Cardiovascular Revascularization Medicine 20 (2019) 799–804

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Effect of Intravascular Cooling on Microvascular Obstruction (MVO) in Conscious Patients with ST-Elevation Myocardial Infarction Undergoing Primary PCI: Results from the COOL AMI EU Pilot Study☆

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ARTICLE INFO

Article history:
Received 19 June 2018
Received in revised form 7 September 2018
Accepted 19 September 2018

Keywords:
STEMI
PPCI
Hypothermia
Microvascular obstruction (MVO)
Cardiac magnetic resonance

ABSTRACT

Objective: COOL AMI EU pilot was a multi-center, randomized controlled trial to assess feasibility and safety of rapid intravascular therapeutic hypothermia (TH) in conscious patients with anterior ST-elevation myocardial infarction (STEMI) undergoing primary PCI (PPCI). We report the effect of hypothermia upon microvascular obstruction (MVO).

Methods: Conscious patients with anterior STEMI and symptom duration <6 h were recruited and randomized to PPCI + TH or PPCI alone. TH was induced using the ZOLL® Proteus™ intravascular temperature management system and rapid infusion of 1 L of cold normal saline, with a target temperature of 32 °C. MVO was measured by cardiac magnetic resonance (CMR) at 4 to 6 days post-MI. MVO larger than 3.9% of LV was considered as extensive MVO.

Results: 50 patients were randomized; mean age was 58 years, and 86% were men. At reperfusion, mean intravascular temperature for the TH group was 33.6 ± 1 °C. The presence of MVO was high and not different in both groups (74% vs. 77%, $p = 0.79$). The proportion of patients with extensive MVO was 11% in the TH group and 23% in the control group (OR 0.4 95%CI 0.07–2.35, $p = 0.30$). Patients with extensive MVO showed reduced EF at 4–6 days (34% versus 43%, $p = 0.01$). The percentage of patients with EF <35% at 30 days was 6% in the TH group versus 24% in the control group ($p = 0.19$).

Conclusion: In the COOL-AMI Pilot Trial, the presence of MVO in both test groups was high and extensive MVO was related with reduced LVEF. The efficacy of therapeutic hypothermia (TH) in MVO reduction should be tested in a pivotal trial.

1. Introduction

Vessel recanalization by primary percutaneous coronary intervention (PPCI) is the standard of care for patients presenting with ST segment elevation myocardial infarction (STEMI) [1,2]. Culprit vessel patency is achieved in >90% of the cases [3], but optimal myocardial perfusion is reached only in around half of them [4]. This is due to multifactorial injury of the coronary microcirculation, a phenomenon often described as microvascular obstruction (MVO) [5]. The presence and extent of MVO after PPCI in STEMI is strongly associated with mortality and hospitalization for heart failure [6,7]. Methods to reduce MVO frequency and burden are required to improve STEMI outcomes.

Therapeutic hypothermia (TH) as a method targeting reperfusion injury has consistently reduced infarct size in myocardial infarction animal models [8]. However, clinical trials in humans have failed to translate its theoretical benefit into clinical outcomes [9–11]. These studies have been limited by slow induction of hypothermia, inadequate temperature reduction at the time of reperfusion and universal patient inclusion independently of myocardial mass supplied by the culprit artery. A recent patient-level pooled analysis of six randomized

☆ ClinicalTrials.gov number: NCT02509832

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https://doi.org/10.1016/j.carrev.2018.09.014
1553-8389/

trials of intravascular cooling as an adjunctive therapy to PPCI in STEMI, showed a significant reduction in infarct size in patients with anterior STEMI who were cooled to <35 °C at the time of reperfusion [12].

The COOL AMI EU Pilot Trial was a multi-center, randomized controlled pilot trial using intravascular TH during PPCI. The primary objective of the study was to investigate the feasibility and safety of more rapid and profound cooling than in previous trials and gather information for sample size calculations for a large pivotal trial. The study showed that patients could be rapidly and safely cooled down to 33.6 °C at the time of reperfusion. The study was not powered to demonstrate reduction in infarct size, but a numerical non-statistically significant 7.1% absolute and 30% relative reduction in infarct size was observed in the hypothermia arm compared to the control arm [13].

In the current analysis, we report the effect of hypothermia on MVO assessed by cardiac MR (CMR) at day 4–6 post STEMI.

