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Cooling as an Adjunctive Therapy to Percutaneous Intervention in Acute Myocardial Infarction: COOL-MI InCor Trial

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Endovascular Therapeutic hypothermia (ETH) reduces the damage caused by postischemia reperfusion injury syndrome in cardiopulmonary arrest and has already established its role in patients with sudden death; however, its role in ST-segment elevation myocardial infarction (STEMI) remains controversial. The objectives of this study were to investigate the safety, feasibility, and 30-day efficacy of rapid induction of therapeutic hypothermia as adjunctive therapy to percutaneous coronary intervention (PCI) in patients with anterior and inferior STEMIs. This was a prospective, controlled, randomized, two-arm, prospective, interventional study of patients admitted to the emergency department within 6 hours of angina onset, with anterior or inferior STEMI eligible for PCI. Subjects were randomized to the hypothermia group (primary PCI+ETH) or to the control group (primary PCI) at a 4:1 ratio. The ETH was induced by 1 L cold saline (1–4°C) associated with the Proteus™ System, by cooling for at least 18 minutes before coronary reperfusion with a target temperature of 32°C ± 1°C. Maintenance of ETH was conducted for 1–3 hours, and active reheating was done at a rate of 1°C/h for 4 hours. Primary safety outcomes were the feasibility of ETH in the absence of (1) door-to-balloon (DTB) delay; (2) major adverse cardiac events (MACE) within 30 days after randomization. The primary outcomes of effectiveness were infarct size (IS) and left ventricular ejection fraction (LVEF) at 30 days. An as-treated statistical analysis was performed. Fifty patients were included: 35 (70%) randomized to the hypothermia group and 15 (30%) to the control group. The mean age was 58 ± 12 years; 78% were men; and associated diseases were 60% hypertension, 42% diabetes, and 72% dyslipidemia. The compromised myocardial wall was anterior in 38% and inferior in 62%, and the culprit vessels were left anterior descending artery (LAD) (40%), right coronary artery (38%), and left circumflex (18%). All 35 patients who attempted ETH (100%) had successful cooling, with a mean endovascular coronary reperfusion temperature of 33.1°C ± 0.9°C. The mean ischemic time was 375 ± 89.4 minutes in the hypothermia group and 359.5 ± 99.4 minutes in the control group. The mean DTB was 92.1 ± 20.5 minutes in the hypothermia group and 87 ± 24.4 minutes in the control group. The absolute difference of 5.1 minutes was not statistically significant ($p = 0.509$). The MACE rates were similar between both groups (21.7% vs. 20% respectively, $p = 0.237$). In the comparison between the hypothermia and control groups, no statistically significant differences were observed at 30 days between mean IS (13.9% ± 8% vs. 13.8% ± 10.8%, respectively, $p = 0.801$) and mean final LVEF (43.3% ± 11.2% vs. 48.3 ± 10.9%, respectively; $p = 0.194$). Hypothermia as an adjunctive therapy to primary PCI in STEMI is feasible and can be implemented without delay in coronary reperfusion. Hypothermia was safe regarding the incidence of MACE at 30 days. However, there was a higher incidence of arrhythmia and in-hospital infection in the hypothermia group, with no increase in mortality. Regarding efficacy, there was no difference in IS or LVEF at 30 days that would suggest additional myocardial protection with ETH. ClinicalTrials.gov: NCT02664194.

Keywords: therapeutic hypothermia, ST elevation myocardial infarct, percutaneous coronary intervention, acute coronary syndrome, left ventricle ejection fraction

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Introduction

Cardiovascular diseases are the leading mortality causes in Brazil, corresponding to 3,493,459 deaths (29%) between 2004 and 2014, and a total of 350,000 in 2016 (DATASUS, 2018). Endovascular therapeutic hypothermia (ETH) reduces the damage by ischemia/reperfusion cell syndrome in cardiac arrests (Negovsky, 1988; Bolli, 1997; Colbourne *et al.*, 1997; Yellon and Hausenloy, 2007); however, its role in ST-segment elevation myocardial infarction (STEMI) patients remains controversial (Neumar *et al.*, 2008, 2015; Gonzalez *et al.*, 2013; Hazinski *et al.*, 2015; O'Gara *et al.*, 2013; Levine *et al.*, 2016; Monsieurs *et al.*, 2015; Nolan *et al.*, 2015; Piegas *et al.*, 2015; Stone *et al.*, 2016). Experimental studies in different animal species showed that mild hypothermia, induced before reperfusion of acute coronary occlusion, can reduce infarct size (IS) (Duncker *et al.*, 1996; Hale *et al.*, 1997; Hale and Kloner, 1999; Dae *et al.*, 2002). So cooling before reperfusion may be an effective adjunct to primary percutaneous coronary intervention (PCI) in STEMI patients to reduce IS and so improve cardiac outcomes (Erlinge, 2011; Hausenloy and Yellon, 2013).

Even though randomized clinical trials including COOL MI (Dixon *et al.*, 2002), ICE-IT (O'Neill *et al.*, 2005), CHILL MI (Erlinge *et al.*, 2014), VELOCITY (Nichol *et al.*, 2015), and COOL AMI EU PILOT (Noc *et al.*, 2017) failed to show a significant reduction in IS, endovascular cooling appeared to be safe and well tolerated. Despite neutral overall results, subsequent unpublished *post hoc* subgroup analysis of COOL MI (Dixon *et al.*, 2002) and ICE-IT (O'Neill *et al.*, 2005), and combined analysis of RAPID MI-ICE (Götberg *et al.*, 2010) and CHILL MI (Erlinge *et al.*, 2014) showed significant reduction in IS in a subgroup of early presenters with anterior STEMI who were cooled below 35°C before reperfusion (Erlinge *et al.*, 2015). Therefore, benefits of therapeutic hypothermia might be achieved by using a rapid cooling to decrease core temperature below 35°C before the opening of acute coronary occlusion (Erlinge *et al.*, 2015).

