pressure ventilation. A multiorgan computed tomography (CT) scan did not show signs of significant bleeding. He underwent emergency coronary angiography, which showed occlusion of the proximal left anterior descending coronary artery (Figure 2A), with severe left ventricular anterior wall and antero-apical hypokinesia, an ejection fraction of 25–30%, and a left ventricular end-diastolic pressure of 35 mmHg. Percutaneous revascularization with placement of a 4.0 mm by 15 mm bare metal stent resulted in Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the left anterior descending coronary artery (Figure 2B). Due to the presence of cardiogenic shock, a 2.5 L Impella percutaneous left ventricular-assist device (LVAD) (ABIOMED, Danvers, MA, USA) and a pulmonary artery catheter were sited.

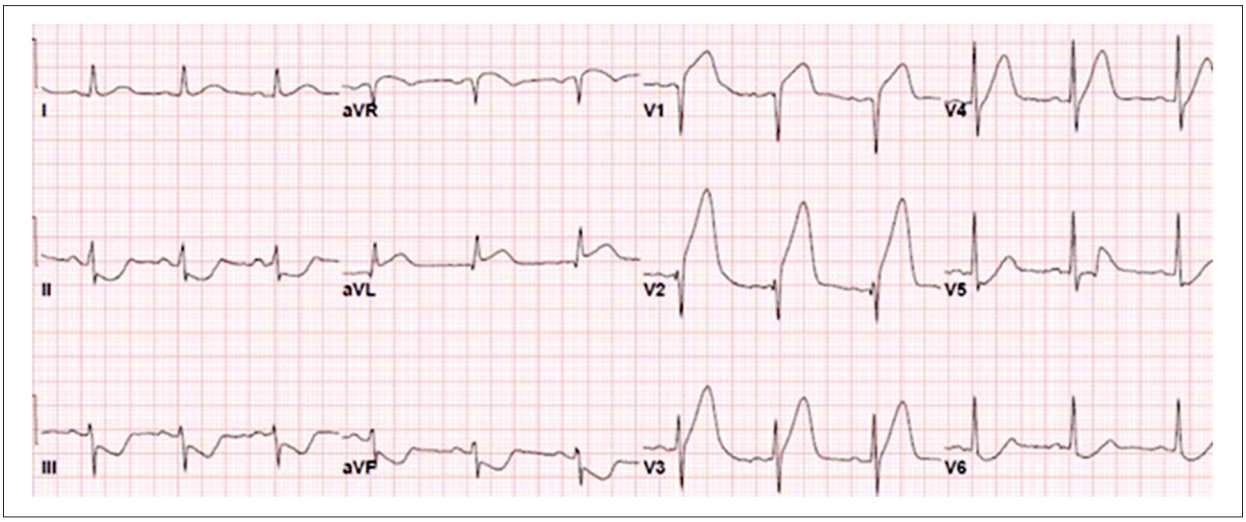

Figure 1. A 37-year-old man with cardiogenic shock. The findings of the initial electrocardiogram at presentation.

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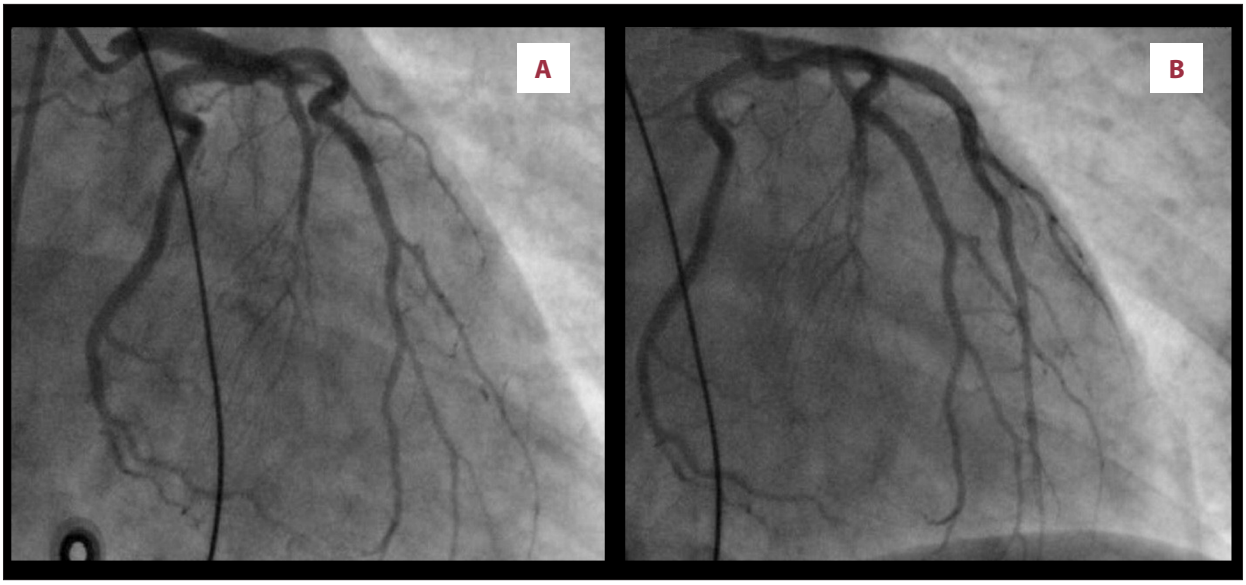