2. Methods

Between May 2016 and February 2017, conscious patients presenting with anterior STEMI, less than six hours of symptom onset were recruited across 16 centres in 8 European countries. Patients with haemodynamic compromise or signs of pulmonary congestion (Killip II and above) were excluded. Other exclusion criteria included: resuscitated cardiac arrest, previous acute myocardial infarction, PCI or coronary artery bypass grafting, atrial fibrillation, end-stage kidney disease or hepatic failure, recent stroke, coagulopathy and pregnancy. Patients were randomized either to PPCI and endovascular cooling with the Proteus™ Intravascular Temperature Management System (ZOLL® Medical Corporation, Chelmsford, MA, USA, Fig. 1) or PPCI alone in 1 to 1 fashion. The study protocol was approved by the local/national ethics committees and all patients gave written informed consent prior to inclusion in the study.

2.1. Hypothermia and anti-shiver protocol

Patients assigned to the hypothermia arm were initially administered 60 mg of oral buspirone and pethidine 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 min, 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 cooling period. When on the catheterization table, patients were placed on a Bair Hugger™ (3M, Maplewood, MN, USA) for skin counter warming. Cooling was initiated with a rapid infusion of up to 1 L of cold saline (4 °C) using pressure bags, followed by the ZOLL® Proteus™ Intravascular Temperature Management System. The cooling catheter was inserted via the femoral vein into the inferior vena cava with the tip positioned at the level of the diaphragm. The Proteus temperature probe (X-Probe™; ZOLL®) 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. Following placement and activation of the cooling catheter, arterial puncture was performed for coronary angiography/PPCI. An interval of 18 min of endovascular cooling from catheter activation to coronary guidewire passing across the acute occlusion was advised. Cooling was maintained for three hours, followed by active rewarming at the rate of 1.0 °C/h to reach 36.0 °C. The catheter was then removed. During the whole period of cooling, patients were monitored and haemodynamic parameters and respiratory rate were documented. Shivering was continuously assessed by the bedside. In case of occurrence further

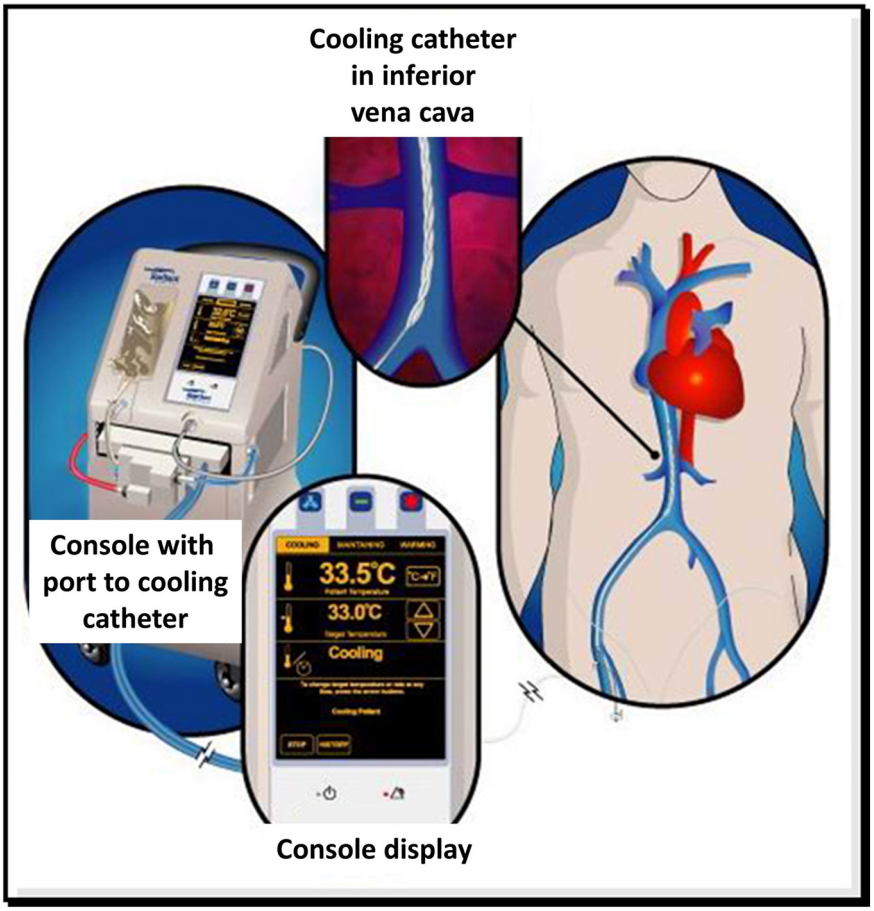

Fig. 1. ZOLL® Proteus™ Intravascular Temperature Management (IVTM) System.

doses of pethidine were given as boluses or the infusion rate was increased. If shivering persisted, the target temperature at the Proteus system was raised stepwise by 0.5 °C until shivering ceased.

