Invasive Hemodynamics and Outcomes in Cardiac Arrest Survivors Undergoing Targeted Temperature Management

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Most important prognostic factors in the postcardiac arrest patients who underwent targeted temperature management (TTM) derive from the periarrest period. Whether early invasive hemodynamics predict survival or neurologic outcomes remains unknown. We retrospectively reviewed all comatose survivors of cardiac arrest who underwent TTM at the Coronary Intensive Care Unit of a Quaternary Center between January 2015 and June 2017. Patients were required to have a set of invasive hemodynamics available at initiation of TTM to be included. Those with cooling initiated before admission and temperature of <36C before obtaining hemodynamics were excluded. Univariate logistic and multivariate regression were conducted to test whether cardiac index (Fick-cardiac index ≥2.2 vs <2.2 L/min/m^2), pulmonary capillary wedge pressure (PCWP ≥18 vs <18 mm Hg), systemic vascular resistance (SVR >1200 vs 800 to 1200 vs <800 dynes·s/cm^5) or Forrester hemodynamic profiles were predictive of survival and favorable neurologic outcomes at hospital discharge. Total of 52 consecutive arrest survivors who underwent TTM were studied demonstrating a wide variability in invasive hemodynamic parameters. There was no association between cardiac index (p = 0.45 and p = 0.10), PCWP (p = 0.90 and p = 0.60), SVR (0.95 and p = 0.17) or Forrester hemodynamic profiles (p = 0.40 and p = 0.42) and survival or favorable neurologic outcome at discharge. In conclusion, comatose arrest survivors who underwent TTM presents with a wide spectrum of invasive hemodynamics highlighting the heterogeneity of the postcardiac arrest syndrome. Early invasive hemodynamics did not predict survival or favorable neurologic outcomes at hospital discharge. **(Am J Cardiol 2019;123:1255–1261)**

Targeted temperature management (TTM) is standard of care in unconscious survivor of out of hospital cardiac arrest stemming from shockable rhythms.[1,2,3] The utilization of TTM is also endorsed by guidelines in those comatose arrest survivors with nonshockable rhythms or in-hospital arrest.[1,2] As a consequence, TTM is often broadly applied to comatose arrest survivors to avoid withholding of a potential lifesaving therapy, yet this comes at the expense of often prolonged hospitalizations with both ethical and financial implications.[4,5,6] Despite the benefits of TTM, a significant proportion of patients do not survive to hospital discharge or survive with significant neurologic impairment.[4] Thus, a great deal of effort has been made to identify patients in whom escalation of therapy with TTM may be considered futile.[5] This pressing need to predict clinical outcomes has led to the creation of a number of predictor tools.[5] Although helpful, these scoring systems are imperfect which highlights the ongoing need for the identification of new predictors. Hemodynamic instability has been associated with trends toward worse outcomes in cardiac arrest patients, yet the prognostic utility of early invasive hemodynamics before cooling in arrest survivors who underwent TTM has not been defined.[7,8,9] The primary purpose of this study is to (1) describe the early invasive hemodynamics in the postcardiac arrest population who underwent TTM and (2) determine their prognostic value.

Methods

We screened 88 consecutive comatose survivors of cardiac arrest who underwent TTM at a quaternary care Cardiac Intensive Care Unit (CICU) between January 2015 and June 2017. We included consecutive adult unconscious arrest survivors, regardless of location or initial rhythm, with invasive hemodynamics available at the time of initiation of TTM (n = 52). Those patient without invasive hemodynamics (n = 12) or with initiated before admission to CICU and systemic temperature of <36°C was noted before obtaining initial invasive hemodynamics (n = 24) were excluded (Figure 1). The nearest set of invasive hemodynamics to return of spontaneous circulation (ROSC) and before cooling initiation (temp >36°C) was defined as

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[1]Both authors contributed equally to conception and creation of this manuscript.

Funding: No funding to disclose.

