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Clinical paper

Impact of hypothermia on cardiac performance during targeted temperature management after cardiac arrest

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Abstract

Introduction: Targeted temperature management (TTM) is a well-accepted neuro-protective intervention in the management of comatose survivors of cardiac arrest (CA). However, the impact of TTM on cardiac performance has not been adequately evaluated.

Methods: We reviewed data on consecutive CA survivors undergoing TTM at a quaternary cardiac intensive care unit between January 2015 and June 2017. Enrollment was restricted to cases with invasive hemodynamics (iHDs) at TTM initiation, every 8 h at target temperature (32–34 °C) and at completion of rewarming (>36 °C), unless precluded by mortality. Cardiac index and cardiac index-derived variables were adjusted for a decreased oxygen consumption during hypothermia. We assessed the serial impact of cooling on iHDs and cardiac performance utilizing longitudinal data analysis accounting for the effects of time as surrogate for the expected change from the post arrest syndrome and instituted treatments. A Frank–Starling construct was used to evaluate changes in cardiac contractility.

Results: We evaluated the effects of cooling on iHDs and cardiac performance in 46 CA survivors. Heart rate decreased with cooling ($p < 0.001$), to return to baseline after rewarming ($p = 0.6$). Mean arterial pressure and pulmonary wedge pressure decreased by cooling ($p < 0.001$ for both), with sustained improvement after rewarming ($p < 0.001$ for both). Systemic vascular resistance was unaffected by hypothermia ($p > 0.05$). Left stroke work index increased with cooling ($p < 0.001$), with return to baseline after rewarming ($p = 0.6$). Cooling was associated with a left-upward shift in the Frank–Starling curve indicative of increased contractility.

Conclusion: Mild hypothermia in CA survivors appears associated to positive changes in iHDs and cardiac performance, including a potential increase in cardiac contractility. Larger studies are needed to conclusively confirm these findings.

Keywords: Targeted temperature management, Cardiac performance, Cardiac contractility, Cardiac arrest

Introduction

Targeted temperature management (TTM) is standard of care in the management of comatose cardiac arrest (CA) survivors.[1] Although the benefits of TTM on survival and neuro-protection are well established, the mechanisms that account for such benefits are less well defined. Most of the benefit arising from TTM is thought to be mediated via cooling-induced changes in brain metabolism, which attenuates the ischemia-reperfusion injuries that the brain sustain following a cardiac arrest.[2,3,4] However, the potential impact of TTM on cardiac performance that could contribute to the aggregate benefits of the intervention are less known.

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Following CA, survivors sustain variable degrees of myocardial stunning that partially overlaps with an ensuing inappropriate vasodilatation that extent into later stages of the post arrest setting. Myocardial function is acutely depressed after CA, occurring as early as 30 min post arrest and extends up to 72 h, playing an important role in the early post arrest hemodynamics. Such myocardial stunning and inappropriate vasodilatation occurs in interplay with the ensuing brain injury and the potential persistence of the initial process that triggered the arrest in the first place as part of the well-known post CA syndrome.[5,6] Even though neurological damage is the dominant contributor to the mortality in this resuscitated population, up to a third of fatalities occur early, a phenomenon attributed to a variable mix of cardiogenic and distributive shock with multi-organ failure.[7] Thus, there has been a growing interest in the potential salutary effects of TTM after cardiac arrest on hemodynamics, cardiac performance and systemic inflammation.[8] Reports from studies in animals and humans undergoing cardiac surgery have reported complex interactions between cooling and cardiac contractility.[9,10] Cooling in animal models seems associated to an increase in cardiac contractility with documented increments in myocyte cell shortening and peak systolic pressures. These effects appear mediated by an enhanced calcium handling.[9,11] Scarce clinical evidence has reported modest improvement in invasive hemodynamics (iHD), including cardiac index in arrest survivor undergoing TTM.[12,13] However, this evidence fails to separate the cardiovascular effects of cooling from the impact of medical treatments and the natural history of the post arrest myocardial stunning and inappropriate vasodilatation.[6] Whether cooling positively impact cardiac performance remains debatable.