2.2. Primary PCI

Coronary angiography and percutaneous coronary intervention were performed in a standard fashion according to international guidelines and local practice. All patients received aspirin and P2Y12 inhibitors. Anticoagulation during the procedure was achieved with unfractionated heparin. The use of aspiration thrombectomy or GP IIb IIIa inhibitors was at the discretion of the treating physician.

2.3. Cardiac magnetic resonance imaging

Patients underwent cardiac magnetic resonance imaging (CMR) 4 to 6 days post the initial presentation and at 30 days follow up. All CMR examinations were performed on 1.5 T scanners from Philips (Philips Healthcare, Best, The Netherlands), Siemens (Siemens AG, Erlangen, Germany), or General Electrics (GE Healthcare, Waukesha, WI, USA). After initial scout images, 0.2 mmol/kg of body weight of a gadolinium-based contrast agent was administered. For evaluation of left ventricular (LV) function, early contrast-enhanced steady-state free precession (CE-SSFP) cine images were obtained approximately five minutes after contrast injection (slice thickness 8 mm with no slice gap, temporal resolution 20 to 30 frames per cardiac cycle). For visualisation of MVO, inversion-recovery gradient-recalled echo sequences, with or without phase-sensitive reconstruction (PSIR) were used (slice thickness 8 mm with no slice gap). Inversion time was adjusted to null the signal of viable myocardium and was typically 200–300 ms. Cine and LGE images were acquired in the short-axis and the three standard long-axis views. LV ejection fraction (EF%) was measured from cine images and MVO was quantified from LGE images using the EWA algorithm [14] with manual adjustments when needed and expressed as a percentage of LV mass (%LV). An MVO volume larger than 3.9% of LV mass has been shown to independently predict worse clinical outcomes [15], thus we assessed the proportion of patients with extensive MVO (>3.9%) between the two groups. Analyses of CMR images were performed by an independent core lab (Imacor AB, Lund, Sweden) using post-processing software (Segment v2.1; http://segment.heiberg.se) [16].

2.4. Statistical analysis

Continuous variables were compared with *t*-test or Wilcoxon rank sum test; categorical variables were compared with Fisher's exact test or chi-square test as appropriate. Presence of MVO is defined as MVO >0% and extensive MVO is defined as >3.9%. Logistic regression with profile-likelihood confidence interval was performed for extensive MVO to calculate odds ratio. All statistical analyses were conducted in SAS 9.2 (NC, USA).

3. Results

273 patients with anterior STEMI were screened against the inclusion/exclusion criteria and 50 patients with first anterior STEMI were recruited and randomized to hypothermia ($n = 25$) or control (n = 25). 22 patients in the TH and 23 in the control group had CMR at day 4–6 and completed follow up at 30 days. Baseline demographics, risk factors, presentation and procedural characteristics are shown in Table 1. Mean age was 56 ± 12 in the hypothermia group and 61 ± 13 in the control, ($p = 0.19$) and the majority of participants were men (92% and 80% respectively, $p = 0.42$). Risk factors and procedural characteristics were comparable between the two groups. The use of Prasugrel/Ticagrelor and Gp IIb/IIIa receptor antagonists was equal in both groups. Symptom onset to device time was 267 ± 73 min for the TH group and 209 ± 69 min in the control group ($p = 0.01$). This difference was mainly driven by a delay from symptoms onset to randomization in the TH arm (213 ± 73 min vs. 174 ± 82 min, $p = 0.08$). The cooling-related time delay to reperfusion was 17 min (95% CI: 4.6–29.8 min).

Table 1
Clinical, angiographic and peri-procedural characteristics.

