Timing of Percutaneous Coronary Intervention and Therapeutic Hypothermia in Patients With ST-Elevation Myocardial Infarction and Out-of-hospital Cardiac Arrest

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The American College of Cardiology/American Heart Association guidelines include a Class 1 recommendation to initiate therapeutic hypothermia (TH) in comatose patients with out-of-hospital cardiac arrest (OHCA) with an initial shockable rhythm who have achieved return of spontaneous circulation. There is also a Class 1 recommendation for immediate angiography in these patients whose initial electrocardiography shows ST-elevation myocardial infarction (STEMI). However, due to a lack of clinical trials evaluating these patients who have received both percutaneous coronary intervention (PCI) and TH, controversy remains regarding whether the two can be safely combined. Furthermore, in patients who receive TH and PCI, another question to address is which therapy to initiate first. This article focuses on how best to manage comatose OHCA survivors who have an initial shockable rhythm and STEMI.

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KEY WORDS

Therapeutic hypothermia • Percutaneous coronary intervention • Out-of-hospital cardiac arrest • ST-elevation myocardial infarction

In 2002, two trials reported the clinical benefit of therapeutic hypothermia (32°C-34°C for 12-24 h) compared with standard therapy in comatose patients with out-of-hospital cardiac arrest (OHCA) after successfully resuscitated ventricular fibrillation arrest.[1,2] ST-elevation myocardial infarction (STEMI) is a common cause of cardiac arrest, and the ability to reduce neurologic damage in these patients is imperative because > 33% of patient mortality in the intensive care unit is secondary to brain injury.[3]

The current standard of care is in favor of combining therapeutic hypothermia (TH) and percutaneous coronary intervention (PCI), based on data and expert opinion (Table 1 illustrates cooling device options).[4,5] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines include both a Class 1 recommendation to initiate TH in comatose patients with STEMI and OHCA with an initial shockable rhythm who have achieved return of spontaneous circulation (ROSC) and a Class 1 recommendation for immediate angiography and PCI in patients whose initial electrocardiogram shows STEMI (even if they have had cardiac arrest).[4] However, it is important to note that there are potential adverse events associated with TH (eg, cardiac dysrhythmias, coagulopathy, and infection),[6] and these adverse events may be more worrisome when performing concomitant PCI. In addition, although there are reports that the combination of TH and PCI is safe and potentially beneficial,[7-9] questions such as which therapy to initiate first in those managed with a combination of TH and PCI have yet to be answered. This article focuses on how best to manage comatose OHCA survivors with an initial shockable rhythm and STEMI.

Safety and Efficacy of Combining TH and PCI

There are no randomized controlled trials, but the literature supports a combination of PCI and therapeutic hypothermia in comatose OHCA patients with an initial shockable rhythm, STEMI, and ROSC.[4,5] Knafelj and colleagues[8] investigated the feasibility and safety of combining primary PCI and TH in these patients. The 40 patients who underwent PCI and TH had significantly better neurologic outcomes compared with the 32 patients who underwent PCI alone (55% with high cerebral function on hospital discharge vs 16%; $P = .001$). Of note, in this study TH was started at various times in relation to PCI (either

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TABLE 1

Cooling Device Options

Cooling Method	Advantages	Disadvantages
Cold IV infusion	Easily accessible Rapid cooling Extensively studied	Large volume of IV fluid Central venous access
Cooling blanket	Easily accessible Able to reuse Extensively studied	Slower induction time Discontinuation for invasive procedures (eg, cardiac catheterization)
Cooling helmet	Early application (in field) Rapid cooling Inexpensive [a]Local brain cooling	Risk of head skin lesion Paucity of data
Intranasal cooling device	Early application (in field) Rapid cooling Inexpensive [a]Local brain cooling	No temperature feedback mechanism Paucity of data

[a]Local brain cooling is listed as an advantage because the local delivery to the brain may lessen the possibility of systemic side effects of hypothermia. However, there are insufficient data if a brain-body temperature gradient may impact myocardial infarction size and left ventricular ejection fraction.
IV, intravenous.

before, during, or after). Another study involving 50 patients initiated TH immediately after PCI and found that 68% of those patients had favorable neurologic outcomes.[9] A meta-analysis of multiple reports showed that, of the 1563 patients who subsequently underwent therapeutic hypothermia and PCI after cardiac arrest, survival to discharge occurred in 55%. Of those survivors, 88% had favorable neurologic function.[10] One concern with both revascularization and TH is the propensity to develop cardiac dysrhythmias. Batista and associates[11] specifically addressed this question and found, in a retrospective review of 160 patients, that cardiac catheterization with PCI in combination with TH did not significantly increase the risk of cardiac dysrhythmia. Although randomized controlled trials are lacking, data show that combining TH and PCI is feasible, relatively safe, and likely results in better outcomes.