Our study aims to investigate the impact of mild hypothermia on cardiac performance in arrest survivors undergoing TTM.

Methods

Patient selection

We retrospectively analyzed prospectively collected data from consecutive comatose arrest survivors who underwent TTM with serial invasive hemodynamic monitoring at a quaternary care cardiac intensive care unit (CICU) from January 2015 to June 2017 (n = 88). Our final sample size consisted of 46 adult survivors of CA, regardless of arrest location or initial rhythm, with serial iHD available at TTM initiation (>36 °C), at target temperature (32–34 °C) and at rewarming completion (>36 °C), unless precluded by death. At minimum, patients had to have one set of hemodynamics prior to cooling and one set during cooling to be included. Patients were excluded (n = 42) if only one set of hemodynamics was recorded (n = 6), pre-cooling invasive hemodynamics were not available (n = 12) or cooling was initiated before admission to CICU and systemic temperature of <36 °C was noted prior to obtaining invasive hemodynamics (n = 24) (Fig. 1). The lack of hemodynamic data in 12 subjects was a consequence of: cooling catheter placement without simultaneous insertion of pulmonary catheter in the catheterization lab after emergent LHC (n = 2); t-PA given for pulmonary embolus (n = 1); transfer out of the CICU (n = 1); double outlet right ventricle anatomy (n = 1); ECMO implantation (n = 1); PA catheter attempted but no hemodynamics available (n = 1); and unknown reasons (n = 5). The Institutional Review Board approved this study, informed consent was waived and data were de-identified.

Post-cardiac arrest care and targeted temperature management

Survivors of an OHCA were admitted to the CICU from the main emergency department (ED) or transferred from local EDs; meanwhile in-hospital arrest patients were rapidly transferred to the CICU following successful resuscitation. Patients with ST-elevation myocardial infarction detected on post-ROSC electrocardiograms were emergently routed from the ED or regular nursing floor to the catheterization laboratory prior to admission to CICU. TTM was initiated for all comatose (Glasgow score <8) survivors of cardiac arrest, regardless of the initial shockable rhythm and ROSC within 60 min of initiation of resuscitation. Absolute contraindications to TTM included uncontrolled bleeding, intracranial bleeding, persistent cardiac arrest, rapidly improving neurological status, or reversible causes of the comatose state. Systemic hypothermia was achieved using an endovascular cooling system (Zoll Medical, Chelmsford, MA) with a goal plateau temperature of 33 °C maintained for 24 h. Core temperatures were continually monitored via a thermistor at the tip of a transurethral catheter. Active rewarming was initiated after 24 h at

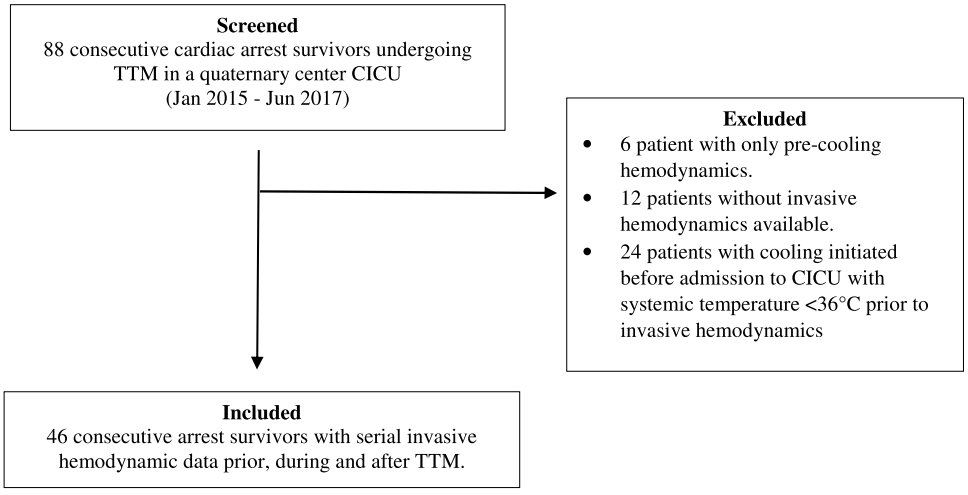

Fig. 1 – Flow chart of patient inclusion.
TTM: targeted temperature management, CICU: cardiac intensive care unit.

goal temperature using the endovascular catheter system at a controlled rate of 0.25 °C–0.5 °C per hour.