	Control (n = 25)	Hypothermia (n = 25)	p
Mean age, years	61 ± 13	56 ± 12	0.19
Male gender	20 (80%)	23 (92%)	0.42
Diabetes	4 (16%)	3 (12%)	1.00
Hypertension	19 (76%)	13 (52%)	0.08
Dyslipidemia	8 (32%)	10 (40%)	0.56
Current smoker	14 (56%)	14 (56%)	1.00
Mean body mass index, kg/m2	26.5 ± 3.6	27.9 ± 3.8	0.19
Symptoms to 1st device, minutes	209 ± 69	267 ± 73	**0.01**
Randomization to 1st device (min)	42 ± 23	59 ± 19	**0.01**
Initial IRA TIMI 0/1	21 (88%)	23 (92%)	0.67
Multivessel coronary disease	3 (12%)	1 (4%)	0.61
Thrombus aspiration	8 (32%)	12 (48%)	0.25
Stenting of IRA	25 (100%)	23 (92%)	0.49
Final IRA TIMI 3	23 (92%)	21 (88%)	0.67
Acetylsalicylic acid	25 (100%)	25 (100%)	1.00
Heparin	25 (100%)	25 (100%)	1.00
Prasugrel/Ticagrelor	21 (84%)	19 (76%)	0.72
GP IIb/IIIa	12 (48%)	11 (44%)	0.78

Data are presented as ≫Intention to treat≪.
Legend: IRA = infarct related artery; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitor.
Bold values indicates significance at p < 0.05.

The safety data from the study have been previously published [13]. In summary there was no difference in death, target vessel revascularisation, definite or probable stent thrombosis, ventricular fibrillation, sustained ventricular tachycardia, bradycardia, cardiogenic shock, pulmonary oedema, pneumonia or deep vein thrombosis at 30 days between the two groups. There was a trend for self-terminating paroxysmal atrial fibrillation in the hypothermia group [2 cases (8%) vs. 8 cases (32%), $p = 0.07$].

3.1. Microvascular obstruction

The presence of MVO assessed day 4–6 by CMR was high and not different in the two groups (74% in the TH arm and 81% in the control group, $p = 0.483$). Intention to treat analysis showed a mean MVO as % of LV was 2.1 ± 2.6 and 2.5 ± 3.5 in the HT and control groups respectively ($p = 0.96$). Per protocol analysis of mean MVO % in the TH group was 1.6 ± 1.8% versus 2.6 ± 3.5% in the control group ($p = 0.56$) (Fig. 2). The proportion of per-protocol patients with extensive MVO was 11% in the TH group and 23% in the control group ($p = 0.30$) (Fig. 3). Fig. 4 demonstrates case examples of modest MVO (2.7%) and extensive MVO (13.1%).

3.2. Left ventricular ejection fraction

Patients with extensive MVO (>3.9%) showed reduced LV EF at 4–6 days (34% vs. 43%, $p = 0.01$) and 30 days (36% vs. 49%, p = 0.01). The percentage of patients with EF <35% at 30 days was 6% in the TH group compared with 24% in the control group ($p = 0.19$). (Fig. 5).

4. Discussion

In the COOL AMI EU pilot study, conscious patients with anterior STEMI were cooled safely to 33.6 °C prior to coronary guidewire crossing, using the ZOLL® Proteus™ Intravascular Temperature Management System and up to 1 L of concomitant infusion of cold saline. Such a reduction in core temperature, achieved within approximately 20 min

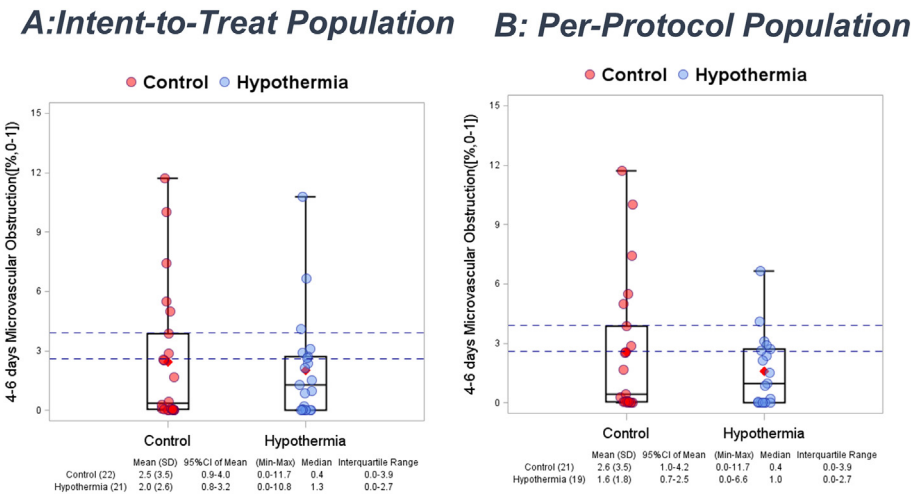

Fig. 2. MVO as measured by cMR at 4–6 days. Shown as both an intention to treat analysis (A) and per protocol analysis (B).

