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Dose-Dependent Cardioprotection of Moderate (32°C) Versus Mild (35°C) Therapeutic Hypothermia in Porcine Acute Myocardial Infarction

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ABSTRACT

OBJECTIVES The study investigated whether a dose response exists between myocardial salvage and the depth of therapeutic hypothermia.

BACKGROUND Cardiac protection from mild hypothermia during acute myocardial infarction (AMI) has yielded equivocal clinical trial results. Rapid, deeper hypothermia may improve myocardial salvage.

METHODS Swine (n = 24) undergoing AMI were assigned to 3 reperfusion groups: normothermia (38°C) and mild (35°C) and moderate (32°C) hypothermia. One-hour anterior myocardial ischemia was followed by rapid endovascular cooling to target reperfusion temperature. Cooling began 30 min before reperfusion. Target temperature was reached before reperfusion and was maintained for 60 min. Infarct size (IS) was assessed on day 6 using cardiac magnetic resonance, triphenyl tetrazolium chloride, and histopathology.

RESULTS Triphenyl tetrazolium chloride area at risk (AAR) was equivalent in all groups ($p = 0.2$), but 32°C exhibited 77% and 91% reductions in IS size per AAR compared with 35°C and 38°C, respectively (AAR: 38°C, 45 ± 12%; 35°C, 17 ± 10%; 32°C, 4 ± 4%; $p < 0.001$) and comparable reductions per LV mass (LV mass: 38°C, 14 ± 5%; 35°C, 5 ± 3%; 32°C 1 ± 1%; $p < 0.001$). Importantly, 32°C showed a lower IS AAR ($p = 0.013$) and increased immunohistochemical granulation tissue versus 35°C, indicating higher tissue salvage. Delayed-enhancement cardiac magnetic resonance IS LV also showed marked reduction at 32°C (38°C: 10 ± 4%, $p < 0.001$; 35°C: 8 ± 3%; 32°C: 3 ± 2%, $p < 0.001$). Cardiac output on day 6 was only preserved at 32°C (reduction in cardiac output: 38°C, -29 ± 19%, $p = 0.041$; 35°C: -17 ± 33%; 32°C: -1 ± 28%, $p = 0.041$). Using linear regression, the predicted IS reduction was 6.7% (AAR) and 2.1% (LV) per every 1°C reperfusion temperature decrease.

CONCLUSIONS Moderate (32°C) therapeutic hypothermia demonstrated superior and near-complete cardioprotection compared with 35°C and control, warranting further investigation into clinical applications.
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ABBREVIATIONS AND ACRONYMS

AAR = area at risk

AMI = acute myocardial infarction

CMR = cardiac magnetic resonance

cTnI = cardiac troponin I

DE-CMR = delayed-enhancement cardiac magnetic resonance

IS = infarct size

LAD = left anterior descending artery

LV = left ventricular

STEMI = ST-segment elevation myocardial infarction

TH = therapeutic hypothermia

TTC = triphenyl tetrazolium chloride

Therapeutic hypothermia (TH) confers a cardioprotective benefit by increasing the tolerance to injury from myocardial ischemia and reperfusion. Due to the broad effect of temperature on most cellular processes, TH may protect from ischemia through a variety of interrelated mechanisms, which are not completely understood. Direct detriments to ATP consumption trigger intracellular acidosis, Na^+/Ca^{2+} overload, and mitochondrial oxygen radical formation, leading to both necrosis and apoptosis (1).

Cardioprotection from TH was previously demonstrated in small and large animal ischemia models (2–7). An earlier observation of TH dose-response was made by Miki et al. (2) in rabbits, where significant cardioprotection was noted with cooling to 32°C, but less protection with cooling to 35°C when TH was administered before reperfusion. Later animal studies confirmed the need to initiate TH before reperfusion to retain myocardial salvage of the therapy (1,8).

Clinically, hypothermia has been shown to be safe and feasible; however, the outcomes of clinical trials, such as the COOL-MI (Cooling As An Adjunctive Therapy To Percutaneous Intervention In Patients With Acute Myocardial Infarction) (9), ICE-IT (Intravascular Cooling Adjunctive To Primary Coronary Intervention) (10), RAPID MI ICE (Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention) (11), and CHILL MI (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction) (12) trials, have not been consistent with the majority of the experimental literature. The recent CHILL MI (12) trial showed a nonsignificant trend of infarct size (IS) reduction by 13% with hypothermia (ice-cold intravenous saline plus endovascular cooling) (13) imaging. Following the trend of previous trials, the subgroup of early (<4 h) anterior ST-segment myocardial infarction (STEMI) showed a significant 33% reduction in IS. Notably, only 76% of patients receiving TH reached the goal temperature <35°C (~9-min increase in door-to-balloon time).

Thus, timing (pre-reperfusion temperature) and depth of cooling have been identified as important factors modulating the efficacy of TH. Moreover, rapid induction of TH is important in the setting of clinical AMI in which minimizing door-to-balloon time and reaching target temperature before reperfusion are crucial for salvaging cardiac muscle. Thus, it is critical to understand the optimal target reperfusion temperature to maximally attenuate MI damage in a clinically relevant model of MI.

In this study, we evaluated the effect of rapid endovascular TH on salvaging myocardial tissue in AMI in a porcine model. We hypothesized that a lower rapid TH target temperature would further reduce the size of infarction resulting in increased cardioprotection.

METHODS

AMI ANIMAL MODEL. Animal care and interventions were in accordance with the Laboratory Animal Welfare Act and all animals received humane care and treatment in accordance with the Guide for Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html). Yorkshire female swine (n = 24) weighing 46 ± 3 kg were randomized into 3 groups: normothermia, hypothermia to 35°C (mild), and hypothermia to 32°C (moderate). Sample size determined using a power analysis based on prior experience with this animal model to see a 30% reduction in IS. Animals were pre-anesthetized with intramuscular Telazol (6 mg/kg) prior to tracheal intubation. Animals were maintained in a surgical plane of anesthesia with inhaled anesthetic isoflurane (1% to 4%) through a volume-controlled ventilator (tidal volume 10 to 15 ml/kg and ventilation rate 8 to 15 breaths/min).

Tidal volume, respiration rate, and FiO_2 were adjusted to maintain normocapnia (end-tidal $PaCO_2$ [$EtCO_2$] 35 to 45 mm Hg) as measured by a capnometer (NPB-75, Nellcor-Puritan-Bennett, Boulder, Colorado) placed on the intubation tube. Electrocardiogram, $EtCO_2$, temperatures (left ventricular [LV], rectal, esophageal), and blood pressures (aortic, central venous) were monitored and recorded throughout using a multichannel data acquisition system (ADInstruments, PowerLab, Colorado Springs, Colorado).

Occlusion ischemia was induced using a coronary balloon advanced to a mid-left anterior descending artery (LAD) location typically proximal to the first diagonal branch and inflated to 3 to 6 atm. Vessel occlusion and ischemia were confirmed with contrast dye injection and ST-segment elevation on electrocardiogram. For animals receiving TH, an endovascular temperature management balloon catheter (Proteus Intravascular Temperature Management System, ZOLL, San Jose, California) was introduced via 12-F femoral venous sheath. The cooling balloon of the catheter was positioned in the inferior vena cava below the right atrium. The Proteus catheter and console controlled core body temperature using a probe passing through a balloon lumen at the user-specified temperature set point.