Figure 2. A 37-year-old man with cardiogenic shock. The coronary angiography findings. (**A**) The initial angiography shows complete occlusion of the left anterior descending coronary artery. (**B**) Angiography following stent placement with revascularization of the left anterior descending coronary artery. The patient had a Thrombolysis in Myocardial Infarction (TIMI) score of 3 after revascularization.

On arrival in the intensive care unit (ICU) he required 30 mcg/Kg/min of intravenous dobutamine, and 80 mcg/min of intravenous norepinephrine to maintain an adequate blood pressure. His pulmonary arterial wedge pressure was 38 mmHg and his cardiac output was 2.1 L/min with the Impella LVAD device (Figure 3). Arterial blood gases showed severe metabolic acidosis with a PH of 7.10 and a lactic acid of 18 mEq/L. His initial troponin level was 35 ng/dl, which later peaked at 189 ng/dl. The patient developed multi-organ dysfunction with respiratory failure, shock liver, and acute kidney injury. Following our institutional therapeutic hypothermia protocol, a Blanketrol III hypothermia device (Cincinnati Sub-Zero, Cincinnati, Ohio) with the addition of ice packs were used to achieve a target core body temperature between 32–34°C that was maintained for 24 hours. After 24 hours, slow rewarming began.

During the first 24 hours of therapeutic hypothermia the patient showed improvement with normalization of lactic acid levels, allowing a progressive decrease in the support with dobutamine, norepinephrine, and the Impella LVAD device, while his cardiac output and urine output increased and his pulmonary wedge pressure decreased (Figure 3, at 24 hours). The patient's hemodynamic profile continued to improve up to 48 hours (Figure 3, at 48 hours). However, during the next 24 hours after rewarming cardiogenic shock worsened with a decline in renal function and urine output, increasing lactic acidosis (increased to 11 mEq/L), a decrease in cardiac output, and an increase in pulmonary capillary wedge pressure to 34 mmHg, requiring up-titration of vasopressors and mechanical ventilation (Figure 3, at 80 hours). Echocardiography showed an ejection fraction of 25% with severe left ventricular anterior wall and antero-apical hypokinesis without associated mechanical complications.

Despite the up-titration of vasoactive agents and an increase in the mechanical circulatory support with the Impella LVAD, the patient remained in refractory cardiogenic shock. After discussing the case with a tertiary center, it was determined that the patient was too unstable to be transferred to another facility with surgical LVAD capabilities. Extracorporeal membrane oxygenation or other means of additional circulatory support were not available at our institution at that time. Considering the acute deterioration after re-warming, therapeutic hypothermia was re-initiated as salvage therapy in an attempt to restore the hemodynamic status. The decision to re-initiate therapeutic hypothermia was based on the patient's initial response and considered the potential benefits of therapeutic hypothermia in cardiac physiology reported previously in the literature [5].

On re-initiation of therapeutic hypothermia, the patient showed progressive improvement in cardiac output, urine output, vasopressor dependence and left ventricular filling pressures (Figure 3, at 84–144 hours). This clinical improvement occurred despite maintaining unchanged levels of hemodynamic vasopressor support or mechanical support, and without additional therapeutic interventions, such as antibiotics or intravenous fluids, which may have led to hemodynamic improvement, or changes in mechanical ventilation. During the next three days, the patient was slowly weaned off vasoactive drugs and the level of mechanical circulatory support was reduced, while the