New available advanced technologies using powerful devices allow cooling the patient much faster (Noc *et al.*, 2017), but it is still unknown whether ETH impacts delays in coronary reperfusion. The purpose of this study was to investigate the safety, feasibility, and 30-day efficacy of rapid induction of therapeutic hypothermia as adjunctive therapy to PCI in patients with anterior and inferior STEMIs.

Methods

This was a single-center, prospective, interventional, randomized controlled two-arm trial performed at InCor–Heart Institute–Clinical Hospital, University of Sao Paulo. Patients admitted to the emergency department (ED) with up to 6 hours of the onset of chest pain, presenting anterior or inferior STEMIs, and eligible for PCI were included.

All procedures were carried out in accordance with the Declaration of Helsinki, and the local/national ethics committees approved the study protocol. All patients gave written informed consent before inclusion in the study. An independent Data and Safety Monitoring Board, consisting of physicians independent of the trial sponsor and operational leadership, monitored the safety of the study based on access to unblinded data.

The study enrolled patients $\geq$18 years of age with a duration of symptoms of $\leq$6 hours presenting with an anterior or inferior STEMI with persistent ST-segment elevation of >0.2 mV in two contiguous leads at arrival to the catheterization laboratory and before randomization. Patients with resuscitated cardiac arrest, previous acute myocardial infarction, PCI or coronary artery bypass grafting, Killip class II–IV at presentation, atrial fibrillation, end-stage kidney disease or hepatic failure, recent stroke, coagulopathy, and pregnancy were excluded. Eligible patients were randomized 4:1 by using a computer-generating system to the ETH group (primary PCI+cooling+standard care) or to the control group (primary PCI+standard care alone). All patients received acetylsalicylic acid, heparin, and $P2Y_{12}$ receptor blockade. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the treating physician.

The patients were randomized electronically, using the online website SealedEnvelope™ (Sealed Envelope, 2015). Those assigned to the ETH group were initially administered 60 mg of oral buspirone and pethidine (meperidine) as an intravenous loading dose of 1 mg/kg (maximum 100 mg) or 0.5 mg/kg if the patient had already received morphine. After 15 minutes, an additional dose of 0.5 mg/kg was given and continued as an infusion at 25 mg/h (up to 80 kg patient) or 35 mg/h (>80 kg patient) for the duration of the hypothermia procedure of 1 or 3 hours, according to the electronic randomization. Patients were placed on a Bair Hugger™ (3M, Maplewood, MN), which covered the catheterization table for skin counter warming. Patients were supposed to remain awaken and comfortable all through the procedure, without shivering. Respiratory rate and pulse oximetry were monitored with targets of >10 breaths/min and arterial oxygen saturation of $\geq$90%. Cooling was initiated with a forced infusion of 1 L of cold saline (4°C) by using pressure bags and continued by the ZOLL® Proteus™ Intravascular Temperature Management System™.

In this study, there were selected patients with anterior or inferior STEMI within 6 hours of symptoms onset and we tested the new ZOLL Proteus Intravascular Temperature Management System (ZOLL Medical Corporation, Chelmsford, MA) (Fig. 1), which is, according to technical specifications, significantly more powerful (cooling rate 9.6°C/h, 430 W) than devices used in previous trials (maximum 3.6°C/h, 175 W).

The cooling catheter was inserted via the femoral vein (12 F sheath) into the inferior vena cava with the tip positioned at the level of the diaphragm. The Proteus temperature probe (X-Probe; ZOLL Medical Corporation) was put through the catheter lumen to the right atrium for continuous measurement of core temperature. The console temperature was set to 32.0°C, and cooling at maximum power started. After placement and activation of the cooling catheter, arterial puncture was performed and coronary angiography/PCI was conducted in a standard way. An interval of at least 18 minutes of endovascular cooling from catheter activation to coronary guidewire passing across the acute occlusion was performed. Cooling was maintained for 1 hour or for 3 hours, according to the electronic randomization, followed by active rewarming at the rate of 1.0°C/h to attain 36.0°C. The catheter was then removed by manual compression. Shivering was continuously assessed by the bedside shivering assessment scale (BSAS) using the following categories:

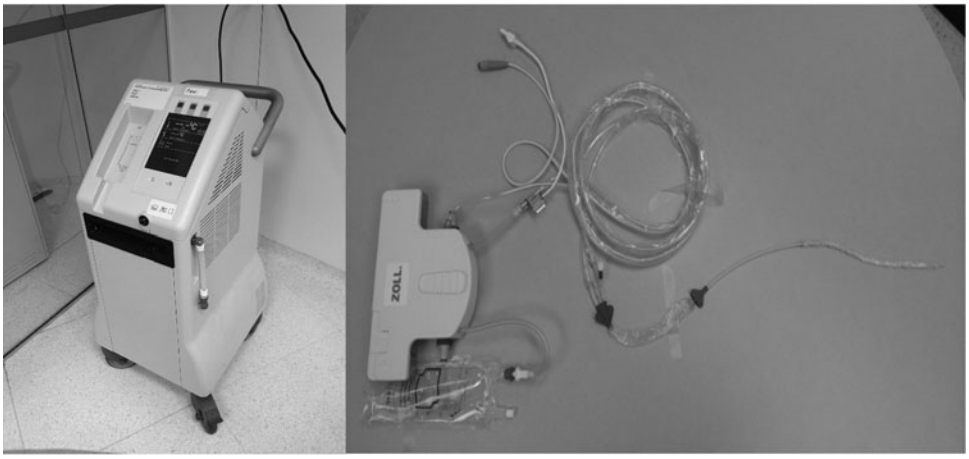


FIG. 1. ZOLL® Proteus™ Intravascular Temperature Management System™ (ZOLL Medical Corporation, Chelmsford, MA, USA). Hypothermia device *(left)*; endovascular hypothermia catheter *(right)*.