See page 1260 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.01.016

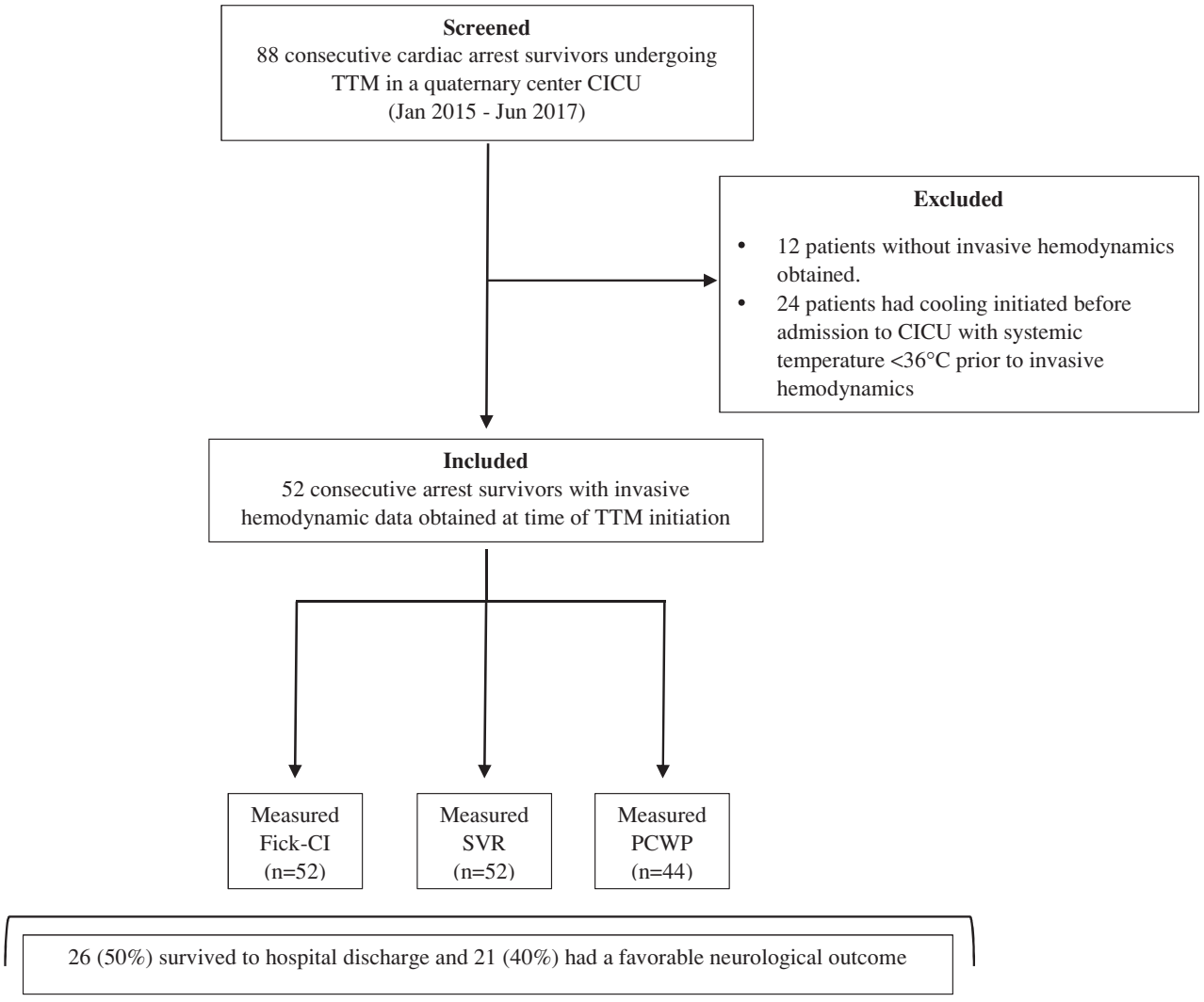

Figure 1. Flow chart of patient inclusion
TTM = targeted temperature management, CICU = Cardiac Intensive Care Unit.

