Original Research

Endovascular therapeutic hypothermia adjunctive to percutaneous coronary intervention in acute myocardial infarction: realistic simulation as a game changer

Luis Augusto Palma Dallan1,2,*, Michael Dae3, Natali Schiavo Giannetti1, Tathiane Facholi Polaстро1, Marian Keiko Frossard Lima1, Carlos Eduardo Rochitte1, Ludhmila Abrahao Hajjar1, Claudia Yanet Bernoche San Martin1, Felipe Gallego Lima1, Jose Carlos Nicolau1, Mucio Tavares de Oliveira Jr1, Luis Alberto Oliveira Dallan1, Expedito Eustaquio Ribeiro da Silva1, Roberto Kalil Filho1, Alexandre Abizaid1, Pedro Alves Lemos Neto1, Sergio Timerman1

1 Department of Cardiology, InCor - Heart Institute, School of Medicine, University of Sao Paulo, 05403-900 Sao Paulo, Brazil
2 Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA
3 Department of Radiology, University of California, San Francisco, CA 94143, USA
*Correspondence: luisdallan@yahoo.com (Luis Augusto Palma Dallan)

Abstract

Background: Endovascular therapeutic hypothermia (ETH) reduces the damage by ischemia/reperfusion cell syndrome in cardiac arrest and has been studied as an adjuvant therapy to percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI). New available advanced technology allows cooling much faster, but there is paucity of resources for training to avoid delays in door-to-balloon time (DTB) due to ETH and subsequently coronary reperfusion, which would derail the procedure. The aim of the study was to describe the process for the development of a simulation, training & educational protocol for the multidisciplinary team to perform optimized ETH as an adjunctive therapy for STEMI. Methods and results: We developed an optimized simulation protocol using modern mannequins in different realistic scenarios for the treatment of patients undergoing ETH as an adjunct to PCI for STEMI starting from the emergency room, through the CathLab, and to the intensive care unit (ICU) using the Proteus® Endovascular System (Zoll Circulation Inc™, San Jose, CA, USA). The primary endpoint was door-to-balloon (DTB) time. We successfully trained 361 multidisciplinary professionals in realistic simulation using modern mannequins and sham situations in divisions of the hospital where real patients would be treated. The focus of simulation and training was logistical optimization and educational debriefing with strategies to reduce waste of time in patient’s transportation from different departments, and avoiding excessive rewarming during transfer. Afterwards, the ETH protocol was successfully validated in a trial randomizing 50 patients for 18 minutes cooling before coronary recanalization at the target temperature of 32 ± 1.0 °C or PCI-only. A total of 35 patients underwent ETH (85.7% [30/35]) in 90 ± 15 minutes), without delays in the mean door-to-balloon time for primary PCI when compared to 15 control group patients (92.1 minutes versus 87 minutes, respectively; p = 0.509). Conclusions: Realistic simulation, intensive training and educational debriefing for the multidisciplinary team propitiated feasible endovascular therapeutic hypothermia as an adjuvant therapy to primary PCI in STEMI. ClinicalTrials.gov: NCT02664194.

Keywords: Therapeutic hypothermia; ST elevation myocardial infarction (STEMI); Percutaneous coronary intervention (PCI); Acute coronary syndrome (ACS); Coronary disease; Simulation; Training; Educational debriefing

1. Introduction

Endovascular therapeutic hypothermia (ETH) is performed to reduce ischemia/reperfusion cell syndrome damage in cardiac arrests [1], however its role in ST-segment elevation myocardial infarction (STEMI) patients still remains controversial [2–10]. Experimental studies showed that mild hypothermia, if rapidly induced before the reperfusion of acute coronary occlusion, can reduce infarct size (IS) [11,12]. So a fast cooling prior to reperfusion may be effective adjunct to primary percutaneous coronary inter-

vention (PCI) in STEMI patients to reduce IS and to improve cardiac outcomes [13,14].

The development of powerful endovascular cooling systems, which are able to cool down the patient to low temperatures in a few minutes [15], brought light for rapid cooling of the patient and its performance in the STEMI scenario. However, there is still concerning regarding a possible delay in the door-to-balloon time (DTB) associated with the implementation of the ETH protocol. Therefore, with the more powerful ETH systems [16], the role of cooling...
as an adjuvant therapy to endovascular cooling in STEMI remains unclear, but delays in ETH certainly would impair the adequate treatment of the patients.