(0) No shivering on palpation of the masseter, neck, or chest wall.
(1) Shivering localized to the neck and/or thorax only.
(2) Shivering with gross movement of the neck, thorax, and upper extremities.
(3) Shivering involving gross movements of the trunk, upper and lower extremities.

If BSAS was ≥ 2, additional boluses of pethidine (25 mg) were used and infusion was increased to a maximum of 35 mg/h. If shivering persisted, the Proteus target temperature was raised stepwise by 0.5°C until shivering disappeared.

Study endpoints

The primary safety outcomes were the feasibility of ETH in the absence of:

(1) Door-to-balloon (DTB) delay;
(2) Major adverse cardiac events (MACE) within 30 days after randomization.

The primary effectiveness endpoints were IS and left ventricular ejection fraction (LVEF) measured by cardiac magnetic resonance (cMR) at 30 days. The secondary effectiveness endpoints were the IS between 1 and 3 hours cooling subgroups, as well as the IS within the anterior wall STEMI's subgroup.

Secondary safety endpoints were followed within 30 days (±7 days) after the index procedure and included MACE, stent thrombosis, arrhythmias, cardiogenic shock, pulmonary edema, deep venous thrombosis/pulmonary embolism, vascular complications requiring intervention, cooling catheter access site, and systemic infection.

The DTB was defined as the interval from the admission of the patient in the ED (''door'') until the time of first insufflation of the catheter balloon for primary PCI

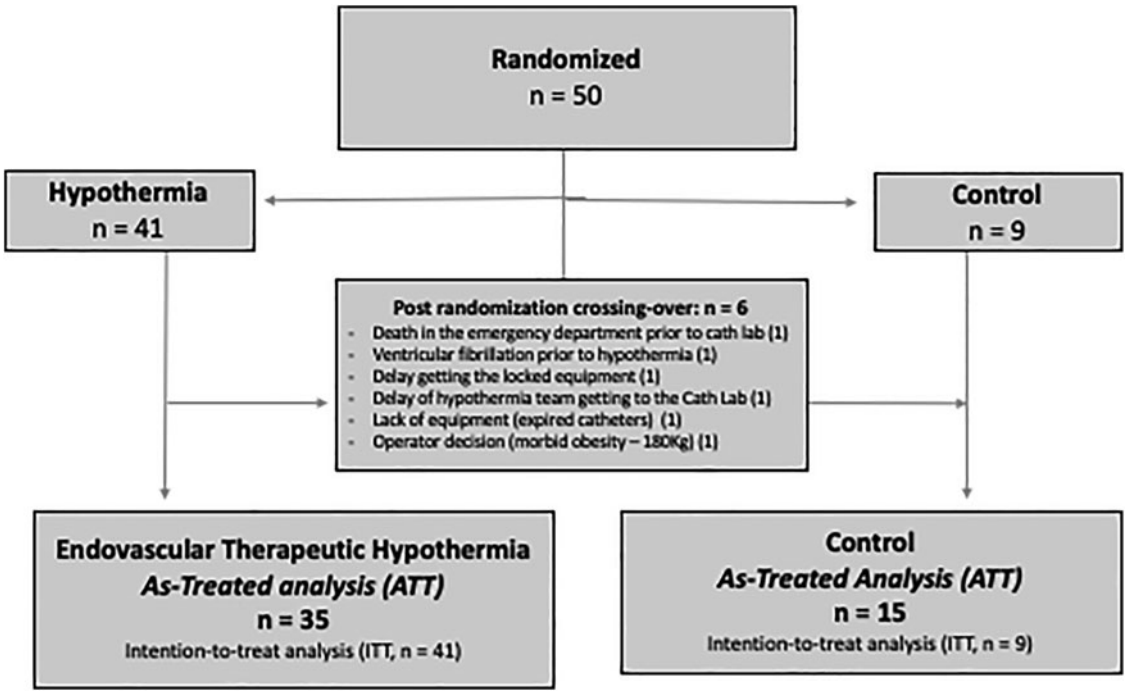


FIG. 2. Flowchart describing the randomization of the patients and reasons for post-randomization crossing-over from the ETH group to the control group. ETH, endovascular therapeutic hypothermia.

(''balloon''). If there was no lesion, the ''balloon'' time was defined as the angiogram's first injection of contrast in the coronary.

Infarction Size (IS) was defined as the gadolinium-enhanced myocardial mass (in grams) for late detection of scar and the percentage of Infarction Size (% IS) as this mass in relation to LV total mass.

Statistical analysis

In this study, evaluation of variables was calculated with number and proportion with an exact 95% confidence interval. For all clinical, angiographic, and periprocedural characteristics and safety outcomes, mean, standard deviation, median, range or frequency, and proportion were reported. For categorical variables, Fisher's exact test or the chi-square test was used to compare between the two treatment groups. For continuous variables, the Wilcoxon rank-sum test and t-test were used to compare between the two treatment groups as appropriate. No imputation was carried out for missing data. Analysis of variance analysis was performed in the comparison among more than two groups. All tests were two-sided. A p-value <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS 17.0 (IBM SPSS, Inc., Chicago, IL). ClinicalTrials.gov identification: NCT02664194.

The groups were compared and analyzed according to the Intention-To-Treat (ITT) analysis and the As-Treated (ATT) analysis. Our results showed a relatively high rate (14.6%) of patients randomized to the hypothermia group who did not receive such therapy at the end, for several different reasons. In the exploratory context of the present study, and to investigate hypothesis generating findings, we chose to concentrate our analyses following the ATT method, which evaluates patients according to the treatment actually received. All data from the ITT analysis were included in the Supplementary section.