"early hemodynamics". The Institutional Review Board approved this study, informed consent was waived and data were deidentified.

Patient demographics, co-morbidities, clinical data, and hemodynamics were extracted from the electronic medical record by study investigators using a predefined form. The desired cardiac arrest variables were obtained in accordance to Utstein guidelines.[10] Patient were stratified based on initial hemodynamics into: (1) Warm (Fick-cardiac index [CI] ≥2.2 L/min/m^2) versus Cold (Fick-CI <2.2 L/min/m^2), (2) Wet (pulmonary capillary wedge pressure [PCWP] ≥18 mm Hg) versus Dry (PCWP <18 mm Hg), and (3) High (>1200 dynes·s/cm^5) versus normal intermediate (800 to 1200 dynes·s/cm^5) versus low (<800 dynes·s/cm^5) systemic vascular resistance (SVR). In addition, patients were clustered based on Forrester classification into 4 profiles: I: warm-and-dry, II: warm-and-wet, III: cold-and-dry and IV: cold-and-wet.[9] The primary outcomes of interest were survival and favorable neurologic outcome (defined as cerebral performance category 1 to 2) at hospital discharge.

At our institution, survivors of an out-hospital cardiac arrest (OHCA) are admitted to the CICU from the main emergency department or transferred from local emergency departments; while in-hospital arrest patients are rapidly transferred to the cardiac intensive unit after successful resuscitation. Patient with ST-elevation myocardial infarction detected on post-ROSC electrocardiogram are emergently routed to the catheterization laboratory before admission to CICU. In our CICU, TTM is initiated for all comatose (Glasgow score <8) survivors of cardiac arrest, regardless of the rhythm and ROSC within 60 minutes of initiation of resuscitation. Absolute contraindications to TTM include uncontrolled bleeding, intracranial bleeding, persistent cardiac arrest, rapidly improving neurologic status, or reversible causes of the comatose state. Systemic hypothermia is achieved using an endovascular cooling system (Zoll Medical, Chelmsford, MA) with a goal plateau temperature of 33°C maintained for 24 hours. Core temperatures are continually monitored through a thermistor at the tip of a transurethral catheter. Active rewarming is initiated

after 24 hours at goal temperature using the endovascular catheter system at a controlled rate of 0.25˚C to 0.5˚C per hour. It is protocol in our cardiac unit that all patients who underwent TTM have pulmonary artery (PA) catheters placed for hemodynamic monitoring upon admission. The initial set of hemodynamics obtained include temperature, heart rate, mean arterial pressure, central venous pressure (CVP), PA pressure, PCWP, mixed venous oxygen (SVO_2), Fick-CI, SVR and serum lactic acid. Temperature, heart rate, mean arterial pressure, CVP, PA pressures are recorded serially every 30 minutes, while more comprehensive hemodynamics including SVO_2, Fick-CI, SVR, and serum lactic acid are obtained every 4 hours or sooner if indicated at the discretion of the treating cardiologist. The management of postarrest patients in our CICU follows standard of care recommendations with the added guidance from invasive hemodynamic data.

Patient information was summarized as mean and standard deviation for all continuous variables and as counts and percentages for all categorical variables. The ANOVA test was used to compare continuous variables, the chi-square test was used for categorical variables, and the Fisher's Exact test was conducted when one or more of the cells had an expected frequency of 5 or less. Logistic regression was used to adjust covariates. We did both univariate logistic and adjusted regression to test whether Fick-CI (warm vs cold), PCWP (wet vs dry), SVR (high vs normal vs low) or hemodynamic profiles were predictive of the primary outcome. We also tested whether Fick-CI, PCWP, SVR as continuous variable were predictive of the outcomes of interest. Correlations in continuous variables were checked, and variables that might cause a colinearity problem were decreased. A backward method was used for variable selections. All analyses were 2-tailed and were performed at a significance level of $p \leq 0.05$. SAS 9.4 software (SAS Institute, Cary, North Carolina) was used for all analyses.

