Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 2, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.06.080

PRECLINICAL RESEARCH

Catheter-Based Transcoronary Myocardial Hypothermia Attenuates Arrhythmia and Myocardial Necrosis in Pigs With Acute Myocardial Infarction

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Objectives This study evaluated the efficacy of catheter-based transcoronary myocardial hypothermia (CTMH) in pigs with acute myocardial ischemia.

Background Although it has been suggested that hypothermia therapy can attenuate myocardial necrosis, few applications have been accepted for clinical use.

Methods This study comprises 2 substudies. In both studies, pigs underwent 60 min of coronary occlusion and 180 min of reperfusion. In study 1, after 15 min of coronary occlusion with an over-the-wire-type balloon (OTWB), pigs in the hypothermia group (H) ($n = 13$) were directly infused with 4°C saline into the coronary artery through the OTWB wire lumen (2.5 ml/min) for 60 min. Pigs in the normothermia group (N) ($n = 15$) received the same amount of 36.5°C saline. In study 2, pigs in the hypothermia-reperfusion group (HR) ($n = 5$) were infused with 4°C saline through the infusion catheter (8 ml/min) for 30 min with a later start (60 min after coronary occlusion), whereas simple reperfusion was used for the reperfusion group (R) ($n = 6$).

Results Catheter-based transcoronary myocardial hypothermia was successful in both studies. In study 1, CTMH significantly decreased ventricular arrhythmia and the ratio of necrosis to ischemic risk area (H: 9 ± 2%; N: 36 ± 4%; $p < 0.0001$) with a significant reduction of enzyme leaks. In study 2, CTMH tended to reduce the ratio of necrosis (HR: 33 ± 2%; R: 45 ± 5%; $p = 0.08$). In both studies, CTMH significantly suppressed the increase of 8-iso-prostaglandin $F_{2\alpha}$ while preserving the coronary flow reserve.

Conclusions Catheter-based transcoronary myocardial hypothermia reduced myocardial necrosis while preserving coronary flow reserve, due, in part, to attenuation of oxidative stress. (J Am Coll Cardiol 2007;49:250–60) © 2007 by the American College of Cardiology Foundation

Coronary reperfusion therapy is widely performed in patients with acute myocardial infarction (MI), although its cardioprotective effect remains unsatisfactory. Reperfusion injury induces persistent myocardial necrosis in conjunction with increased oxidative stress (1–3) and activity of cytokines (4,5), which are believed to be major factors contributing to the deterioration of cardiac function after coronary reperfusion therapy. Although several agents, such as antioxidants (6), genes (7), and hormones (8), have been administered as adjuncts to coronary reperfusion, their efficacy for preventing ischemic damage has been found lacking. Findings from preliminary animal studies, however, have shown that mild hypothermia markedly ameliorates tissue damage after the onset of ischemia in many organs (9–12). As for the heart, several experimental studies have demonstrated that mild hypothermia can minimize myocardial necrosis resulting from acute MI (13–16). Ongoing research into systemic core cooling with an endovascular cooling system for patients with acute MI has shown its safety (17). With this method, however, sufficient cooling of the ischemic myocardium cannot be attained due to severe shivering caused by lowering the whole body temperature, so that the apparent myocardial protective effect is negated.

Therefore, we developed a new method involving cold saline infusion into an infarct-related coronary artery by means of a catheter. With this method, the cooling effect

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Manuscript received February 16, 2006; revised manuscript received June 9, 2006, accepted June 19, 2006.

was restricted to the ischemic myocardium, thus resulting in a substantial reduction in systemic complications. Furthermore, this technique is simple, so that it may be suitable for widespread clinical application. The purpose of the study presented here was to determine whether this method could effectively induce regional hypothermia as well as attenuate arrhythmia and myocardial injury in pigs with acute MI.

Methods

This study comprises 2 substudies. In study 1, we evaluated whether direct infusion of cold saline into the coronary artery could induce regional hypothermia and attenuate myocardial injury in pigs with ongoing ischemia. In study 2, to examine the clinical feasibility and efficacy of this procedure for acute MI, hypothermal-reperfusion therapy was initiated after a longer period of coronary occlusion and the result was compared with that obtained with simple immediate reperfusion-therapy in pigs with established MI.

Subjects. Thirty-nine Yorkshire pigs (28 for study 1, 11 for study 2) were used, and the study procedure conformed to the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health.