Results

From January 2016 to August 2018, among 705 screened patients with anterior and inferior STEMI, 50 patients (7.1%) were enrolled and randomized in the trial. The ATT analysis consisted of 35 patients (70%) in the ETH group and 15 patients (30%) in the control group. Six patients enrolled to the ETH group did not get cooled down for several reasons: 1 died at the ED before the cath lab arrival, 1 ventricular fibrillation before hypothermia, 1 delay getting the locked equipment, 1 delay of hypothermia team getting to the Cath Lab, 1 lack of equipment (expired catheters), and 1 patient excluded for operator decision because of morbid obesity (180 kg); therefore, a total of 35 patients were cooled down.

Therefore, according to the main ATT analysis, 35 patients (70%) were included in the ETH group and 15 patients (30%) in the control group. There was also another secondary ITT analysis performed, consisting of 41 patients (82%) in the ETH group and 9 patients (18%) in the control group. A flow chart describing the patients' allocation and the reasons for post-randomization crossing-over are presented in Figure 2.

The clinical characteristics of each group are described in Table 1. There were no statistically significant differences in baseline and angiographic characteristics between both groups. The ETH group and the control group were comparable in terms of age, sex, body mass index, and risk factors for coronary disease. The mean age was 58 ± 12 years, predominantly male (78%), hypertension (60%), type 2 diabetes (42%), and dyslipidemia (72%). There were high-risk patients with high-risk outcome scores, including average thrombolysis in myocardial infarction (TIMI) risk score 3.6 ± 1.9, Global Registry of Acute Coronary Events (GRACE) risk score 119 (±28) and ROXANA bleeding risk score 15.3 (±6.3).

Table 1. Clinical and Angiographic Characteristics in the As-Treated Analysis

Characteristics	*Hypothermia group,* n = *35*	*Control group,* n = *15*	p
Average age (years)	59 ± 9.3	55.5 ± 11.2	0.262
Male gender	28 (80%)	11 (73.3%)	0.713
Weight (kg) type 2 diabetes	80.3 ± 13.7	81.3 ± 22	0.844
BMI	28.1 ± 5	28.8 ± 6.5	0.706
Hypertension	25 (71.4%)	9 (60%)	0.486
Type 2 diabetes	17 (48.6%)	6 (40%)	0.341
Dyslipidemia	18 (51.4%)	5 (33.3%)	0.341
Previous CAD	29 (82.8%)	10 (66.6%)	0.147
Previous smoking	12 (34.3%)	6 (40%)	0.749
Baseline temperature (°C)	36.5 ± 0.5	36.5 ± 0.5	0.985
GRACE risk score	121 ± 27	119 ± 34	1
TIMI risk score	3.7 (±2)	3.4 (±2.2)	1
ROXANA risk score	14.8 (±6)	15.7 (±6.4)	1
Anterior wall myocardial infarct	16 (45.7%)	3 (33.3%)	0.327
Inferior wall myocardial infarct	19 (54.3%)	12 (80%)	0.327
Infarct culprit artery			
LAD	17 (48.5%)	3 (20%)	0.478
RCA	13 (37.1%)	6 (40%)	1
LCx	7 (17.5%)	5 (33.4%)	0.341
Initial TIMI 0–1 flow	32 (91.4%)	13 (86.7%)	0.587
Final TIMI 2–3 flow	34 (97.1%)	14 (93.3%)	1
Coronary obstruction pattern			
One-vessel disease	15 (42.9%)	4 (26.7%)	0.215
Two-vessel disease	12 (37.1%)	6 (40%)	0.858
Multivessel	7 (20%)	2 (20%)	1
CABG	3 (8.6%)	3 (20%)	0.172

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events risk score; LAD, left anterior descending artery; LCx, left circumflex; RCA, right coronary artery.

We observed predominantly inferior wall involvement (62%), and the left anterior descending (LAD) coronary artery was the predominant culprit vessel (38%), followed by the right coronary artery in 38% and left circumflex in 18%. The initial TIMI flow was ≤ 1 in 90% cases, and the final TIMI flow was ≥ 2 in 98% cases after the procedure. From the total, 47 patients (94%) underwent primary PCI. Among the patients who did not undergo primary PCI, one patient died in the ED before the cath lab arrival, one patient had TIMI 3 flow in a multivessel scenario, and the other patient was diagnosed as having myocarditis.

Anti-shivering medication administered before and during the cooling included morphine, buspirone, and pethidine, and

Table 2. Endovascular Therapeutic Hypothermia Periprocedural Characteristics in the As-Treated Analysis

	1-Hour hypothermia group, n=*12*	*3 Hours hypothermia group,* n=*23*	*Total hypothermia group,* n=*35*	*Control group,* n=*15*	p *Value (total vs. control)*	p *Value (1 hour vs. 3 hours vs. control)*
No. of patients undergoing hypothermia	12 (100%)	23 (100%)	35 (100%)	0		
Ticagrelor	9 (75%)	10 (43.5%)	19 (54.3%)	7 (46.7%)	0.621	0.184
Anti-shivering protocol						
Buspirone 60 mg	12 (100%)	23 (100%)	35 (100%)	2 (13.3%)	<0.001	<0.001
Pethedine	12 (100%)	23 (100%)	35 (100%)	2 (13.3%)	<0.001	<0.001
Cold saline	12 (100%)	17 (73.9%)	29 (82.9%)	1 (6.7%)	<0.001	<0.001
Heating blanket	12 (100%)	23 (100%)	35 (100%)	0	<0.001	<0.001
Shivering scale						
BSAS 0	9 (75%)	17 (73.9%)	26 (74.3%)	5 (33.3%)		
BSAS 1	3 (25%)	5 (21.7%)	8 (22.9%)	0		
BSAS 2	0	1 (4.3%)	1 (2.9%)	0		
BSAS 3	0	0	0	0		
Mean baseline temperature (°C)	36.7 (±0.5)	36.4 (±0.4)	36.5 (±0.5)	36.5 (±0.5)	0.955	0.263
Mean temperature in the ''balloon'' time (°C)	33.1 (±1.1)	33.1 (±0.9)	33.1 (±1)	36.5 (±0.5)	<0.001	<0.001
Mean delta temperature	3.6 (±0.6)	3.3 (±0.5)	3.4 (±0.5)	0	<0.001	<0.001
Time arterial puncture to balloon (minutes)	27.6 (±11)	31.9 (±9.3)	31.7 (±10.6)	23.6 (±5.7)	0.245	0.214
Time of hypothermia to balloon (minutes)	21±5.3	20±5	21±5	N/A		
Temperature <35°C at balloon time	11 (91.7%)	22 (95.7%)	33 (94.3%)	0	<0.001	<0.001
Temperature 32°C±1.0°C in maintenance phase	5 (41.7%)	11 (47.8%)	16 (45.7%)	0	<0.001	<0.001
Temperature 32°C±1.0°C in the maintenance phase	11 (91.7%)	21 (91.3%)	35 (100%)	0	<0.001	<0.001
Hypothermia duration (minutes)	142.9 (±116)	182.5 (±63.2)	169.7 (±84.2)	0	0.135	0.135
Rewarming duration (minutes)	165.3 (±111)	224.6 (±63.5)	206.1 (±84.1)	0	0.604	0.604
Hypothermia maintenance (minutes)	100.9 (±132)	112.2 (±70.4)	109 (±89.8)	0	0.261	0.261
Indwell catheter time (minutes)	348.8 (±78.2)	425.2 (±66.7)	399 (±78.8)	0	0.287	0.287