The aim of the study was the development of a simulation, training & educational protocol for the multidisciplinary team to perform optimized ETH as an adjunctive therapy for STEMI without delays in DTB which would derail the procedure.

2. Methods

2.1 Simulation, training and debriefing

Aim: Provide a training program for STEMI Cool trial sites that simulates the procedural flow as described in the trial protocol. This realistic simulation program was created to familiarize site personnel with the procedures required in the protocol and also manage potential complications as listed in the trial protocol that might be related to cooling, while motivating site performance in avoiding delays in the DTB and procedural times consistent for all patients regardless of randomization. All the aspects and a comprehensive description of all the aspects of the simulation intervention are depicted in Table 1 [17].

2.2 Realistic simulation performance criteria

Performance criteria has been established to limit the difference between study arms regarding DTB time to be inferior to 10 minutes. The objective was to quickly perform and complete all procedural steps up to the point where the guide wire is advanced across the lesion. The timing data from the simulation of a patient randomized to the cooling arm was compared to the current average DTB time of the institution, in order to confirm if the difference between study arms regarding DTB time is inferior 10 minutes. Ideally the cases should be performed with a final DTB <90 minutes. The workflow overview is shown in Fig. 1.

2.3 Keys to success

A successful realistic simulation program requires the following:

• Assigning roles and responsibilities upfront for each team member;
• Execution of assigned tasks in a timely manner;
• Execution of relevant protocol steps in parallel to reduce total procedural time.

Metrics were assessed regarding each team’s performance and reviewed during the debriefing at the end of each simulation.

2.4 Training requirements

The realistic simulation training took place in the Emergency Department, Cath Lab, Intensive Care Unit or Simulated Lab (hereby named Sim Lab) during the Site Initiation Visit (SIV), according to the hospital’s allowance.

Fig. 1. Realistic simulation workflow overview. The green bar is the time needed for screening and enrollment tasks required to conduct any trial in the STEMI population (enrollment steps). The yellow bar (PCI preparation) represents the routine steps for performing percutaneous coronary intervention (PCI) for the STEMI population. Both Green and Yellow steps were required in both the control and cooling groups. The blue bar (cooling steps) represents the additional steps that are required in the cooling group. Since some but not all of the cooling steps are conducted in parallel to others, the difference in DTB time between the control and cooling groups is expected to be inferior than 10 minutes.

2.5 Timeframe requirements

(1) Expectations and intro: 20 minutes. Prior to the simulation, this was a short recap of the expectations and purpose of the simulation. The study protocol and device training had already taken place earlier in the SIV.

(2) Realistic simulation run: 60 minutes. The start point was the patient arrival to the ED. The finish point was the action of the guidewire crossing the lesion during the PCI procedure.

(3) Debriefing: 60 minutes. The debriefing should take place immediately after the simulation was completed.

2.6 Patient scenario

Patient scenarios for use in the simulations were sham mannequins in STEMI situations, from stable to complex cases. For consistency, all the cases were pre-specified, and the initial simulation training conducted at the SIV.