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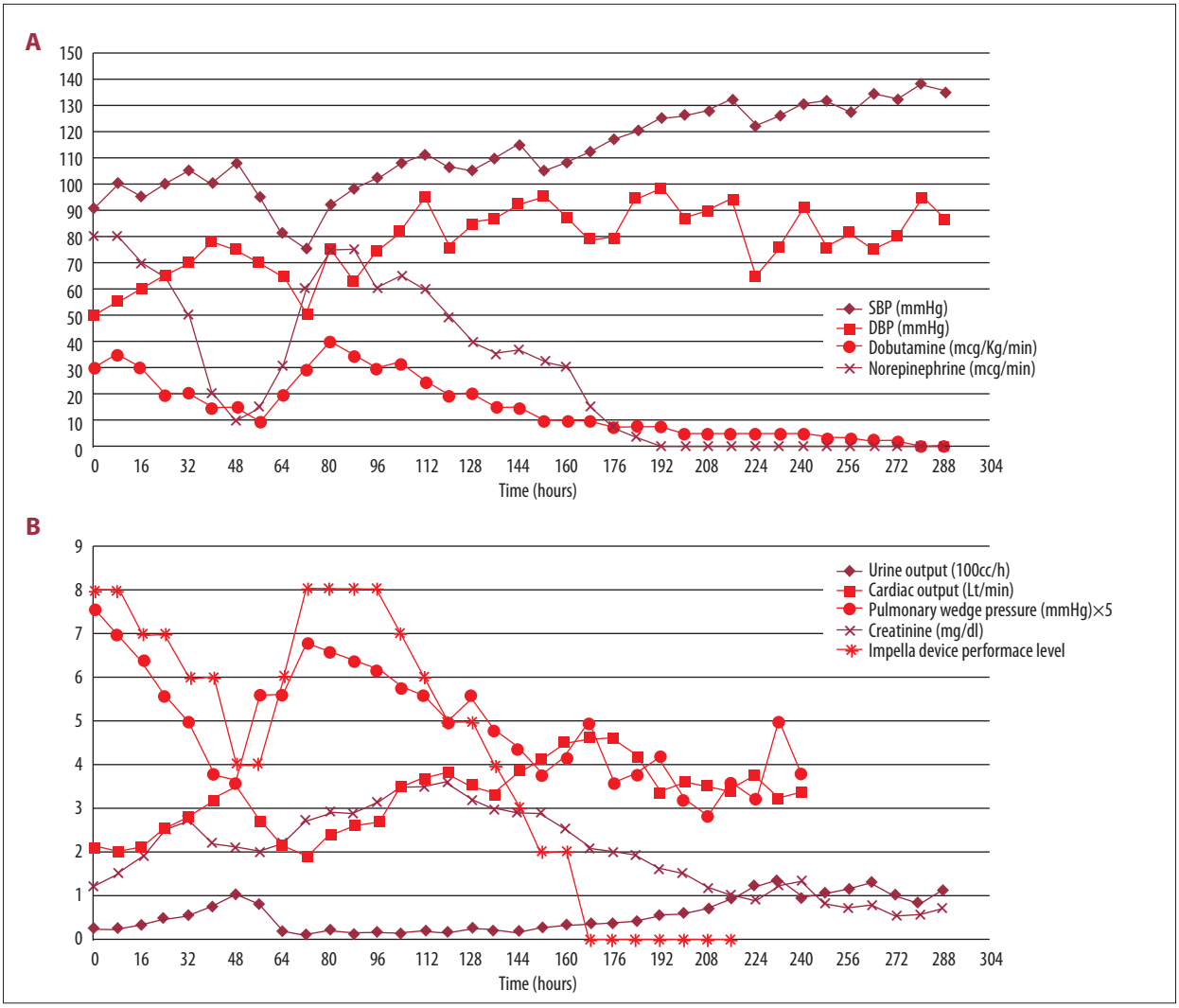

Figure 3. A 37-year-old man with cardiogenic shock. The hemodynamic profile during the therapeutic hypothermia cycles while in the intensive care unit (ICU). (**A**) Trends of blood pressure and vasopressor support. (**B**) Trends of urine output, cardiac output, pulmonary wedge pressure, creatinine and circulatory mechanical support. SBP – systolic blood pressure; DBP – diastolic blood pressure.

patient remained in therapeutic hypothermia. During this period of time the levels of lactic acid decreased from 11 mEq/L to 2.1 mEq/L, alanine transaminase (ALT) decreased from 2,709 u/L to 433 u/L, and the pH improved from 6.82 to 7.47. The patient was rewarmed (Figure 3, at 144–160 hours) with stable hemodynamic parameters. On day 7 following admission, the Impella LVAD device was removed and the patient was weaned off vasopressors. Treatment with low-dose beta-blockers, angiotensin converting enzymes (ACE) inhibitors, and aldosterone blockers was started. In-hospital, phase I cardiac rehabilitation commenced on discharge from the ICU and the patient recovered without any residual neurological deficit.