BSAS, bedside shivering assessment scale.

by its administration, all patients remained conscious and comfortable during the angioplasty procedure at all stages of ETH and rewarming in the intensive care unit, with BSAS ≤ 1 in all patients (100%), without uncontrolled shivering. There was a successful cooling (target temperature 32°C±1.0°C) in all 35 patients with attempted cooling (100%), as shown in Table 2 and Figure 3. The mean interval between the Proteus system activation and coronary balloon time was 21±5 minutes, range 10–35 minutes. At this point, the mean intravascular temperature reached 33.1°C±1°C in the ATT analysis. As for the control group, the mean temperature by the time of the guidewire crossing the lesion was 36.5°C±0.5°C.

Primary endpoints

The timelines from symptoms onset until primary PCI reperfusion are shown in Table 3 and Figure 4. The median DTB time was 92.1±20.5 minutes in the ETH group and 87±24.4 minutes in the control group ($p=0.509$). There was no statistically significant cooling-related delay to reperfusion, and the absolute difference of 5.1 minutes was not statistically significant. The total ischemic time (symptoms onset to reperfusion delta) was not statistically different between the two groups (375±89.4 minutes vs. 359.5±99.4 minutes, respectively; $p=0.46$). There were no statistically significant differences in angiographic features, primary PCI result, or periprocedural medication between the groups.

The cMR was performed in 40 out of 50 patients (80%) at 5 days of follow-up and in 38 patients (76%) at the 30-day follow-up. The main reasons for not performing cMR were: refusal of four patients (8%), claustrophobia in three patients (6%), acute renal failure making the examination impossible due to the risk of systemic nephrosclerosis in two patients (4%), one patient submitted to myocardial revascularization before cMR (2%), and death in two patients (4%). The CMR image data are depicted in Table 4.

Table 3. Timeline from Symptom Onset Until Reperfusion in the As-Treated Analysis

	Hypothermia group	*Control group*	p
Time from symptom onset to the emergency department	287.2 (±83.5)	273.1 (±86.7)	0.592
Door-to-balloon time	92.1 (±20.5)	87 (±24.4)	0.509
Total time from symptom onset to balloon	375 (±89.4)	359.5 (±99.4)	0.635

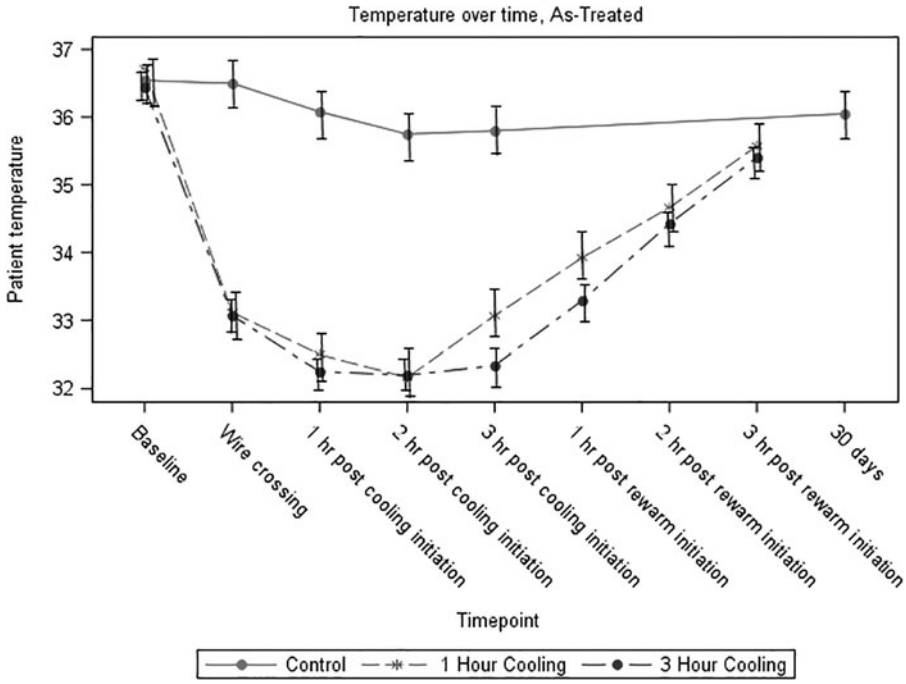


FIG. 3. Temperature over time in hypothermia (1 and 3 hours subgroup) and control groups in the ATT analysis at baseline randomization, at guidewire crossing, after PCI, and during rewarming. ATT, as-treated; PCI, percutaneous coronary intervention.