2.7 Logistical optimization

Another focus of simulation and training was the logistical optimization with strategies to reduce waste of time in the patient’s transportation from different departments, and avoiding excessive rewarming of the patient during the moving. After several simulations transporting mannequins throughout real sections of the hospital, an appropriate logistical was defined and implemented.
| Elements                          | Subelements                        | Description                                                                                                                                                                                                 |
|----------------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Participant orientation          | Orientation to the simulator       | *Expectations and intro:* 20 minutes. Prior to the simulation, this was a short recap of the expectations and purpose of the simulation, as well as the study protocol. All the professionals must have been trained in Advanced Life Care Support (ACLS) in the Simulation Center prior to the TH simulation.  
*Realistic simulation run:* 60 minutes. The start point was the patient arrival to the ED. The finish point was the action of the guidewire crossing the lesion during the PCI procedure.  
*Debriefing:* 60 minutes. The debriefing should take place immediately after the simulation was completed. |
| Orientation to the environment    |                                    | The participants were oriented to the environment according to the proposed HT procedure. There was a real body-size mannequin that was used both to do the TH procedure and to be transferred from one unit to the other according to the timeline of the simulation. The professionals being trained were trained in different sections of the hospital. Therefore, they started at the Emergency Department (ED), then went to the cath lab and finished at the intensive care unit (ICU). 15 minutes for orientation, 30 minutes for each section (ED, cath lab, ICU) and 15 minutes for conclusion, for a total of 2 hours training. The content for the training was specific for each of the scenarios. |
| Simulator type                   | Simulator make and model           | The training was performed using the original Proteus® Cooling System (Zoll Circulation Inc™, San Jose, CA, USA) with sham temperature targets.                                                                    |
| Simulator functionality          |                                    | The simulator was the real Proteus device with connections to a software that mimicked the temperature of the patient for each time point. It was possible to determine specific temperatures according to the scenario. The limitations were the same inherent to any simulator, i.e., no human being was involved as part of the simulator, only mannequins, so there was no feedback regarding bleedings or subjective feelings. Arrhythmias were simulated using monitors and defibrillators. |
| Simulation environment           | Location                           | The simulation was conducted in situ clinical environment. Therefore, they started at the Emergency department, then went to the cath lab and finished at the intensive care unit (ICU).                                         |
|                                  | Equipment                          | It was used one of the 3 original Proteus® Cooling Systems² (Zoll Circulation Inc™, San Jose, CA, USA) available at the hospital, each of them located at the ED, cath lab and ICU. Also, there were real defibrillators available in each of the units. |
|                                  | External stimuli                   | There were external stimuli such as background noise in all the units. We secured that the simulation Training did not interfere in real clinical practice in each of the units, once the simulations were performed in the real units of the hospital. |
| Simulation event/scenario        | Event description                  | All the scenarios were previously programmed and scripted, and they would change according to the training’s reactions. All scenarios were STEMI patients with meet inclusion and exclusion criteria’s that would have had been included in the trial and therefore required TH. They all followed the consistent pathway and progression of the TH across the different units were they were performed. |
|                                  | Learning objectives                 | - Assigning roles and responsibilities upfront for each team member.  
- Execution of assigned tasks in a timely manner.  
- Execution of relevant protocol steps in parallel to reduce total procedural time. |
|                                  | Group vs. individual practice      | The simulation was conducted in groups, once the TH is a multidisciplinary procedure.                                                                                                                       |
|                                  | Use of adjuncts                    | No other adjuncts were used.                                                                                                                                                                                 |
|                                  | Facilitator/operator characteristics| All the facilitators were from the multidisciplinary team involved directly and responsible for the therapeutic hypothermia procedure. They were all high-skill experienced health care professionals. |
### Table 1. Continued.

| Elements                        | Subelements                        | Description                                                                                                                                 |
|---------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Pilot testing                   | Atotal of 5 pilot testing’s with 2-hour duration were conducted one month prior to the full training of the team, so that pitfalls could be corrected and optimizations could be implemented. |
| Actors/standardized/simulated patients | All the simulations were performed in mannequins. There were no actors involved. All the scenarios were conducted by experienced clinicians with experience in simulator education. |
| Instructional design            | Duration                           | The total duration of each simulation was 140 minutes.                                                                                       |
|                                 | Timing                             | The simulation should be performed prior to the initiation of the clinical trial. All the professionals involved in the TH procedure should be trained. |
|                                 | Frequency/repetitions              | There was only one formal training/simulation per professional, but there would be the possibility of re-training if the clinical team considered necessary to repeat the process for quality enhancement. |
|                                 | Clinical variation                 | A unique template script was used for the training once all the situations involved the same scenario: a STEMI patient that should undergo therapeutic hypothermia concomitant to the percutaneous coronary intervention. |
|                                 | Standards/assessment               | As a multi-disciplinary team, all the professionals were assessed at the end of the debriefing to understand if they had assimilated the concepts and if they were able to apply it in the clinical practice, but there was no formal testing at the end of the simulation. |
|                                 | Adaptable of intervention          | All the simulations were performed in groups, but with individual learning focus on the role of each multidisciplinary professional in the TH procedure. |
|                                 | Range of difficulty                | Therapeutic hypothermia is a very complex procedure, therefore all the scenarios were focused on a critical situation involving STEMI and primary PCI concomitant to the TH. |
|                                 | Nonsimulation interventions and adjuncts | As for the nonsimulation interventions, a debriefing should take place immediately after the simulation was completed, and was performed in small group discussions. |
|                                 | Integration                        | The intervention was integrated into curriculum as part of the armamentarium for all the multidisciplinary team in our facility, as a new skill for all the different professionals. |
| Feedback and/or debriefing      | Source                             | The feedback was performed using the simulator itself, the computer through a didactic approach from the facilitator.                          |
|                                 | Duration                           | The total duration of each simulation was 140 minutes.                                                                                       |
|                                 | Facilitator presence               | At least one high-skilled experienced facilitator was present in all the simulations.                                                        |
|                                 | Facilitator characteristics        | All the facilitators were from the multidisciplinary team involved directly and responsible for the therapeutic hypothermia procedure. They were all high-skill experienced health care professionals. |
|                                 | Content                            | The simulation focused on teamwork and development of clinical skills in all the aspects of therapeutic hypothermia.                        |
|                                 | Structure/method                   | The debriefing was performed using the simulator itself, the computer through a didactic approach from the facilitator. The whole simulation was revised, all the possible diversions were corrected and all the clarifications and questions were solved. |
|                                 | Timing                             | The feedback was conducted both concurrent to the simulation event, with guidance and orientation when necessary, as well as an extensive debriefing at the end of the simulation. |
|                                 | Video                              | Video could be recorded during the simulation to help in the education feedback when necessary, especially during the final debriefing when appropriate, but it was not compulsory to record all the simulation events. |
|                                 | Scripting                          | A unique template script was used for the training once all the situations involved the same scenario: a STEMI patient that should undergo therapeutic hypothermia concomitant to the percutaneous coronary intervention. |
2.8 Validation – COOL MI InCor trial