Clinicians must be able to determine which patients are appropriate candidates for TH and PCI. Unfavorable resuscitation features such as unwitnessed arrest, initial nonshockable rhythm, delays in cardiopulmonary resuscitation (CPR), >30 minutes to ROSC, ongoing CPR, hemodynamic instability, organ hypoperfusion, age >85 years, and end-stage renal disease were all poor prognostic features.[12] All of these features adversely affect the procedural risk and survival benefit of PCI. Thus, the use of therapeutic hypothermia in combination with emergent angiography should be decided on a case-by-case basis.

Benefits of Initiating TH Prior to PCI

The combination of TH and PCI is supported by guidelines, but another question to address is which therapy to provide first. The International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science recommend that TH "should be initiated as soon as possible."[13] However, the ACC/AHA STEMI guidelines recommend PCI "within 90 minutes of presentation to a facility," and there is concern that the initiation of TH may interfere with this goal.[4] Some argue that TH should be initiated prior to taking the patient for angiography. However, many hospitals do not operate in this order.

A large part of the rationale in starting TH before PCI is that neurologic outcomes improve with earlier initiation of hypothermia. One registry database found that poor neurologic outcomes increased significantly with each 5-minute delay in initiating TH (odds ratio [OR] = 1.06; 95% CI, 1.02-1.1).[13] Additionally, the odds of a poor neurologic outcome for every 30-minute delay in time to reach target temperature were significantly greater (OR = 1.17; 95% CI, 1.01-1.36).[14] These outcomes suggest that earlier initiation of TH is preferable. This prompted the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care statement, "therapeutic hypothermia is recommended in combination with primary PCI, and should be started as early as possible, preferably before initiation of PCI."[13] In addition, the AHA's 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care suggest that "angiography and/or PCI need not preclude or delay other therapeutic strategies including therapeutic hypothermia."[5]

Proponents in favor of initiation of TH before PCI argue that TH may reduce infarct size if started before revascularization. Hypothermia may reduce the metabolic demand of ischemic/infarcted myocardium, enhance mitochondrial membrane stability, and improve microvasculature flow.[15-17] Several studies in animals demonstrate that hypothermia has a cardioprotective effect in acute myocardial infarction (MI).[18,19] Rapid hypothermia before reperfusion reduced myocardial infarct size and microvascular obstruction. Reduction in infarct size was more pronounced in animals that received cooling prior to reperfusion than in those that received cooling after reperfusion.[18] In human studies, there is evidence that infarct size is reduced in patients with acute MI who received endovascular cooling for several hours.[20] One study from Germany found that patients presenting with acute MI who were rapidly cooled before reperfusion had a reduced infarct size (measured by cardiac magnetic resonance imaging) without significantly delaying door-to-balloon time.[21] Results of the Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention (ICE-IT) study, which randomized patients with acute MI to hypothermia protocol versus standard of care, initially found no

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difference in final infarct size (the primary endpoint) in the hypothermia group. However, post-hoc analysis found that patients with anterior MI appeared to have a reduction in infarct size.[22] The above evidence is suggestive of enhanced cardioprotection in addition to the known neurologic benefits when initiating earlier TH.

Wolfrum and colleagues[23] reported outcomes of 16 consecutive patients who presented after OHCA with initial shockable rhythm, ROSC, and STEMI who were managed with immediate initiation of TH. These patients were compared with similar patients who were treated 2 years prior at the same institution. They continued TH during primary PCI and found that door-to-balloon times were not delayed (82 min in the control group vs 85 min in the experimental group). Furthermore, there was a trend toward lower mortality after 6 months and improved neurologic outcomes.[23] Sunde and colleagues[24] implemented a standardized treatment protocol for OHCA survivors with ROSC that included initiation of TH shortly after arrival to the emergency room. The authors found that discharge rate from hospital, neurologic outcomes, and 1-year survival improved after their protocol was implemented compared with OHCA survivors from before the protocol was initiated.

Hospitals have started to develop protocols for STEMI patients with OHCA. Abbott Northwestern Hospital (Minneapolis, MN) is one example of a successful protocol in this type of patient. Their "Cool It" protocol begins treatment of OHCA survivors and STEMI with aspirin, clopidogrel, and heparin, followed by cooling initiation.[25] An Arctic Sun® (Medivance, Louisville, CO) device is used for cooling so that groin access can be easily obtained when the patient is transferred to the cardiac catheterization laboratory. Once the patient is in the catheterization laboratory, each member of the heart team has a specific role with regard to management of TH and PCI. Neurologic outcomes were extremely impressive in STEMI survivors and door-to-balloon times were only mildly increased (by ~6 min).[25]