Results

A total of 52 patients met inclusion criteria for this study (Figure 1). Important demographics, clinical and arrest characteristics are described in Table 1. The mean time from hospital admission to acquisition of invasive hemodynamics was 4.8 hours**.** Of the 52 patients, 26 (50%) survived, and 21 (40%) had a favorable neurologic outcome upon discharge.

There was marked heterogeneity in invasive hemodynamics in the cohort studied (Figure 2). Fick-CI ranged from 1.1 to 6.78 L/min/m^2 (mean 2.57 ± 1.3 L/min/m^2), PCWP ranged from 6 to 30 mm Hg (mean 17 ± 6.6 mm Hg) and SVR from 339 to 4240 dynes·s/cm^5(mean 1394 ± 718 dynes·s/cm^5). About half of the patients (53.9%) had a low Fick-CI, while 61.4% had a low PCWP, and 51.9% had a high SVR. Warm-and-dry (34%) was the most common Forrester profile identified driven by predominant low PCWP, followed by cold-and-dry (27.3%) and cold-and-wet (27.3%) profiles (Figure 2).

Based on univariate analysis (Table 2), multivariate models testing Fick-CI, PCWP, SVR, and hemodynamic profiles were created incorporating age, initial rhythm, time to ROSC and c-GRAPH (Supplements 1 and 2). There was no association between Fick-CI (warm vs cold), PCWP (wet vs dry), SVR (high vs normal vs low) or Forrester hemodynamic profiles and survival or favorable neurologic outcomes at hospital discharge. (Figure 3) This lack of association persisted even when analyzing Fick-CI, PCWP, and SVR as continuous variables (Supplements 3 and 4). After multivariate adjustment and regression modeling, younger age, shorter time to ROSC, and lower c-GRAPH score remained independently associated with survival and favorable neurologic outcomes at hospital discharge (Supplement 1 to 4).

Table 1
Cohort demographic, clinical and cardiac arrest characteristics (n = 52)

Variable	
Age (years)	61 ± 12
Men	36 (69%)
Body mass index (kg/m^2)	31 ± 8
Hypertension	45 (87%)
Diabetes mellitus	11 (21%)
Smoking	40 (77%)
Coronary artery disease	28 (54%)
Congestive heart failure	25 (48%)
Cerebrovascular disease	16 (31%)
Cardiac arrest characteristics	
Out-hospital Arrest	42 (81%)
Shockable rhythm	37 (71%)
Witnessed arrest	40 (77%)
Cardiopulmonary resuscitation by bystander	28 (54%)
Time to ROSC (minutes)	21.8 ± 15.5
STEMI	10 (19%)
Admission data	
Glasgow score	5 ± 2
Admission temp (˚C)	36.4 ± 1.0
Admission Ph	7.24 ± 0.15
Lactate (mg/dl)	3.6 ± 3.4
LVEF (%)	32 ± 4
c-GRApH score	2.3 ± 1
Coronary angiogram (%)	26 (50%)
Percutaneous coronary intervention	8 (15%)
Temp >38˚C in first 96 hours	11 (21%)
Circulatory support	
Intra-aortic balloon pump	7 (13%)
Other mechanical support (Impella, ECMO)	2 (4%)
Outcomes at hospital discharge	
Survival	26 (50%)
CPC 1-2	21 (40%)

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

Discussion

In the studied cohort, we observed a significant interpatient variability in early invasive hemodynamics. Half of the patients presented with low cardiac output postarrest and the majority had elevated SVR and a low PCWP. Meanwhile, the most common hemodynamic profile observed was warm and dry driven by a predominance of low PCWP. Interestingly, early invasive hemodynamic (Fick-CI, PCWP, SVR, or Forrester hemodynamic profiles) did not predict survival or neurologic outcomes at hospital discharge.