After completing the training of all healthcare professionals that would be involved in the ETH protocol, the patient inclusion started in January 2016. It was a single-center, prospective, interventional, randomized controlled, two-arm trial, performed at InCor – Heart Institute – Clinical Hospital, University of Sao Paulo (Sao Paulo, SP, Brazil). The complete methodology has been described in the COOL MI InCor Trial [10].

2.9 Statistical analysis

Evaluation of variables was calculated with number and proportion with exact 95% confidence interval. 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. All tests were two-sided. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17.0 (IBM SPSS Inc., Chicago, IL, USA). ClinicalTrials.gov identification: NCT02664194.

3. Results

From July 2015 to January 2016, we successfully developed an optimized simulation protocol using modern mannequins in different realistic scenarios for the treatment of patients undergoing ETH adjunctive to PCI for STEMIs starting from the emergency room, through the CathLab, and to the intensive care unit (ICU) using the Proteus® Endovascular System. The comprehensive aspects of the Simulation Intervention are detailed in Table 1, and the workflow overview is shown in Fig. 1.

We successfully trained 361 multidisciplinary professionals in realistic simulation using modern mannequins and sham situations in divisions of the hospital where real patients would be treated. The focus of simulation and training was logistical optimization and educational debriefing with strategies to reduce waste of time in patient’s transportation from different departments, and avoiding excessive rewarming of the patient during the moving, as seen in Fig. 2.

 Afterwards, the ETH protocol was successfully validated in the COOL MI InCor trial [10] randomizing 50 patients for 18 minutes cooling before coronary recanalization at the target temperature of 32 ± 1.0 °C or PCI-only. A total of 35 patients underwent ETH without delays in the mean door-to-balloon time for primary PCI when compared to 15 control group patients (92.1 minutes versus 87 minutes, respectively; 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, as demonstrated in Fig. 3. From the ETH group, 85.7% (30/35) of the patients underwent primary PCI with DTB 90 minutes (standard deviation [SD] 18 minutes, 95% confidence interval [95% CI], 60–138) compared to 86.7% (13/15) in the control group (SD 28 minutes, 95% CI, 50–150).

4. Discussion

In the critical STEMI scenario, where every minute counts to spare viable myocardium cells, it would be hard imagining to perform further time-consuming procedures without impacting in the over-delay for coronary reperfusion [1–10]. With that said, ETH have never been applied before due to the inherent delay of this procedure, which used to take many hours to cool down the body, therefore it has been incompatible with this emergency scenario. The new available advanced technology allowed cooling much faster, with target temperatures as low as 32 °C being reached in less than 20 minutes. Nevertheless, there was still the problem that even those 20 minutes would impact negatively the coronary reperfusion time, and the revealed solution came from the interaction between conjoined procedures and logistical optimization. This complex equation could only be solved with the application of a high disciplined triad: simulation, training & education.