Surgical preparation. The pigs were sedated with intramuscular ketamine hydrochloride (20 mg/kg) and atropine sulfate (0.05 mg/kg). After tracheal intubation, deep anesthesia was induced with mechanical ventilation of oxygen and sevoflurane. Through a median sternotomy and systemic heparinization (100 U/kg intravenously/h), the pericardium was incised, and a deep body thermister (Coretemp CM-210, Terumo Co., Tokyo, Japan) to monitor the myocardial temperature at 5- to 6-mm depth was placed directly onto the area at risk of ischemia. A 6-F Swan-Ganz catheter (CCOM catheter; Terumo Co.) was advanced via the left internal jugular vein into the pulmonary artery to monitor cardiac output. A 5-F catheter was then inserted through the right internal jugular vein into the coronary sinus for blood sampling, while a 2-F micromanometer-tipped catheter (Millar Instruments, Houston, Texas) was advanced into the left ventricular (LV) cavity through a 5-F pigtail catheter via the right femoral artery for measuring peak positive first derivative of LV ($LVdP/dt_{max}$) and time constant of LV relaxation (tau). Finally, a 7-F angioplasty-guiding catheter (Heartrail, Terumo Co.) was used for entry into the left coronary from the right carotid artery.

Experimental procedure. Figure 1 provides an overview of the study protocols. First, baseline hemodynamics, myocardial and rectal temperature, and blood samples were obtained. After coronary angiography, an over-the-wire type percutaneous transluminal coronary angioplasty balloon (OTWB) mounted on a 0.014-inch wire was advanced into the left anterior descending coronary artery (LAD), positioned at approximately one-third of the distance from the apex and inflated to occlude the LAD for 60 min. After 15 min of coronary occlusion, the pigs in study 1 were randomly assigned to the hypothermia or the normothermia group. For animals in the hypothermia group, cooled saline (4°C) was infused into the ischemic myocardium through the wire lumen of the OTWB at 2.5 ml/min (the maximum flow rate possible for this wire lumen). Pigs in the normothermia group were administered the same amount saline, but at 36.5°C in the same manner. After 60 min of coronary occlusion, reperfusion was achieved by complete deflation of the OTWB, and intracoronary saline infusion was continued for 15 min after reperfusion in both groups.

In study 2, the LAD was occluded at the same position by using an infusion balloon (Helios, Avantec, Vascular Corporation, Sunnyvale, California), which has a larger lumen than conventional OTWB so that a higher volume of saline could be infused. After 60 min of coronary occlusion, pigs were assigned to the hypothermia-reperfusion group or the reperfusion group. For pigs in the hypothermia-reperfusion group, cooled saline (4°C) was infused through the infusion balloon at 8 ml/min for 30 min followed by complete balloon deflation. For pigs in the reperfusion group, simple reperfusion was used after 60 min of coronary occlusion. In both studies, reperfusion was observed for 180 min.

Incidence of arrhythmia. Twenty-four-hour Holter recordings (Holtrec, Terumo Co.) were obtained and reviewed with the Holtrec Analysis System software to determine the total number of ventricular premature beats and sustained ventricular tachycardia (sVT). Ventricular premature beats were defined as the presence of at least 2 of 3 criteria: 1) atypical QRS configuration with alteration or inversion of the T wave; 2) post-extrasystolic pause; and 3) atrioventricular dissociation. Sustained ventricular tachycardia was defined as a fast ventricular rhythm of 15 or more beats in accordance with the Lambeth Conventions (18).

Coronary flow velocity measurements. Intracoronary Doppler flow measurements were performed with a 0.014-inch Doppler-tipped guidewire (FloWire; Volcano Therapeutics, Inc., Rancho Cordova, California) and a velocimeter (FloMap; Volcano Therapeutics Inc.) at baseline, 60 min, and 180 min after reperfusion. Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity (APV) during 2 cardiac cycles. After measurement of the baseline APV, the hyperemic APV for intracoronary papaverine (10 mg) injection was recorded, and the coronary flow reserve (CFR) was obtained as the ratio of hyperemic APV to baseline APV.

Abbreviations and Acronyms

- **APV** = time-averaged peak velocity
- **CFR** = coronary flow reserve
- **CKMB** = creatinine kinase MB isozyme
- **cTnT** = cardiac troponin T
- **LAD** = left anterior descending coronary artery
- **LV** = left ventricle/ventricular
- **$LVdP/dt_{max}$** = peak positive first derivative of left ventricle
- **MI** = myocardial infarction
- **OTWB** = over-the-wire-type balloon
- **sVT** = sustained ventricular tachycardia
- **tau** = time constant of left ventricular relaxation
- **8-iso-$PGF_{2\alpha}$** = 8-iso-prostaglandin $F_{2\alpha}$