from endovascular catheter activation is at least 1.1 °C lower than in previous cooling trials [13].

Regarding the effect of TH on microvascular function our study showed:

- The presence of MVO was high and similar among the study arms.
- The incidence of extensive MVO in the TH group was 11% vs. 24% in the control, but this numerical difference was not statistically significant.
- Patients with extensive MVO had significantly worse LVEF at 4–6 and at 30 days.

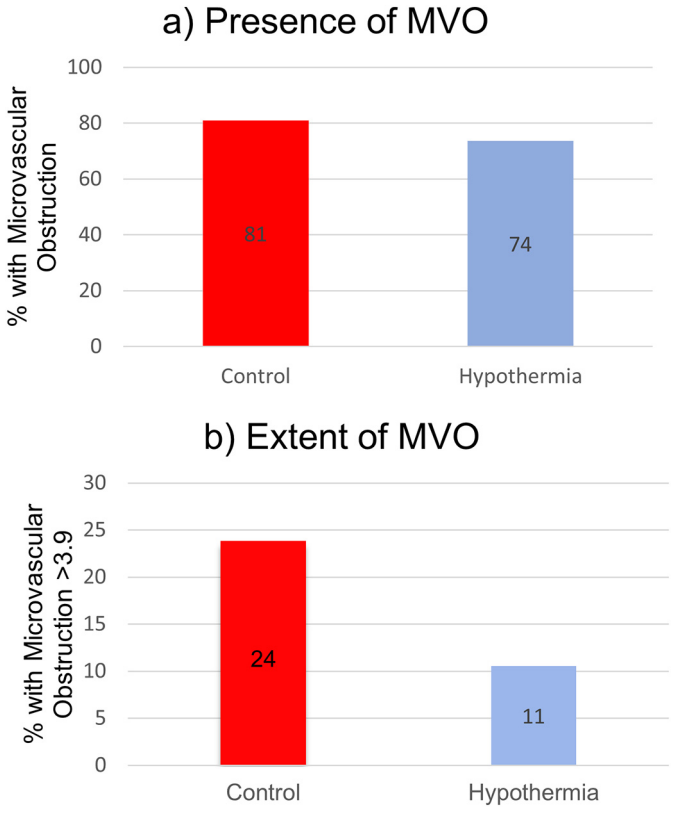

Fig. 3. a) Presence of MVO in both control and hypothermia groups. b) Extent of MVO - percentage of patients with MVO > 3.9% of LV in both control and hypothermia groups.

In patients presenting with STEMI, primary PCI achieves rapid recanalization and reperfusion of the occluded epicardial coronary artery. However, in a significant number of cases myocardial tissue perfusion will not be restored. This phenomenon of no myocardial flow is due to severe microvascular dysfunction and/or loss of microvasculature integrity and is often described as microvascular obstruction (MVO). The pathophysiology of MVO is complex involving four interacting mechanisms: ischaemia-related injury, reperfusion-related injury, distal embolization, and individual susceptibility of the microcirculation to injury [17]. Although MVO can be assessed by coronary angiography, ST-segment resolution on electrocardiography and myocardial contrast echocardiography; cardiac MRI is the most accurate test for MVO diagnosis and quantification. On contrast-enhanced cardiac MRI, MVO is signified by the lack of gadolinium enhancement within the hyperenhanced infarcted area [6,18]. The presence and extent of MVO has important clinical implications. In a recent analysis of patient data from 7 randomized control trials ($n = 1688$), MVO assessed within 7 days after reperfusion by CMR using late gadolinium enhancement imaging was strongly associated with mortality and hospitalization for heart failure within 1 year [7]. There was a graded response between the extent of MVO and clinical outcomes as every 1% absolute increase in MVO extent was independently associated with a 14% relative increase in 1-year all-cause mortality and an 8% increase in 1-year heart failure hospitalization [7]. In this regard, MVO is an important therapeutic target in the management of ST segment elevation myocardial infarction.