There was no statistically significant difference between mean IS at 30 days between hypothermia and control groups (13.9% ± 8% vs. 13.8% ± 10.8%, respectively, $p = 0.801$), as shown in Figure 5. There was no difference between the mean final 30-day LVEF between the hypothermia and control groups, 43.3% ± 11.2% in the hypothermia group versus 48.3% ± 10.9% in the control group ($p = 0.194$), as shown in Figure 6.

Regarding the subgroup of patients with exclusively anterior wall infarction, no statistically significant differences were observed between mean IS between hypothermia and control groups (13.9% ± 8% vs. 13.8% ± 10.8%, respectively, $p = 0.801$) at 30 days, as well as in the analysis of subgroups of patients undergoing 1 or 3 hours of hypothermia (10.9% ± 7.6% vs. 15.7% ± 7.8%, respectively; $p = 0.801$).

Adverse events

The adverse events are described in Table 5. Between the ETH and the control group, there were no statistically significant differences in the rates of all-cause mortality (2.9% vs. 6.7%, respectively; $p = 0.237$) or MACE (21.7% vs. 20%, respectively; $p = 0.237$).

There were no statistically significant differences in adverse events between the two groups in the composite of MACE, stroke, cardiogenic shock, pulmonary edema, ventricular fibrillation, surgical vascular complications, or bleeding (37.1% vs. 20%, respectively; $p = 0.234$).

However, there were statistically significant differences in adverse events, including in-hospital infections, observed in 25.7% of the ETH group and none in the control group ($p = 0.043$) and self-terminating paroxysmal atrial fibrillation (AF), documented in 51.4% of cooled patients versus 13.3% in the control group ($p = 0.014$). All paroxysmal AF resolved spontaneously to sinus rhythm (100%) during the rewarming phase. None of the other variables showed statistically significant differences.

Discussion

In the light of our knowledge, this is the first trial showing that endovascular cooling is feasible without delays in DTB.

Table 4. Cardiac Magnetic Resonance According to the As-Treated Analysis

	1-Hour hypothermia group, n = *12*	*3 Hours hypothermia group,* n = *23*	*Total hypothermia group,* n = *35*	*Control group,* n = *15*	p *Value (total vs. control)*	p *Value (1 hour vs. 3 hours vs. control)*
cMR at day 30						
Number cMR	10 (83.3%)	18 (78.2%)	28 (80%)	10 (66.7%)		
LVEF (%)	40.9 (±11.7)	44.6 (±11)	43.3 (±11.2)	48.3 (±10.9)	0.194	0.229
Infarct size (%)	10.9 (±7.6)	15.7 (±7.8)	13.9 (±8)	13.8 (± 10.8)	0.801	0.245
Anterior wall subgroup at day 30	5 (41.7%)	14 (60.9%)	19 (54.3%)	6 (40%)		
Number cMR	5 (83.3%)	10 (71.4%)	15 (78.9%)	5 (83.3%)		
LVEF (%)	40.1 (±11.7)	44.6 (±11)	43.8 (±12)	48.3 (±10.8)	0.395	0.229
Infarct size (%)	15 (±10.7)	18.3 (±7.2)	17.3 (±8.1)	10.9 (±9)	0.156	0.263

cMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.

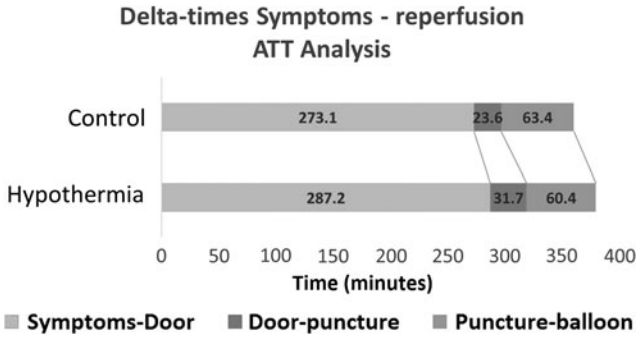


FIG. 4. Comparison of delta-times from the symptom onset until coronary reperfusion between the hypothermia group and the control group in the ATT analysis.

The primary PCI could be performed within 92.1 minutes DTB time, as compared with 87 minutes in the control group, and the absolute 5.1 minutes' difference was not statistically significant. International guidelines recommend that DTB should be within 90 minutes in top-performing institutions (Krumholz *et al.*, 2011; Menezes *et al.*, 2013; Levine *et al.*, 2015).

These results could be achieved through a systematic continuous training plan and by performing the cooling procedure at the Cath Lab concomitant to the angiogram. This was also possible due to current improved technology of the new endovascular Proteus Cooling System, which is much more powerful than the previous devices. It is implanted through a simple femoral vein puncture with the introduction of the cooling catheter, which takes a few minutes to be performed. Other recent similar trials failed to show the absence of DTB delays when ETH was performed (Testori *et al.*, 2019). In the COOL AMI EU Pilot trial (Noc *et al.*, 2017), the mean DTB time was 105 minutes, and there was a 17 minute cooling-related delay in the DTB.

For instance, delays in DTB would not only be dangerous to the patient, because the prolonged ischemic time could raise myocardium necrosis (Miller *et al.*, 1995; Burns *et al.*, 2002; Götberg *et al.*, 2008), but they would also be unethical. On the other hand, the cooling protection generated by the hypothermia procedure would allow some degree of delay, which would be therefore overwhelmed by the hypothermia protection in the reperfusion phase (Dixon *et al.*, 2002; O'Neal *et al.*, 2005; Götberg *et al.*, 2010; Erlinge *et al.*, 2014). Nevertheless, we were able do all the cooling procedures without delays in DTB, thus avoiding any criticism.