Invasive hemodynamic monitoring

Per CICU protocol, all patients undergoing TTM were required to have PA catheters placed for hemodynamic monitoring unless contra-indicated. PA catheter were mostly introduced at the same time of cooling catheter placement upon arrival to CICU. The initial set of hemodynamics obtained included temperature, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), PA pressures, pulmonary capillary wedge pressure (PCWP), mixed venous oxygen (SVO2), Fick cardiac index (Fick-CI), systemic vascular resistance (SVR) and serum lactic acid. Temperature, HR, MAP, CVP, PA pressures were recorded serially every 30 min, while comprehensive hemodynamics also including SVO2, Fick-CI, SVR and serum lactic acid, which were obtained every 4 h or sooner if indicated at the discretion of the treating cardiologist. The management of post-arrest patients in our CICU followed standard of care recommendations with the added guidance from invasive hemodynamic data.

Hemodynamic measurements obtained immediately after placement of PA catheter and before cooling induction initiation were considered baseline measurements. We recorded one set at baseline (prior to cooling), 3 sets every 8 h during cooling maintenance (32–34 °C), and one final set after re-warming was achieved (>36 °C). Even though PCWP was only measured at baseline or when clinically indicated for safety reasons, this parameter was derived from the baseline diastolic PA pressure-to-PCWP relationship for subsequent hemodynamic assessment during cooling and rewarming.[14] We measured CI using the Fick equation estimating oxygen consumption based on body surface area as previously described.[15,16] To accommodate the change in body temperature, we adjusted for a drop of 16% in oxygen consumption during mild hypothermia as reported in a prior study.[17] The left (LVSWI) and right (RVSWI) ventricular stroke work indices were calculated at each pre-specified time using formulas described elsewhere using adjusted CI.[18] Finally, Frank–Starling curves were constructed by plotting LVSWI (surrogate for LV output) against PCWP (surrogate of LV input). This was used to determine if cooling-induced changes in LVSWI were due to either the sole result of changes in preload or to added changes in contractility. No change in cardiac contractility was assumed if every change in LVSWI was fully explained by a change in PCWP falling along the same Frank–Starling curve. Conversely, a left-upward and right-downward into a different Frank–Starling curve were interpreted as increased and decreased contractility, respectively.[19,20]

Statistical analysis

Patient information collected was summarized as mean and standard deviation for all normally-distributed continuous variables, as median [P25, P75] for non-normally distributed continuous variables, and as counts and percentages for all categorical variables. In all analyses, a p value of <0.05 was taken to represent significance.

To separately quantify the impact of hypothermia, and the changes (i.e. improvement) in cardiac performance over time, we conducted a longitudinal analysis by separately taking account of the effect of time, which reflects a natural history of post arrest syndrome (including myocardial stunning) and medical treatments, and the effect of temperature at each time point which reflects the impact of cooling. We applied a Linear Mixed Effects model with unstructured covariance for random effects using SPSS (SPSS Inc. Chicago, IL). This method, in contrast to repeated-measures analysis of variance, is less sensitive to missing data, can accommodate an uneven number of data points during follow up, and is not bound by a specific structure of variance/covariance matrix. In this mixed effect model, we treated hypothermia and time from admission to the CICU as covariates. Hypothermia was quantified using body temperature measured as a continuous variable at each time point. Time was quantified as a time interval, measured in hours, starting from the initial measurement of hemodynamics after admission to CICU. We also tested whether numerical transformations of time values improved the model. Finally, we tested for the possible interaction between time and body temperature.

Results

The serial hemodynamics of 46 consecutive arrest survivors undergoing TTM that met inclusion criteria were analyzed (Table 1). Total of 39 patients had full sets of hemodynamics before, during and after hypothermia, 5 patients had one or multiple PCWP or CI discrete data points throughout the treatment, and 4 patients had full data from before and during hypothermia but not after rewarming due to early mortality. The serial changes in hemodynamics and cardiac performance indices at baseline, during mild hypothermia and after rewarming are presented in Fig. 2.