Table 2
Association of survival and neurologic outcome with clinical and hemodynamic parameters.

Variable	n	Overall (N = 52)	n	Survivors (N = 26)	n	Non survivors (N = 26)	p value	n	CPC 1-2 (N = 21)	N	CPC 3-5 (N = 31)	p value
Fick-CI—L/min/m^2	52		26		26		0.99[c]	21		31		0.46[c]
Cold (<2.2)		28 (53.8%)		14 (53.8%)		14 (53.8%)			10 (47.6%)		18 (58.1%)	
Warm (≥2.2)		24 (46.2%)		12 (46.2%)		12 (46.2%)			11 (52.4%)		13 (41.9%)	
PCWP - mm Hg	44		22		22		0.35[c]	18		26		0.35[d]
Dry (<18)		27 (61.4%)		15 (68.2%)		12 (54.5%)			13 (72.2%)		14 (53.8%)	
Wet (≥18)		17 (38.6%)		7 (31.8%)		10 (45.5%)			5 (27.8%)		12 (46.2%)	
SVR—dynes·s/cm^5	52		26		26		0.86[d]	21		31		0.22[d]
High		27 (51.9%)		13 (50.0%)		14 (53.8%)			8 (38.1%)		19 (61.3%)	
Low		7 (13.5%)		3 (11.5%)		4 (15.4%)			3 (14.3%)		4 (12.9%)	
Normal		18 (34.6%)		10 (38.5%)		8 (30.8%)			10 (47.6%)		8 (25.8%)	
Hemodynamic profiles	44		22		22		0.68[d]	18		26		0.54[d]
Warm and dry (I)		15 (34.1%)		8 (36.4%)		7 (31.8%)			8 (44.4%)		7 (26.9%)	
Warm and wet (II)		5 (11.4%)		3 (13.6%)		2 (9.1%)			2 (11.1%)		3 (11.5%)	
Cold and dry (III)		12 (27.3%)		7 (31.8%)		5 (22.7%)			5 (27.8%)		7 (26.9%)	
Cold and wet (IV)		12 (27.3%)		4 (18.2%)		8 (36.4%)			3 (16.7%)		9 (34.6%)	
Age	52	61.4 ± 11.8	26	58.3 ± 11.8	26	64.6 ± 11.2	0.055[a]	21	57.8 ± 12.2	31	63.9 ± 11.1	0.068[a]
Location of arrest	52		26		26		0.99[d]	21		31		0.99[d]
In-hospital		10 (19.2%)		5 (19.2%)		5 (19.2%)			4 (19.0%)		6 (19.4%)	
Out of hospital		42 (80.8%)		21 (80.8%)		21 (80.8%)			17 (81.0%)		25 (80.6%)	
Rhythm	51		26		25		0.064[d]	21		30		0.11[d]
Nonshockable		14 (27.5%)		4 (15.4%)		10 (40.0%)			3 (14.3%)		11 (36.7%)	
Shockable		37 (72.5%)		22 (84.6%)		15 (60.0%)			18 (85.7%)		19 (63.3%)	
ROSC	51	21.9 ± 15.5	26	16.0 ± 12.8	25	28.1 ± 15.9	***0.004***[a]	21	14.4 ± 11.3	30	27.2 ± 16.0	***0.003***[a]
c-GRApH	52	2.3 ± 1.04	26	1.8 ± 0.97	26	2.8 ± 0.91	***<0.001***[a]	21	1.7 ± 0.90	31	2.7 ± 0.94	***<0.001***[a]

Statistics presented as Mean ± SD or N (column %).
p values: a = ANOVA, c = Pearson's chi-square test, d = Fisher's Exact test.
Fick-CI = Fick cardiac index; PCWP = pulmonary capillary wedge pressure; ROSC = return of spontaneous circulation; SVR = systemic vascular resistance.