Hypothermia influences a number of mechanisms during ischemia (i.e. reduces metabolism, preserves ATP, stabilizes mitochondrial membrane, inhibits reactive oxygen species production) and during reperfusion (i.e. decreases microvascular injury, induces heat shock proteins, activates Akt and nitric oxide production, inhibits apoptosis, inhibits inflammation) [19]. Experimental studies on animal models have shown that hypothermia improves the no-reflow phenomenon/MVO. A study of topical cooling of rabbit hearts, initiated at 20 min into a 30-min coronary artery occlusion reduced the no-reflow defect to a greater extent than would be expected by the reduction in myocardial necrosis alone [20]. Gotberg et al. [21] showed that instituting hypothermia just at reperfusion reduced MVO in pig hearts as measured with ex vivo MRI, although infarct size was not reduced. A further study of topical cooling of rabbit heart, showed that hypothermia reduced no-reflow even when applied after reperfusion, an effect not seen with infarct size [22]. A more recent study on a rat ischemia/reperfusion model showed similar results, as delayed hypothermia after reperfusion protected against the no-reflow phenomenon independently of infarct size [23]. These studies

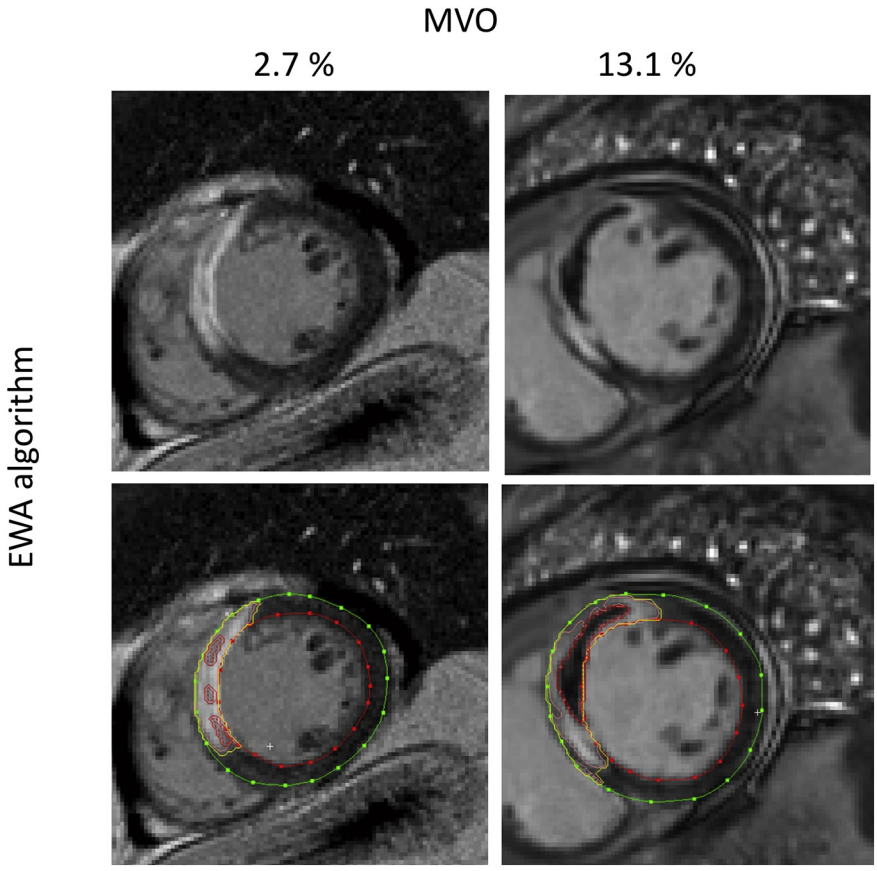

Fig. 4. MVO case examples. Late gadolinium CMR images from two patients with reperfused myocardial infarction and microvascular obstruction (MVO). Left panels shows a patient with 2.7% MVO and right panels show a patient with 13.1% MVO. Bottom panels show delineations of epicardium (green), endocardium (red), extent of infarction (yellow), core of infarction (pink), MVO extent (red solid line) and MVO core (red dashed line).

suggest that the microvasculature may be particularly responsive to protection by hypothermia. Contrary to what happens with infarct size, hypothermia reduces the extent of MVO even when applied after reperfusion. The only previous clinical study where the effect of hypothermia on MVO was reported showed similar results between the hypothermia and control groups: 0.24% (IQR: 0% to 9.35%) versus 0.12% (IQR: 0% to 5.25%) [11]. However, this study was not powered to show an effect on MVO.