Table 1 – Patient sample demographic, clinical and cardiac arrest characteristics (n = 46).

Demographics and comorbidities	
Age (years)	61 ± 12
• Men	30 (65%)
• Body mass index (kg/m^2)	31 ± 8
• Hypertension	41 (89%)
• Diabetes mellitus	9 (20%)
• Smoking	35 (76%)
• Coronary artery disease	24 (52%)
• Congestive heart failure	22 (48%)
• Cerebrovascular disease	9 (20%)
Cardiac arrest characteristics	
• Out-hospital arrest	38 (83%)
• Shockable rhythm	34 (74%)
• Witnessed arrest	36 (78%)
• Cardiopulmonary resuscitation by bystander	26 (56%)
• Time to ROSC (minutes)	21.2 ± 15.5
• Shock on admission (%)	18 (39%)
• STEMI (%)	12 (26%)
Admission data	
• Glasgow score	5 ± 2
• Admission temp (°C)	36.1 ± 1.0
• Admission Ph	7.23 ± 0.14
• Lactate (mg/dl)	2.6 ± 3
• LVEF (%)	41 ± 14
• Time to TTM initiation (hours)	6.3 ± 0.1
• Time from TTM initiation to target temperature (hours)	2.2 ± 0.1
Outcomes at hospital discharge	
• Survival	24 (52%)
• CPC 1-2	20 (43%)

CPC, cerebral performance category, ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction.