Following discharge from hospital, the patient's prior normal functional status resumed and he returned to work with no symptoms of heart failure, and with complete neurologic recovery. Three months after his acute coronary event, his ejection fraction had improved to 45–50%.

Discussion

Current international guidelines recommend the induction of therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest to improve neurologic recovery [6,7]. A recent systematic review on therapeutic hypothermia in adults after cardiopulmonary resuscitation concluded that there was moderate evidence from published studies that mild therapeutic hypothermia improved the neurologic outcome following out-of-hospital cardiac arrest when compared with no

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modification of temperature [8]. This systematic review did not find sufficient evidence to support the effects of therapeutic hypothermia for patients with in-hospital cardiac arrest and non-cardiac causes of cardiac arrest [8].

Although there is some evidence of neurological recovery with therapeutic hypothermia, its role in the management of acute myocardial infarction (AMI) and cardiogenic shock remains to be determined by controlled studies. Small studies in experimental animals and clinical case series have suggested that therapeutic hypothermia may have a favorable hemodynamic and systemic effect in cardiogenic shock, although current clinical data is limited [9]. In the present case report, a patient is presented who had cardiogenic shock following AMI that was refractory after an initial cycle of therapeutic hypothermia, despite revascularization, contemporary medical management, and temporary circulatory support. In this case, therapeutic hypothermia was re-initiated as an adjunctive salvage therapy, which resulted in clinical stabilization and resolution of cardiogenic shock.

To our knowledge, there have been no previously published case reports on clinical outcome following re-initiation of therapeutic hypothermia in refractory cardiogenic shock to improve hemodynamic function. In this case, the rationale for therapeutic hypothermia was based on the initial improvement observed within the first 48-hours, and the patient's rapid deterioration on rewarming without any other reason that could explain the acute hemodynamic decline. In addition to the patient's clinical response, the clinical decision was based on limited published evidence. Currently, data from clinical trials that have studied therapeutic hypothermia for patients with AMI have included only small numbers of patients and have lacked sufficient power to determine statistical significance. However, recent combined analysis of individual studies has shown consistent clinical benefits of limiting the myocardial infarct size and reducing the development of heart failure [9,10]. The Rapid MI-ICE and CHILL-MI trials showed that initiation of therapeutic hypothermia in patients with anterior wall AMI prior to revascularization decreased the infarct size and improved cardiac function [10]. The feasibility of therapeutic hypothermia in patients with severe cardiogenic shock was evaluated in two small trials, the COOL Shock I and II studies, which showed no adverse effects and improved cardiac function [11]. Although these individual studies have included insufficient numbers of study participants to show a survival benefit, these studies showed improved hemodynamics with an increase in the cardiac index, stroke volume, cardiac output, and mean arterial pressure [11], which supports the findings of the measured clinical parameters in the patient presented in this report. Also, Skulec et al. undertook a retrospective clinical study that showed cardiovascular mortality and neurological morbidity was lower than expected in a group of patients with cardiogenic shock when maintained in therapeutic hypothermia [12].

Although the patient in the present case report benefited from a second cycle of therapeutic hypothermia after rewarming, the Targeted Temperature Management Trial showed that lowering body temperature to 33°C in unconscious survivors of out-of-hospital cardiac arrest did not confer additional benefit when compared with maintaining body temperature at 36°C [13]. Also, patients who received therapeutic hypothermia for 48 hours had a higher incidence of adverse events and a longer length of stay in the intensive care unit (ICU), with no additional benefit when compared with the used of therapeutic hypothermia for the first 24 hours [13]. The potential benefits of therapeutic hypothermia in the ischemic myocardium at the cellular level remain poorly understood and are particularly difficult to study in the human myocardium in the setting of cardiogenic shock. However, in animal models, the combination of early therapeutic hypothermia and early reperfusion were shown to decrease myocardial infarct size by 47% when compared with normothermic reperfusion alone [14].