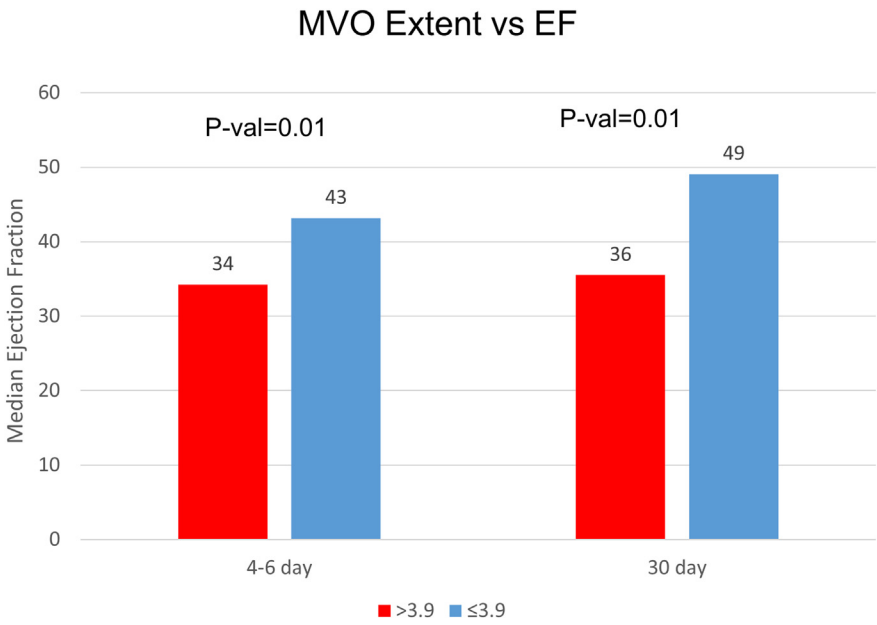

Fig. 5. shows the median ejection fraction of all patients divided into those with >3.9% LV MVO, and <3.9% LV MVO at both 4–6 and 30 days. MVO >3.9% LV leads to a significantly worse EF at both 4–6 and 30 days.

In the COOL AMI EU pilot study, the incidence of MVO was high in both study groups (74% in the TH and 81% in the control group vs. 57% in the study by de Waha et al.). An important contributor to that was the fact that only anterior STEMIs were included in our study. It has been shown that anterior infarct location is an important determinant of the extent of MVO [7]. The binary MVO occurrence was similar between the two study groups, but the incidence of extensive MVO was numerically lower in the hypothermia group. That was despite the fact that the hypothermia group had 28% longer ischaemic time (+58 min). Ischaemic time is another known determinant of MVO [7]. Similarly to what has been shown in animal models, it can be speculated that if the ischaemic time were similar between groups, the beneficial effect of TH would likely be even greater. In the present study extensive MVO was associated with worse LVEF both at 4–6 and 30 days. It has been shown before that the absence of MVO post STEMI is an independent predictor of improved left ventricular ejection fraction over time [24,25]. Given the important clinical consequences of MVO, therapies that specifically target no-reflow/MVO should be developed and their long-term results tested in clinical trials [26].

4.1. Limitations

The main limitation of this study was the small number of patients. Accordingly, the study was a pilot study not powered to demonstrate possible reductions in MVO by hypothermia. Based on the results of the study, a pivotal trial of 500 patients has been designed and powered to demonstrate an infarct size reduction by therapeutic hypothermia (COOL-AMI EU Pivotal Trial, NCT03173313). The pivotal trial is powered to detect an absolute infarct size reduction of ≥3.5%.

5. Conclusion

In the COOL-AMI pilot Trial, the incidence of MVO was high in both treatment arms and extensive MVO was associated with worse LVEF. MVO post STEMI is an important therapeutic target and the effects of therapeutic hypothermia upon it should be tested in a pivotal trial powered for efficacy.