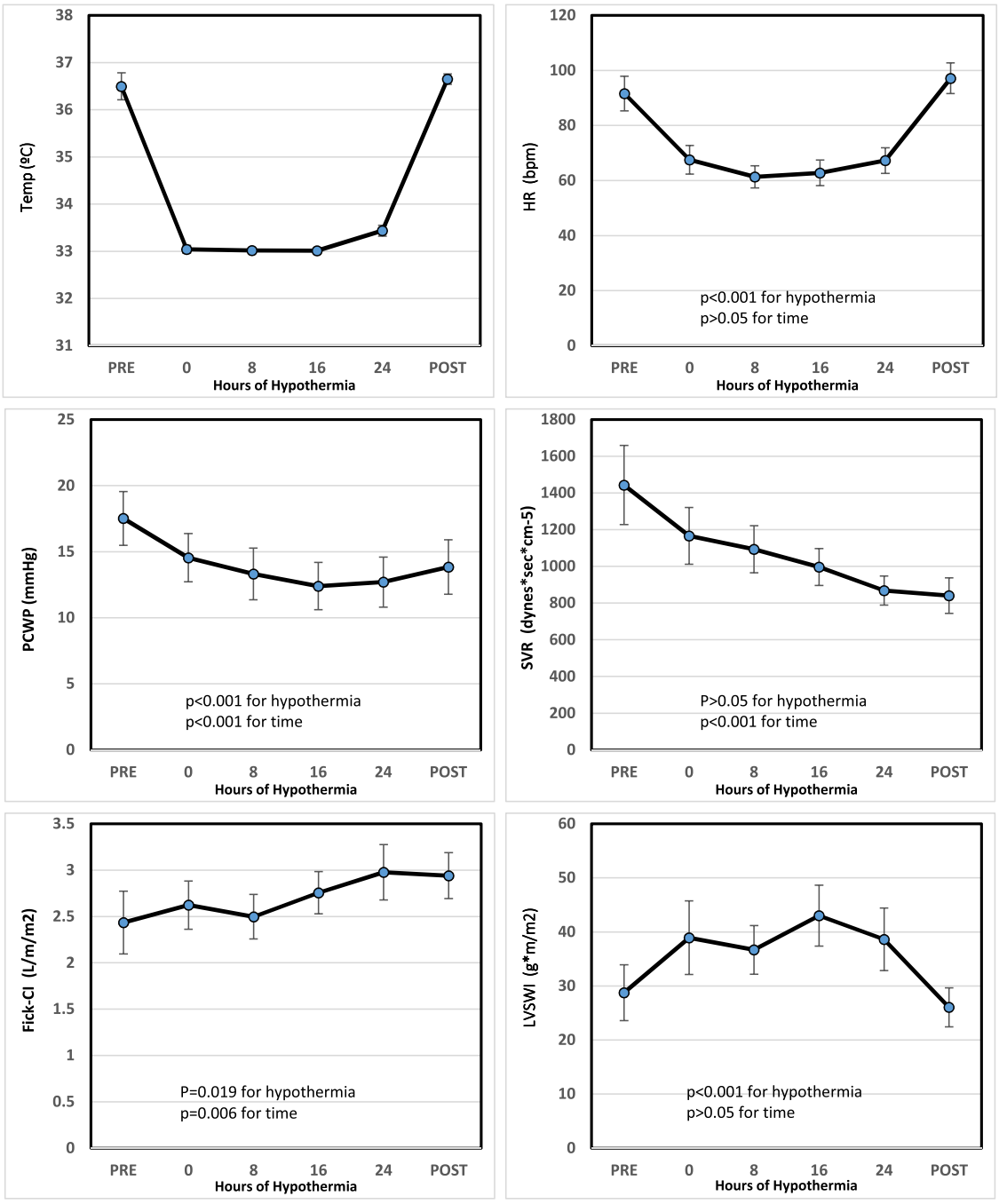

Fig. 2 – Impact of mild cooling on cardiac performance and invasive hemodynamics during TTM. Temp: temperature, HR: heart rate, PCWP: pulmonary capillary wedge pressure, SVR: systemic vascular resistance, Fick-CI: Fick cardiac index, LVSWI: left ventricle stroke work index.

The observed HR decreased with mild hypothermia ($p < 0.001$), to then return to baseline values upon rewarming ($p = 0.6$). Conversely, MAP and PCWP decreased with mild cooling ($p < 0.001$ for both) with sustained reductions upon rewarming ($p < 0.001$ for both). The CI calculations and derived variables (SVR, LVSWI, RVSWI) were adjusted for a 16% drop in oxygen consumption during cooling based on prior reports.[17] The CI increased with mild hypothermia ($p < 0.019$), with persistent improvements after rewarming ($p = 0.006$). Meanwhile, SVR was not affected by mild hypothermia with significant reduction over time ($p < 0.001$). Conversely, LVSW increased during mild hypothermia ($p < 0.001$) and returned to baseline values upon rewarming ($p = 0.6$). The RVSW values were not affected by hypothermia. Time to ROSC did not affect baseline values of cardiac performance parameters ($p > 0.1$ for all correlations). In addition, to ascertain the impact of time to ROSC on changes in cardiac performance, we added it as a covariate to our mixed effect model. Time to ROSC did not influence the changes in any of the cardiac performance parameter ($p > 0.1$ for all parameters).

Finally, the left ventricle (LV) Frank–Starling construct with 95% confidence error bars is presented in Fig. 3. From a baseline contractility estimate (A), mild cooling is associated with a left-upward shift in estimates to a higher contractility curve (B, C, D & E). This effects reverses upon rewarming with contractility estimates back to the baseline contractility (F). The leftward shift of rewarming estimates (F) along the baseline Frank–Starling curve compared to baseline estimate (A) indicates comparable contractility and is explained by a reduction in PCWP.

Discussion

We describe the effects of mild hypothermia (32–34 °C) on iHDs and cardiac performance indices during TTM after cardiac arrest. In our cohort, mild cooling was independently associated to a decrease in HR, MAP, RAP, and PCWP, and increments in CI and LVSWI. Conversely, cooling did not affect SVR or RVSWI. Time, as a surrogate for the cardiovascular changes related to the post cardiac arrest syndrome and the impact of medical treatments, was associated to decrements in MAP, SVR, and PCWP, and increments in CI. Interestingly, mild hypothermia was associated to an increase in LV contractility as indicated by the left-upward shift of estimates to a high contractility curve during cooling maintenance. This phenomenon occurred despite reduction in LV filling pressure and fully reversed with rewarming. The noted improvements in hemodynamics and cardiac performance, including contractility, appears to be multifactorial, but in part explained by cooling.