Realistic simulation has been an important component of health professionals’ training [18–21]. The caveats of dealing with health in emergent situations do not allow unanticipated mistakes, which would have life-threatening consequences. Advanced cardiac life support (ACLS) courses has long been using realistic simulation as an important tool for teaching and learning, with successful results [22–27]. We utilized our great experience with this kind of training to come up with realistic scenarios and intensive training before starting the real-world procedures. We started training the multidisciplinary team 2 months prior to the patients’ inclusion. Only after our timing targets were reached, we initiated the in-vivo protocol. And at the end of the day, this was the key to the success: recognizing the potential pitfalls and troubles that could emerge during the ETH, solving it, and then by continuous and recurrent training, we were able to overcome a problematic situation and to come up with an optimized protocol.

Simulation, training and debriefing are the triple foundation of the protocol [18–24]. The first step of the protocol was the realistic simulation. The creation of simulated scenarios using mannequins and pre-determined intercourses during the development of the case brought knowledge and confidence to the multi-professional team. The second step was intensive training, continuous and recurrent, so that there would be no mistakes during the case. The third step was the educational debriefing. After every simulated or real case, the details of the attendance were widely discussed and shared among the multidisciplinary team. Suggestions and corrections we taken into account so that the protocol could be updated and improved over.
Fig. 2. Pictures of the multidisciplinary team being trained in the Simulation Laboratory (Sim Lab) and real procedure in the catheterization laboratory (Cath Lab). (A) Realistic simulation. (B) Educational debriefing. (C) Real procedure in the Cath Lab. (D) Proteus® Intravascular Temperature Management System (Zoll Circulation Inc™, San Jose, CA, USA) device in detail.

Time. Of note, the protocol has a dynamic profile, so it can be reinvented and improved whenever the situation requires it [18–24].

Current improved technology of the new endovascular Zoll™ Proteus Cooling System™ (more powerful than the previous devices) also contributed to the development of a feasible protocol in a timely manner. It is implanted through a simple femoral vein puncture with the introduction of the cooling catheter, which takes few minutes to be performed. On the other hand, it requires 2 different interventionists working at the same time on the patient if the intention is to perform cooling and angiography at the same time, so a dedicated physician is necessary for all cooling procedures.

It is also important to highlight the focusing on logistical optimization for moving the patient among the different departments of the hospital, i.e., from the ER to the Cath Lab, and them to the Coronary Unit. This logistical planning is important not only to avoid any further delays in the DTB, but also to avoid precocious rewarming of the patient during the transportation. Previous trials already have shown the extremely harmful effects of unstable temperature control during temperature target management, so it is utmost to guarantee a stable maintenance of the core temperature.
Fig. 3. Comparison of door-to-balloon times between the endovascular hypothermia group and the control group. Of note, the 5.1 minutes difference was not statistically significant.

After consistent protocol training for 361 healthcare professionals, the protocol was initiated. As far as we know, this was the first trial showing that ETH was feasible without further delays in DTB [10]. The primary PCI could be performed within a mean DTB of 92.1 minutes compared to 87 minutes in the control group. The absolute 5.1 minutes’ difference was not statistically significant ($p = 0.509$). Other recent similar trials failed to show the absence of DTB delays when EHT was performed. In the COOL AMI EU Pilot trial [15], which used the same endovascular system, the mean DTB time was 105 min, and there was a significant DTB cooling-related delay of 17 minutes.

From the ETH group, 85.7% of the patients underwent primary PCI in a timely manner. International guidelines suggest that DTB should be <90 minutes in more than 90% of patients in top-performing institutions [2–9]. Eventual DTB intentional delays due to cooling procedures would be considered unethical and maybe harmful to the patient, once the larger ischemic period could increase myocardium necrosis [11]. Contrarily, one could advocate that the cardio-protective effects of cooling would overwhelm the impairment of the eventual delay, so the myocardial salvage would be greater in hypothermia-induced patients even with the delay.

Even though randomized clinical trials including COOL MI [28], ICE-IT [29], CHILL MI [30] and VELOCITY [31] failed to show a significant reduction in infarct size, endovascular cooling appears to be safe and well tolerated. Despite neutral overall results, subsequent unpublished post hoc subgroup analysis of COOL MI [28] and ICE-IT [29], and combined analysis of RAPID MI-ICE [32] and CHILL MI [30] showed significant reduction in infarct size in a subgroup of early presenters with anterior STEMI who were cooled below 35 °C prior to reperfusion [33]. Thereby, benefits of therapeutic hypothermia might be achieved by using a rapid cooling to decrease core temperature below 35 °C prior to the opening of acute coronary occlusion to justify the ETH as an adjunctive therapy in STEMI [33].