Cardioprotective strategies in ETH may be directly related to the total ischemic time (Villablanca *et al.*, 2016; Noc *et al.*, 2017), especially to the time from the symptom onset until the arrival at the ED. We observed a mean total ischemic time of 375 minutes in the hypothermia group and 359.5 minutes in the control group. This prolonged total ischemia time was predominantly caused by the delta from symptom onset to the ED arrival (287.2 vs. 273.1 minutes, respectively) and not due to DTB delay (92.1 vs. 87 minutes, respectively; $p = 0.509$).

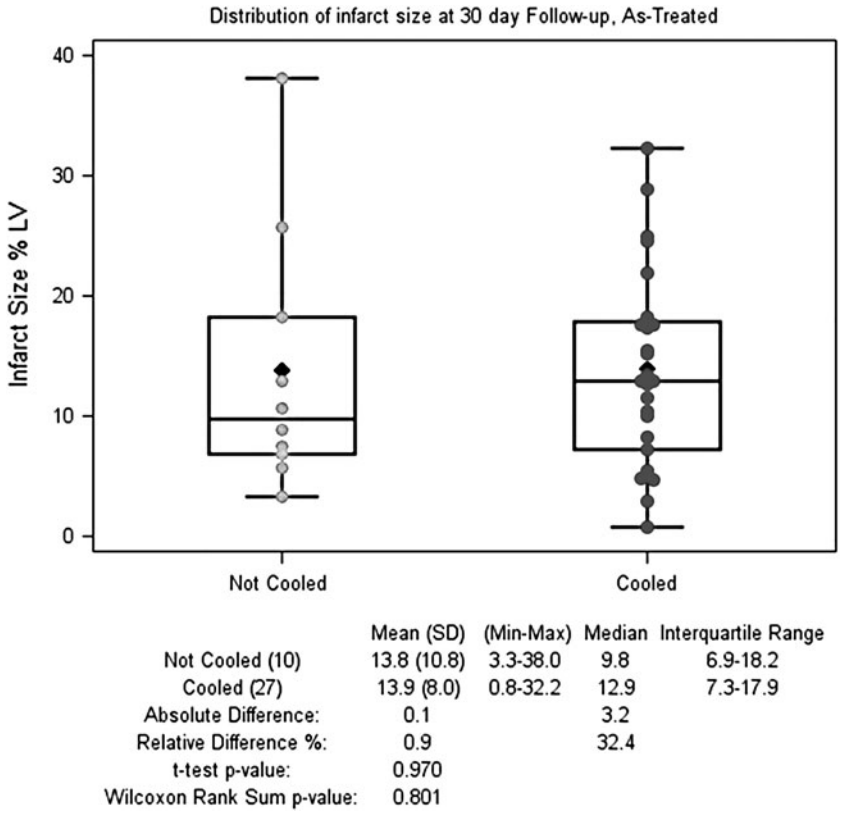
This ischemia time is much longer than data from previous studies from CHILL MI (132 minutes) (Erlinge *et al.*, 2014), VELOCITY (172 minutes) (Nichol *et al.*, 2015), RAPID MI ICE (174 minutes) (Götberg *et al.*, 2010), COOL MI (205 minutes) (Dixon *et al.*, 2002), and COOL AMI EU Pilot Trial (260 minutes) (Noc *et al.*, 2017) studies. This may have undermined all the benefits that would be provided by ETH in an earlier presentation scenario.

In our study, no statistically significant differences in infarction size were observed in both hypothermia (13.9% ± 8%) and control (13.8% ± 10.8%) groups, as well as between 1-hour subgroups (10.9% ± 7.6%) and 3-hour subgroups (15.7% ± 7.8%) of hypothermia. Even in the subgroup of patients with anterior wall AMI, there was no difference between hypothermia (17.3% ± 8.1%) and control (10.9% ± 9%) groups.

Table 5. Clinical Events in the As-Treated Analysis in 30 Days

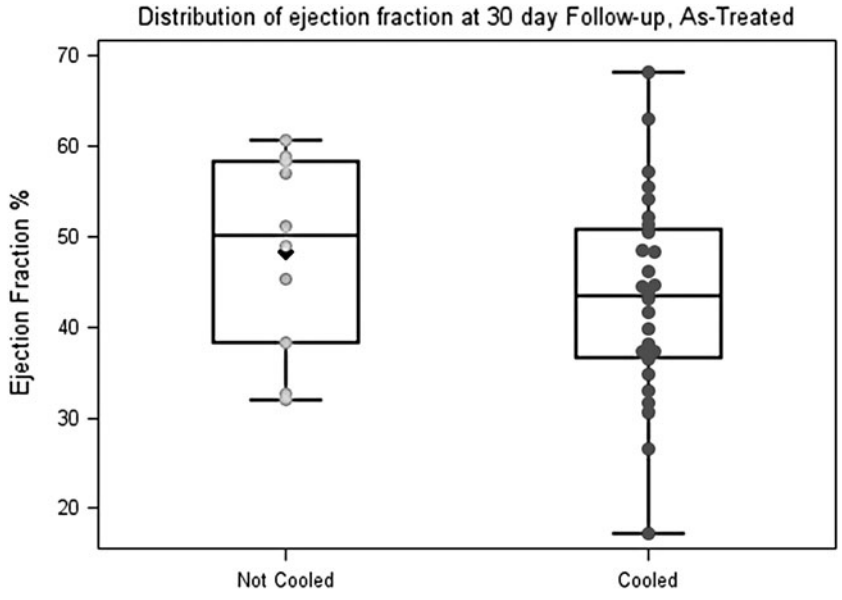
Adverse events in 30 days	*Hypothermia group (*N = *35)*	*Control group (*N = *15)*	p
MACE	5 (21.7%)	3 (20%)	1
Death	1 (2.9%)	1 (6.67%)	0.514
Recurrent myocardial infarct	2 (5.7%)	1 (6.67%)	1
Target vessel revascularization	2 (5.7%)	1 (6.67%)	1
Stroke	0	0	
Cardiogenic shock	4 (11.4%)	0	0.302
Pulmonary embolism	0	0	.
Ventricular fibrillation	7 (20%)	1 (6.67%)	0.407
Surgical vascular complications	3 (8.6%)	1 (6.67%)	1
Bleedings	1 (2.9%)	0	1
Any of the above	13 (37.1%)	3 (20%)	0.234
Acute renal impairment	2 (5.7%)	0 (0%)	1
Medication-related adverse event	2 (5.7%)	0 (0%)	1
Psychomotor agitation	3 (8.6%)	1 (6.7%)	1
Anemia	2 (5.7%)	0 (0%)	1
Paroxysmal atrial fibrillation	18 (51.4%)	2 (13.3%)	0.014
Infection	9 (25.7%)	0 (0%)	0.043
Thrombocytopenia	1 (2.9%)	0 (0%)	
Stent thrombosis			
Acute stent thrombosis (0–24 hours)	0	0	
Subacute stent thrombosis (24 hours to 30 days)	2 (5.7%)	1 (6.7%)	1