The positive inotropic effect noted by the increase in cardiac output in the patient in this case report during both cycles of therapeutic hypothermia (Figure 3), may have been due to increased stores of calcium in the sarcoplasmic reticulum, fractional release of calcium, and improved responsiveness of myofilaments to calcium, resulting in enhanced myocardial contractility [15]. A further possible mechanism underlying the protective effects of therapeutic hypothermia is decreased metabolism, as many enzyme systems in cell membranes, including adenosine triphosphatase, are temperature-sensitive [16]. As the core temperature decreases, the cardiac and systemic metabolic rate decreases and results in reduced oxygen and glucose consumption and carbon dioxide production, which help hypothermic hearts endure ischemia for longer periods of time [16]. The cardioprotective effect of hypothermia includes a reduction in metabolic demands with preserved adenosine triphosphatase and glycogen stores and reduced tissue accumulation of lactate [17]. As noted in the case presented in this report, marked improvement in the patient's lactic acidosis occurred after the second cycle of therapeutic hypothermia. Hypothermia is also associated with a decrease in calcium and sodium overload during ischemia-reperfusion injury and reduced release of reactive oxygen species (ROS) [18].

Following ischemia and reperfusion, myocardial cells may recover to varying degrees, become necrotic, or may enter a pathway to apoptosis (programmed cell death). Hypothermia inhibits pro-apoptotic calcium-induced mitochondrial permeability transition pores and promotes anti-apoptotic pathways [19]. There is evidence from gene array analysis that therapeutic hypothermia protects the ischemic heart by enhancing

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signaling pathways that promote anti-apoptotic factors while promoting mitochondrial membrane stability following ischemia-reperfusion injury [20]. Also, therapeutic hypothermia has been shown to mediate cardioprotection through the reperfusion injury salvage kinase signaling pathways, including PI3, Akt, nitric oxide (NO), and ERK [21]. A recent study in hypothermic rats has reported that therapeutic hypothermia deregulates the expression of micro-RNAs (miRNAs) [22]. Pilotte and colleagues showed that hypothermia regulates miRNA expression through enhanced processing of pre-miRNAs by active Dicer complexes (endoribonuclease Dicer) [23], which are regulated by the cold-response protein Rbm3, a glycine-rich RNA-binding protein [24]. In a pig model of cardiogenic shock, mild induced therapeutic hypothermia down-regulated plasma levels of miR-122 [25], which is a miRNA that has been shown to be a predictive biomarker of outcome after out-of-hospital cardiac arrest in a sub-group analysis of patients from the Targeted Temperature Management Trial [26,27]. Further research is needed to determine whether miRNAs are key players in the neuroprotective effects of cooling, as a novel class of neuroprotective agents.

It is possible that the findings of recent clinical trials using therapeutic hypothermia to reduce myocardial injury following ischemia-reperfusion could also be due to variable core temperatures achieved in these studies. Preclinical data on neuroprotection from therapeutic hypothermia suggests that a target temperature of 32°C may confer more consistent cardioprotection than the higher temperatures used in previous clinical trials [28]. Potential complications of therapeutic hypothermia include hyperglycemia, transient immunosuppression, abnormalities in drug metabolism, hemodynamic deterioration, and increased oxygen consumption through shivering. Most of these complications are rare when contemporary therapeutic hypothermia protocols are used, and the patient is appropriately monitored in the critical care setting [29]. A unique concern in patients undergoing therapeutic hypothermia in the setting of AMI is a possible increased bleeding risk. Hypothermia can affect platelet function and other steps in the coagulation cascade, including sequestration of platelets in the spleen and liver, which can re-enter the circulation after rewarming. Despite these concerns, therapeutic hypothermia in patients following revascularization has not been shown to be associated with increased bleeding risk [29]. Further studies are needed to determine the potential protective effects of therapeutic hypothermia on cardiac myocytes. Therefore, large multicenter, controlled clinical trials and mechanistic studies, including molecular integration models are required to determine the role of therapeutic hypothermia and to provide evidence for its clinical use.

Conclusions

Therapeutic hypothermia is not currently considered as a recommended treatment for refractory cardiogenic shock, and the evidence to support its use awaits the results of controlled clinical studies. The first case is described in which therapeutic hypothermia was re-initiated as a successful salvage therapy for cardiogenic shock in a patient with an anterior wall acute myocardial infarction (AMI) complicated by cardiac arrest where no other hemodynamic support alone was successful. To our knowledge, this is the first reported case where therapeutic hypothermia was successfully re-initiated in refractory cardiogenic shock despite pharmacologic and mechanical circulatory support. Further studies are needed to evaluate the efficacy of therapeutic hypothermia in patients with refractory cardiogenic shock after rewarming.

Conflict of interest

None.

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