To the best of our knowledge, this is the first study to investigate the impact of hypothermia on invasive hemodynamics and cardiac performance indices independently from time effects (including among other the impact of the post CA syndrome and instituted treatments) in arrest survivors undergoing TTM. Our study is in agreement with previous studies reporting an association between hypothermia and beneficial hemodynamic changes[12,13,21,22]. Such studies identified an association between hypothermia and reductions in HR, MAP, PCWP and SVR. Despite the drop in HR, there was a significant and sustained improvement of CI throughout the treatment, and this continued to be so even after accounting for metabolic changes under hypothermic conditions.[12,13,21] The current study confirms that these changes in HR, MAP, PCWP and CI are independently associated with hypothermia. The reduction in PCWP noted with hypothermia likely represents the results of cold diuresis. Conversely, this study argues against the counterintuitive reported reduction in SVR with cooling. The SVR was not affected by mild hypothermia, but rather decreased by the effect of time. This is perhaps the result of the delayed vasodilation experienced during the post-CA syndrome and treatment effects from perhaps vasodilators.

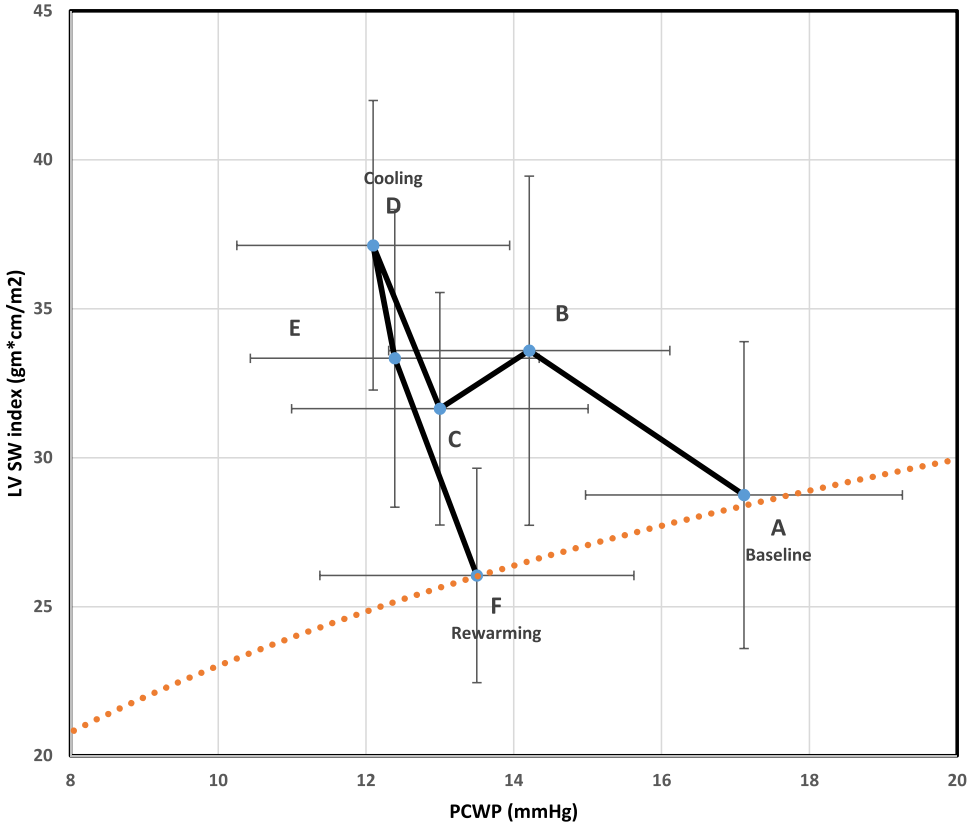

Fig. 3 – Plot of left ventricular stroke work (y axis) against pulmonary capillary wedge pressure (Frank–Starling relationships) at baseline, during cooling, and after rewarming rewarming. Time point A: baseline measurements, time points B–E: consecutive measurements during hypothermia, time point F: measurement after rewarming. Orange line represents baseline Frank Starling relationship curve assuming constant contractility. Area above the orange line represents improved contractility. Area below and to the right of the orange line represents worsened contractility. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