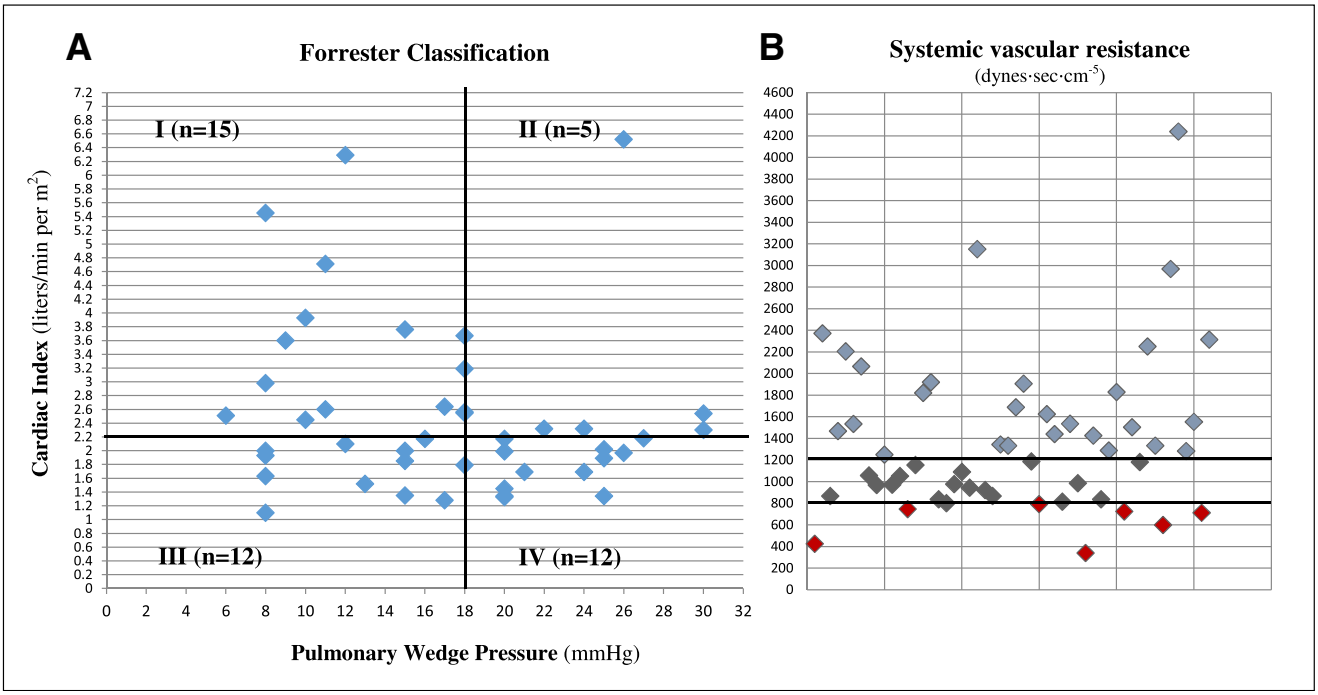

Figure 2. Distribution of arrest survivors who underwent TTM based on initial cardiac index, pulmonary capillary wedge pressure and systematic vascular resistance. **Panel A.** Distribution of patients across the four quadrants of Forrester classification: I: warm-and-dry, II: warm-and-wet, III: cold-and-dry and IV: cold-and-wet. Each patient is represented by a blue diamond. **Panel B.** Distribution of patients by systemic vascular resistance. Red diamonds: patients with low systematic vascular resistant, dark gray diamonds: patient with normal systemic vascular resistance, Light gray diamonds: patients with high systemic vascular resistance.