5. Limitations

Our results, however, should be interpreted in the light of several limitations. The protocol was single-center and therefore easier to get all professionals trained. Secondly, we did not evaluate the learning curve for the professionals, once some of them already had been exposed to ETH procedures. Third, there was no physician exclusively responsible for the cooling procedure, it was performed concomitant to the interventional procedure, which might imply in delays in the DTB. Last, the inherent limitations of mannequin simulators must be taken into account, such as the impossibility of subjective feedback or bleeding events [34].

6. Conclusions

Realistic simulation, intensive training and educational debriefing for the multidisciplinary team propitiated feasible endovascular therapeutic hypothermia as an adjuvant therapy to primary PCI in STEMI, without delays in door-to-balloon time.

Author contributions

LAPD contributed substantially in collecting data, as well as data interpretation, analysis, writing and reviewing the manuscript. NSG, TFP, MKFL, CYBS-M, CER, LAH, FGL, JCN, MTO-J, LAOD, MD, EER-S, RK-F and AA contributed substantially in the analysis and interpretation of data. PAL-N and ST are the co-senior authors of this manuscript and had access to all the data, contributed in data interpretation, and reviewing the manuscript for important intellectual content.

Ethics approval and consent to participate

All the patients have provided permission to assess the data, all the research was performed according to the ethics committee statements, and the identity of the patients has been protected. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved both by the Regional Ethics Committee (CAPPesq approval number: 0242/11) and by the National Ethics Committee (CONEP approval number: 16568). ClinicalTrials.gov identification: NCT02664194.

Acknowledgment

The authors are grateful to all nurses, technicians, and physicians who care for our patients with images used in this manuscript.
Funding
This study was financed in part by Zoll Circulation Inc and in part by the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior - Brasil (CAPES) - Finance Code 001.

Conflict of interest
Michael Dae is a consultant for ZOLL Circulation Inc (San Jose, CA, USA). None of the other authors have conflicts of interest related to this article.