Concerns Regarding TH Initiation Prior to PCI

Despite the reported successes, there are potential drawbacks of initiating the hypothermia protocol prior to revascularization. The trials described above found that TH initiation was feasible without significant door-to-balloon delay, but these were small trials. Concern remains that earlier initiation of TH will delay time to reperfusion. Furthermore, hypothermia can increase the risk of access site complications and infection. Nielsen and coworkers[26] found that, in 726 patients treated with TH, bleeding and infection were more common after invasive procedures. Another problem institutions may have with initiation of TH prior to PCI is the need for increased staff in the cardiac catheterization laboratory. Hypothermia affects multiple organ systems, electrolyte imbalances, insulin resistance, and coagulopathy, and causes hemodynamic changes.[27] More intensive monitoring is required for these adverse effects. Hypothermia is usually achieved through cold saline infusion[28] or external cooling techniques (eg, cooling blankets), and careful monitoring of body temperature is required. The extra monitoring required may remove staff focus from the procedural aspect. In the future, novel cooling devices such as a transnasal cooling device[29] and cooling helmets[30] may make it easier to reach target temperatures regardless of location without increased rates of pulmonary edema. With newer and easier ways of inducing hypothermia, there will be a benefit to prehospital cooling in future trials. However, there is still a lack of proof that earlier induction is associated with better outcomes.

TH may increase risk of stent thrombosis due to its coagulopathic state and the lower liver metabolism of drugs that inhibit the adenosine diphosphate $P2Y_{12}$ receptors and thromboxane A2 synthesis.[31] On a molecular level, hypothermia may induce a prothrombotic state.[32] In addition, data exist that the antiplatelet effect of clopidogrel is reduced in hypothermic patients.[33] There is some evidence of increased rates of stent thrombosis in patients treated with TH compared with non–TH-treated patients.[31,34] These data are concerning for patients treated with TH prior to PCI, or even after PCI. The most recent PCI guidelines do not recommend routine platelet reactivity testing.[35] However, in patients with high risk for poor outcomes, platelet function testing may be considered.[35] One study of 44 patients with acute MI and cardiac arrest treated with TH compared platelet inhibition of clopidogrel, prasugrel, and ticagrelor. The authors found that, on day 3, 85% of patients on clopidogrel had ineffective

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platelet inhibition, compared with 6% and 0% for those on prasugrel and ticagrelor, respectively.[36] A similar study compared clopidogrel, prasugrel, and ticagrelor platelet inhibition in patients with acute MI and both normothermia and TH. The platelet inhibitory effect in patients treated with TH was significantly reduced in the clopidogrel-treated patients. Prasugrel and ticagrelor improved platelet inhibition but did not completely prevent nonresponsiveness.[37] A recent study found that, in 98 patients treated with PCI and hypothermia, there was less in-stent thrombosis with the use of ticagrelor than clopidogrel (11.4% vs 0%; $P = .04$).[38] Platelet reactivity was not measured in these patients; therefore, it is still unclear if this would impact clinical outcomes. More studies are needed to compare clopidogrel with other $P2Y_{12}$ inhibitors, and assess the clinical utility of platelet function testing in this population.

Conclusions

Based on current studies, it is difficult to decide when to initiate the therapeutic hypothermia in relation to PCI in comatose survivors of ventricular fibrillation cardiac arrest and STEMI. There is still controversy regarding whether the two should be combined. The risks of an invasive procedure and the survival benefit must be weighed when deciding which patient to take to the catheterization laboratory and/or in whom to initiate TH. There are certain features that adversely affect the procedural risk and survival benefit in cardiac arrest patients. Thus, the use of therapeutic hypothermia and emergent angiography should be carefully decided on a case-by-case basis. Many institutions start TH if the catheterization laboratory team has not yet arrived, or delay TH if the catheterization laboratory is immediately prepared. Other institutions are not equipped to staff TH protocol in the catheterization laboratory, and will start TH immediately after catheterization. Based on available data from literature and expert consensus, it is evident that we must ensure the PCI is completed with a 90-minute door-to-balloon time, and that TH is started as soon as possible. However, there is still a need for additional studies regarding the timing of PCI and TH. ■

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MAIN POINTS

- The American College of Cardiology/American Heart Association guidelines include a Class 1 recommendation to initiate therapeutic hypothermia (TH) in comatose patients with out-of-hospital cardiac arrest with an initial shockable rhythm who have achieved return of spontaneous circulation. There is also a Class 1 recommendation for immediate angiography in these patients whose initial electrocardiography shows ST-elevation myocardial infarction.
- Unfavorable resuscitation features such as unwitnessed arrest, initial nonshockable rhythm, delays in cardiopulmonary resuscitation (CPR), >30 minutes to return of spontaneous circulation, ongoing CPR, hemodynamic instability, organ hypoperfusion, age >85 years, and end-stage renal disease were all poor prognostic features. All of these features adversely affect the procedural risk and survival benefit of percutaneous coronary intervention (PCI). Thus, the use of therapeutic hypothermia in combination with emergent angiography should be decided on a case-by-case basis.
- Proponents in favor of initiation of TH before PCI argue that TH may reduce infarct size if started before revascularization. Hypothermia may reduce the metabolic demand of ischemic/infarcted myocardium, enhance mitochondrial membrane stability, and improve microvasculature flow.
- There is some evidence of increased rates of stent thrombosis in patients treated with TH compared with non–TH-treated patients. These data are concerning for patients treated with TH prior to PCI, or even after PCI.

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