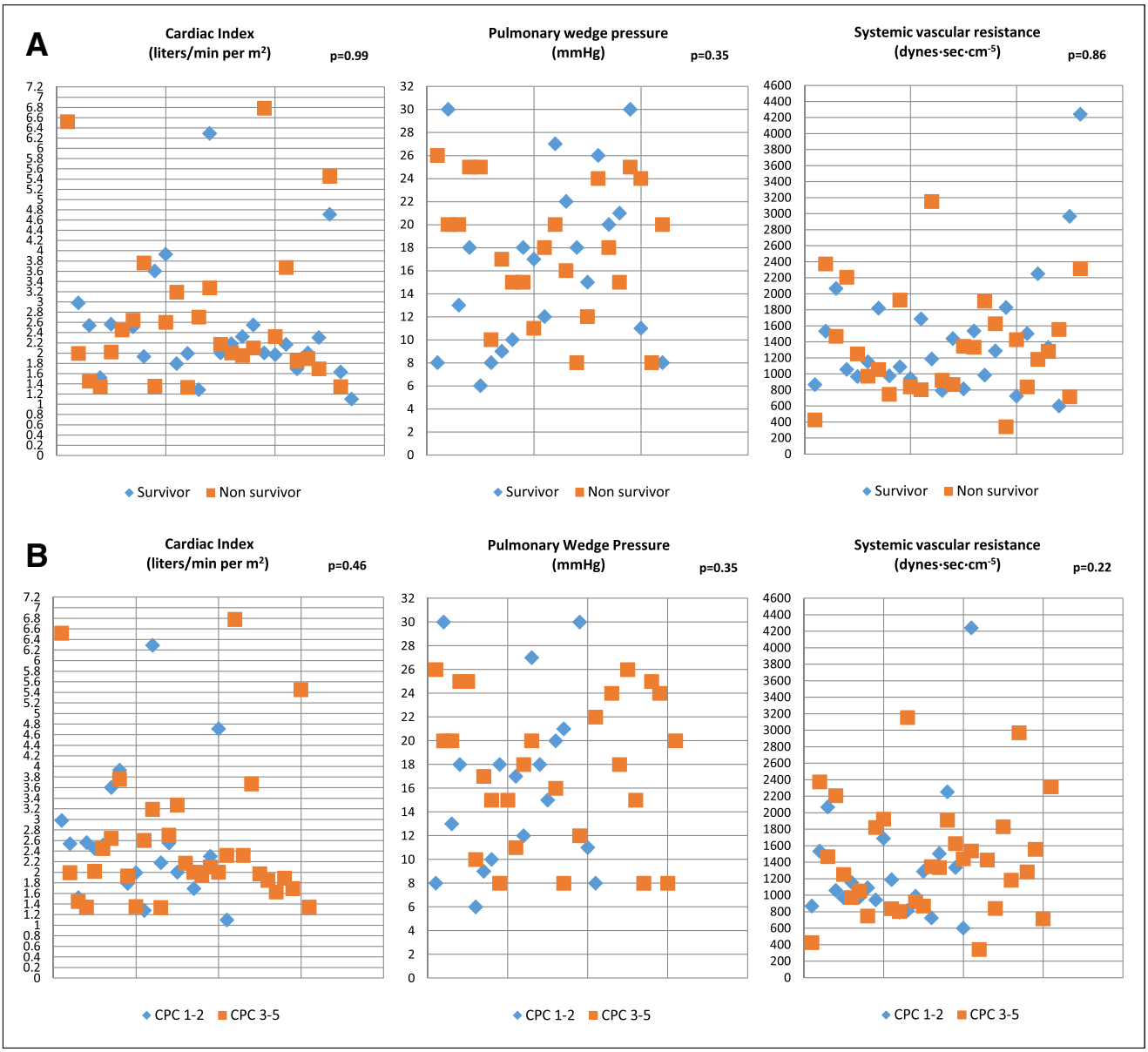

Figure 3. Distribution of early invasive hemodynamics based on survival status and neurological outcomes.
Panel A. Distribution of cardiac index, pulmonary wedge pressure and systematic vascular resistance dichotomized into survivors and nonsurvivors. **Panel B.** Distribution of cardiac index, pulmonary wedge pressure and systematic vascular resistance dichotomized into patient with good neurological outcome (CPC 1 to 2) and those with poor neurological outcome (CPC 3 to 5).