References
[1] Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. New England Journal of Medicine. 2007; 357: 1121–1135.
[2] Piegaas LS, Timerman A, Feitosa GS, Nicolau JC, Mattos LAP, Andrade MD, et al. V Guideline of the Brazilian Society of Cardiology on Acute Myocardial Infarction Treatment with ST Segment Elevation. Arquivos Brasileiros de Cardiologia. 2015; 105: 1–105.
[3] Bernoco C, Timerman S, Polastri TF, Giannetti NS, Siqueira AWDS, Piscopo A, et al. Atualização da Diretriz de Resuscitação Cardiopulmonar e Cuidados Cardiovasculares de Emergência da Sociedade Brasileira de Cardiologia-2019. Arquivos Brasileiros de Cardiologia. 2019; 113: 449–663. (In Portuguese)
[4] Neumar RW, Nolan JP, Adrie C, Aibihi M, Berg RA, Bottiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognosis. A consensus statement from the International Liaison Committee on Resuscitation. Journal of the American Heart Association. 2015; 6: 115–135.
[5] Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, et al. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132: S315–S367.
[6] Nolan JP, Hazinski MF, Aickin R, Bhanji F, Billi JE, Callaway CW, et al. Part 1: Executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation. 2015; 95: e1–e31.
[7] O’Gara PT, Kushner FG, Ascheim DD, 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. Circulation. 2013; 127: e362–e425
[8] Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cerquek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction: an Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Journal of the American College of Cardiology. 2016; 67: 1235–1250.
[9] Maconochie IK, Bingham R, Eich C, López-Herce J, Rodríguez-Núñez A, Rajka T, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015; 95: 1–80.
[10] Dallan LAP, Giannetti NS, Rochitte CE, Polastri TF, San Martin CYB, Hajjar LA, et al. Cooling as an Adjunctive Therapy to Percutaneous Intervention in Acute Myocardial Infarction: COOL-MI InCor Trial. Therapeutic Hypothermia and Temperature Management. 2021; 11: 135–144.
[11] Duncker DJ, Klassen CL, Ishihashi Y, Herrlinger SH, Pavek TJ, Bache RJ. Effect of temperature on myocardial infarction in swine. The American Journal of Physiology. 1996; 270: H1189–H1199.
[12] Dae MW, Gao DW, Sessler DI, Chaint J, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. American Journal of Physiology. 2002; 282: H1584–H1591.
[13] Erlinge D. A Review of Mild Hypothermia as an Adjunctive Treatment for ST-Elevation Myocardial Infarction. Therapeutic Hypothermia and Temperature Management. 2011; 1: 129–141.
[14] Hausenloy DJ, Yellon DM. Myocardial ischaemia-reperfusion injury: a neglected therapeutic target. The Journal of Clinical Investigation. 2013; 123: 92–100.
[15] Noc M, Erlinge D, Neskovic AN, Kafezdzic S, Merkely B, Zima E, et al. COOL AMI EU Pilot Trial: a multicentre, prospective, randomized controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. EuroIntervention. 2017; 13: e531–e539.
[16] Wills JF, Boss O, Keller E. Safety, feasibility, and efficiency of a New Cooling Device Using Intravenous Cold Infusions for Fever Control. Neurocritical Care. 2019; 30: 149–156.
[17] Cheng A, Kessler D, Mackinnon R, Chang TP, Nadkurni VM, Hunt HA, et al. Reporting guidelines for health care simulation research: extensions to the CONSORT and STROBE statements. Advances in Simulation. 2016; 1: 25.
[18] Electronic randomization website Sealed Envelope. 2015. Available at: http://www.sealedenvelope.com (Accessed: 25 July 2020).
[19] Endacott R, Gale T, O’Connor A, Dix S. Frameworks and quality measures used for debriefing in team-based simulation: a systematic review. BMJ Simulation and Technology Enhanced Learning. 2019; 5: 61–72.
[20] Fanning RM, Gaba DM. The role of debriefing in simulation-based learning. Simulation in Healthcare. 2007; 2: 115–125.
[21] Cooper JB, Taqueti VR. A brief history of the development of manikin simulators for clinical education and training. Quality & Safety In Health Care. 2004; 13: 111–118.
[22] Delasobra BE, Goodwin TL, Streblow M, Gilbert G, D’Souza P, Alok A, et al. Evaluating the efficacy of simulators and multimedia for refreshing ACLS skills in India. Resuscitation. 2010; 81: 217–223.
[23] Davis LE, Storjohann TD, Spiegel JJ, Beiber KM, Barletta JF. High-fidelity simulation for advanced cardiac life support training. American Journal of Pharmaceutical Education. 2013; 77: 59.
[24] Wayne DB, Didwania A, Feinglass J, Fudala MJ, Barsuk JH, McGaghie WC. Simulation-based education improves quality of care during cardiac arrest team responses at an academic teaching hospital: a case-control study. Chest. 2008; 133: 56–64.
[25] Rodgers DL, Securro S, Pauley RD. The effect of high-fidelity simulation on educational outcomes in an advanced cardiovascular life support course. Simulation in Healthcare. 2009; 4: 200–206.
[26] Hoadley TA. Learning advanced cardiac life support: a comparison study of the effects of low- and high-fidelity simulation. Nursing Education Perspectives. 2009; 30: 91–95.
[27] DeMaria S, Silverman ER, Lapidus KAB, Williams CH, Spivack J, Levine A, et al. The impact of simulated patient death on...
medical students’ stress response and learning of ACLS. Medical Teacher. 2016; 38: 730–737.

[28] Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. Journal of the American College of Cardiology. 2002; 40: 1928–1934.

[29] O’Neill WW, Dixon SR, Grines CL. The year in interventional cardiology. Journal of the American College of Cardiology. 2005; 45: 1117–1134.

[30] Erlinge D, Götberg M, Lang I, Holzer 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. Journal of the American College of Cardiology. 2014; 63: 1857–1865.

[31] Nichol G, Strickland W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, et al. Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment-elevation myocardial infarction. Circulation: Cardiovascular Interventions. 2015; 8: e001965.

[32] Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circulation: Cardiovascular Interventions. 2010; 3: 400–407.

[33] Erlinge D, Götberg M, Noc M, Lang I, Holzer M, Clemmensen P, et al. Therapeutic hypothermia for the treatment of acute myocardial infarction—combined analysis of the RAPID MI-ICE and the CHILL-MI trials. Therapeutic Hypothermia and Temperature Management. 2015; 5: 77–84.

[34] Dreifuert KT. Using Debriefing for Meaningful Learning to Foster Development of Clinical Reasoning in Simulation. Journal of Nursing Education. 2012; 51: 326–333.