More importantly, this study suggests that mild cooling during TTM is associated to an improvement in LV contractility. This suggested salutary association between cooling and contractility likely contributes to the overall improvement in hemodynamics. A cooling-associated enhancement in cardiac contractility is supported by the Frank–Starling constructs that revealed a left-upward shift of contractility estimates from baseline upon cooling induction. All this occurred despite sustained reductions in filling pressures (PCWP) and fully reversed back to baseline contractility estimates upon rewarming, which support the hypothesis that cooling rather myocardial recovery after CA or ongoing treatment explains improvement in LV contractility. These findings are in agreement with several animal studies that reported enhanced intrinsic contractility of the myocardium in hypothermic conditions.[23,24,25,26,27] This hypothermia-induced inotropism is commonly credited to an increased sensitivity of cardiac myofilaments to intracellular calcium via increased contraction and relaxation kinetics, in addition to increased calcium release from the sarcoplasmic reticulum.[11] Despite reduction in the rate of actin/myosin cross bridge formation that could reduce contractility, there appears to be a higher impact in calcium handling pathways that lead to an state of increased intracellular calcium and hence contractility.[28,29] Moreover, a human study evaluating patients undergoing cardiac bypass surgery reported that the interaction between cooling and LV contractility is rather complex. It appears that contractility decreases when the heart is artificially paced during hypothermia and the salutary effects on hypothermia requires a longer cardiac cycle length.[10]

It is very clear that larger studies are needed before a definitive conclusion can be made on the impact of cooling on cardiac performance, especially regarding contractility. Nonetheless, these findings are promising and add to the current literature, suggesting that hypothermia is safe and perhaps beneficial in these critically ill post CA survivors. Moreover, it raises the question on the potential benefits of expanding mild hypothermia to patients with post-acute coronary syndrome cardiogenic shock. It could be hypothesized that a potential cooling-induced increase in cardiac contractility, reduction in the double product (as surrogate of oxygen consumption), and blunting effects on the local and systemic ischemic-reperfusion cascades might be very helpful in this cohort of patients.

The results of this study must be interpreted as hypothesis generating given several limitations. This study is limited by its retrospective design, but strengthened by the prospective and protocolized acquisition of hemodynamic data. Despite the screening of consecutive CA arrest patients admitted to the CICU, the sample size was small with a significant proportion of patients excluded due to lack of hemodynamic data. This might have significantly skewed the results of this study. Moreover, significant systematics errors could have resulted from the estimation of serial PCWP after the initial measurement as well as by the adjustment of CI for the estimated decrease in oxygen consumption during cooling. Finally, even though we separated the effect of hypothermia from the effect of times in an attempt to exclude the natural history of the post arrest syndrome, treatment effect and other unknown factors, there still exist the possibility that confounding could have explained the reported results.

Conclusion

Mild hypothermia during TTM after CA appears independently associated to salutary changes in hemodynamics and cardiac performance, including a potential association with an increment in LV contractility. Such improvements in hemodynamics and cardiac performance appears to be multifactorial, but appears in part explained by cooling. Larger studies are needed to confirm these findings.

Authors' contributions

Kevin Chen and Aldo Schenone contributed equally to the conception, design and completion of this study. Kevin Chen, Aldo Schenone, Abhijit Duggal, Zoran B. Popović and Venu Menon had substantial contributions to the conception and design of the work. Kevin Chen and Aldo L Schenone contributed equally to this manuscript. Kevin Chen, Aldo Schenone, Bashaer Gheyath were responsible for the acquisition of data. Kevin Chen, Aldo Schenone, Bashaer Gheyath, Nyal Borges, Abhijit Duggal, Zoran B. Popović and Venu Menon were responsible for the analysis and interpretation of data for this manuscript. Kevin Chen, Aldo Schenone, Nyal Borges, Abhijit Duggal, Zoran B. Popović and Venu Menon were responsible for drafting and key revisions of this manuscript. All authors have approved the final version of the manuscript and are accountable for all aspects related to the accuracy or integrity of this manuscript.

Declaration

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Conflict of interest statement

None to declare.

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