Acknowledgements

Authors would like to thank also to ZOLL team (Renee Kochevar, Michael Dae) for their support and Anne Dee for statistical analysis.

Funding

The study was funded by ZOLL Circulation, 2000 Ringwood Avenue, San Jose, CA 95131.

Conflict of interest statement

Marko Noc, Beata Średniawa, Daniel Aradi and Michael Holzer received consultation fees from ZOLL. Håkan Arheden is a shareholder of Imacor AB. Other authors have no conflict of interest related to this study.

References

[1] O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.
[2] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.
[3] Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946–59.
[4] Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. Eur Heart J 2016;37:1024–33.
[5] Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. J Am Coll Cardiol 2010;55:1649–60.
[6] Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–72.
[7] de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J 2017;38:3502–10.
[8] Erlinge D. A review of mild hypothermia as an adjunctive treatment for ST-elevation myocardial infarction. Ther Hypoth Temp Manag 2011;1:129–41.
[9] O'Neil W. A prospective randomized trial of mild systemic hypothermia during PCI treatment of ST elevation MI. The COOL MI Trial. Abstract TCT; 2003 (Washington DC, USA).
[10] Grines C. Intravascular cooling adjuctive to percutaneous coronary intervention for acute myocardial infarction. The ICE-IT Trial. Abstract TCT; 2004 (Washington DC, USA).
[11] Erlinge D, Götberg M, Lang I, Holzer M, Noc M, Clemmensen P, et al. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. J Am Coll Cardiol 2014;63:1857–65.
[12] Dae M, O'Neill W, Grines C, Dixon S, Erlinge D, Noc M, et al. Effects of endovascular cooling on infarct size in ST-segment elevation myocardial infarction: a patient-level pooled analysis from randomized trials. J Interv Cardiol 2017. https://doi.org/10.1111/joic.12485 [Epub ahead of print].
[13] Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, et al. COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. EuroIntervention 2017;13:e531–9.
[14] Engblom H, Tufvesson J, Jablonowski R, Carlsson M, Aletras AH, Hoffmann P, et al. A new automatic algorithm for quantification of myocardial infarction imaged by late gadolinium enhancement cardiovascular magnetic resonance: experimental validation and comparison to expert delineations in multi-center, multi-vendor patient data. J Cardiovasc Magn Reson 2016;18:27.
[15] Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. JACC Cardiovasc Imaging 2014;7:940–52.
[16] Heiberg E, Sjögren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of segment–freely available software for cardiovascular image analysis. BMC Med Imaging 2010;10:1.
[17] Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–92.
[18] Ambrosio G, Savino K. CMR assessment of microvascular obstruction in STEMI: ready for prime time? J Am Coll Cardiol 2014;64:1227–30.
[19] Dae M. Hypothermia and percutaneous coronary intervention during acute myocardial infarction. Interv Cardiol 2012;4:235–43.
[20] Hale SL, Dae MW, Kloner RA. Hypothermia during reperfusion limits "no-reflow" injury in a rabbit model of acute myocardial infarction. Cardiovasc Res 2003;59:715–22.
[21] Gotberg M, Olivecrona GK, Engblom H, Ugander M, Van der Pals J, Heiberg E, et al. Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. BMC Cardiovasc Disord 2008;8:7.
[22] Hale SL, Herring MJ, Kloner RA. Delayed treatment with hypothermia protects against the no-reflow phenomenon despite failure to reduce infarct size. J Am Heart Assoc 2013;2:e004234.
[23] Dai W, Hale S, Kloner RA. Delayed therapeutic hypothermia protects against the myocardial no-reflow phenomenon independently of myocardial infarct size in a rat ischemia/reperfusion model. Int J Cardiol 2017;236:400–4.
[24] Nijveldt R, Beek AM, Hirsch A, Stoel MG, Hofman MBM, Umans VA, et al. Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. J Am Coll Cardiol 2008;52:181–9.
[25] Orn S, Manhenke C, Greve OJ, Larsen AI, Bonarjee VV, Edvardsen T, et al. Microvascular obstruction is a major determinant of infarct healing and subsequent left ventricular remodelling following primary percutaneous coronary intervention. Eur Heart J 2009;30:1978–85.
[26] Kloner RA. The importance of no-reflow/microvascular obstruction in the STEMI patient. Eur Heart J 2017;38:3511–3.