MACE, major adverse cardiac event.



	Mean (SD)	(Min-Max)	Median	Interquartile Range
Not Cooled (10)	13.8 (10.8)	3.3-38.0	9.8	6.9-18.2
Cooled (27)	13.9 (8.0)	0.8-32.2	12.9	7.3-17.9
Absolute Difference:	0.1		3.2	
Relative Difference %:	0.9		32.4	
t-test p-value:	0.970			
Wilcoxon Rank Sum p-value:	0.801			

FIG. 5. Infarct size assessed by cMR at 30 days in the ATT analysis. cMR, cardiac magnetic resonance.



	Mean (SD)	(Min-Max)	Median	Interquartile Range
Not Cooled (10)	48.3 (10.9)	31.8-60.6	50.1	38.3-58.3
Cooled (28)	43.3 (11.2)	17.2-68.2	43.5	36.6-50.8
Absolute Difference:	5.0		6.6	
Relative Difference %:	10.4		13.1	
t-test p-value:	0.229			
Wilcoxon Rank Sum p-value:	0.194			

FIG. 6. LVEF assessed by cMR at 30 days in the ATT analysis. LVEF, left ventricular ejection fraction

Our findings, however, are consistent with all the previous studies, once no randomized clinical trial has ever shown a reduction in the IS with ETH. Only metanalysis (Villablanca *et al.*, 2016) and subanalysis of previous clinical trials suggested a reduction in IS in a subgroup of early presenters with anterior STEMI who were cooled below 35°C before reperfusion (Erlinge *et al.*, 2015; Testori *et al.*, 2019). Therefore, our finding that it is possible to reach a mean temperature of 33.1°C by the time of coronary reperfusion, that is, way below 35°C, may signalize that eventual benefits from ETH would have been achieved.

Our trial showed high rates of adverse events, including in-hospital infections and paroxysmal AF. Of note, we are the first investigators to document statistically significant higher rates of self-terminated paroxysmal AF associated with ETH (51.4%), three times bigger (51.4%) compared with the control group (13.3%). Nevertheless, the AF resolved spontaneously to sinus rhythm in all patients (100%) during the rewarming phase. In the COOL AMI EU Pilot trial (Noc *et al.*, 2017), there was a trending toward it, but without statistical significance.

Previous studies had already shown the occurrence of adverse events associated with ETH in STEMI (Erlinge *et al.*, 2015; Nichol *et al.*, 2015; Testori *et al.*, 2019). The incidence of ventricular fibrillation, despite the absence of a statistically significant difference, was three times higher (21%) than in the control group (6.7%), so it cannot be neglected. However, with continuous monitoring and adequate intensive care support, the chances of death even in these extreme cases were small as shown.

In the ETH group, two patients (5.7%) had stent thrombosis compared with one patient (6.7%) in the control group. There were no vascular complications, significant bleeding, or infection related to the access site. Testori *et al.* described higher rates of bleeding in the control group when compared with the hypothermia group when performing prehospital cooling before ETH. Our study did not show any statistical difference regarding bleeding (Testori *et al.*, 2019).

Limitations

Our results, however, should be interpreted in the light of several limitations. First, it was a single-center study, with a low number of patients, which may have, once our team is expert in hypothermia procedures, contributed to the good DTB results. However, due to the limited number of patients included in our study, our results are associated with a considerable risk of a statistical type II error.

Second, it is necessary for one exclusive physician to be responsible for the cooling of the patient, concomitant to the interventional cardiologist, who will be performing the angiogram and the primary PCI concomitantly. So, if there is only one physician available to conduct the whole procedure, including PCI plus ETH, there might be a delay in the DTB.

Third, there was a high number of crossing-over patients from the hypothermia group to the control group (14.1%), and it took a very long time from the patient́s symptom onset to the ED, which may have impaired the cooling protection due to the high total ischemic time.

Lastly, the higher incidence of inferior wall STEMIs documented in our study may have contributed to the higher incidence of atrial and ventricular arrhythmias, which may be harmful for the patients. Nevertheless, there is already a multicenter ongoing trial trying to establish the safety and effectiveness of ETH.

Conclusions

The ETH as an adjuvant therapy to primary PCI in awakened STEMI patients is feasible within ~90 minutes' DTB time and can be implemented without delay in coronary reperfusion.

Hypothermia was safe regarding the incidence of MACE at 30 days. However, there was a higher incidence of arrhythmia and in-hospital infection in the hypothermia group, with no increase in mortality.

Regarding efficacy, there was no difference in IS or LVEF at 30 days that would suggest additional myocardial protection with ETH.

Author Disclosure Statement

Dr. Dae is a consultant for Zoll Circulation. None of the other authors has conflicts of interest.

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