Survivors of cardiac arrest are known to sustain variable degrees of neurologic dysfunction, myocardial depression, and systemic ischemia/reperfusion response as part of the postcardiac arrest syndrome.[11,12] This study confirms the wide heterogeneity in invasive hemodynamics encountered in the postcardiac arrest syndrome with patients occupying all quadrants of the hemodynamic Forrester classification. Given the lack of reliability of traditional physical exam techniques to determine perfusion status in the setting of induced hypothermia, further studies are required to evaluate the whether the utilization of a Swan-Ganz catheter alters length of stay, morbidity, or mortality in this cohort.[13,14,15]

Contrary to the postmyocardial infarction and septic shock cohorts, the early characterization of invasive hemodynamics does not seem to predict outcomes in arrest survivors who underwent TTM.[9,16] This results contrast with some reports from the pre- and post-TTM era that linked hemodynamic instability, changes in the mean perfusion pressure, and postarrest CI with survival and/or neurologic outomes.[7,8,12,17] However, other studies support these findings based on a lack of correlation between initial CVP, myocardial depression (defined as cardiac index (<1.5 L/m/m2), SVO_2, or SVR and outcomes after cardiac arrest.[13,18,19] It is important to recognize when analyzing the results of this study that the clinicians were unblinded to the invasive hemodynamics, thus these likely impacted the subsequent management of the patients, and perhaps their outcomes. Until more definitive evidence is available, the decision to withhold TTM should not be influenced by on invasive hemodynamics but rather using established prognostic factors such as presenting rhythm and time to achieve ROSC.

This study has several limitations that restrict the generalizability of the results. First, it was a retrospective study with the inherent biases, although the data itself was prospectively acquired. The sample size was small with a not insignificant risk of Type II statistical error. Although we included all consecutive comatose cardiac arrest survivors who underwent TTM with recorded invasive hemodynamics at time of TTM initiation, a number of patients were excluded due invasive hemodynamic data being unavailable or due to hemodynamic recorded after cooling initiation with systemic temperature <36°C. Finally, we were not able to account for hemodynamic effects of vasoactive medications or intervention administered before the acquisition of invasive hemodynamics which may have resulted in misclassification of hemodynamic profiles in select cases.

Conclusion

In conclusion, cardiac arrest survivors who underwent TTM present with heterogeneous invasive hemodynamics highlighting the complexity of the postcardiac arrest syndrome. In the studied cohort, early invasive hemodynamics did not predict survival or favorable neurologic outcome at hospital discharge. Larger studies are needed to conclusively determine the prognostic value of early invasive hemodynamics in this population.

Conflict of Interest Statement

The investigators have no conflicts of interest to disclose.

Declaration

None of the investigatos involved with this manuscript have any financial and personal relationships with other people or organizations that could inappropriately influence or bias their work.

Authors' Contributions

Aldo Schenone, Kevin Chen, Abhijit Duggal and Venu Menon had substantial contributions to the conception and design of the work. Aldo Schenone, Kevin Chen, Bashaer Gheyath were responsible for the acquisition of data. Aldo Schenone, Kevin Chen, Bashaer Gheyath, Nyal Borges, Manshi Li, Xiaofeng Wang, Abhijit Duggal and Venu Menon were responsible for the analysis and interpretation of data for this manuscript. Aldo Schenone, Kevin Chen, Nyal Borges, Abhijit Duggal and Venu Menon were responsible for drafting and key revisions of this manuscript. All investigators have approved the final version of the manuscript and are accountable for all aspects related to the accuracy or integrity of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.016.

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