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RAPID PROGRESSIVE CENTRAL COOLING TO 29 °C BY EXTRACORPOREAL CIRCUIT PRESERVES CARDIAC FUNCTION AND HEMODYNAMICS IN IMMATURE SWINE

Xue-Han Ning, Outi Hyyti, Ming Ge, David L Anderson, and Michael A. Portman

Division of Cardiology, Department of Pediatrics, University of Washington, and Children's Hospital and Regional Medical Center

Abstract

The International Liaison Committee on Resuscitation (ILCOR) consensus statement includes recommendations and guidelines for therapeutic hypothermia in infants and children. The information supporting these recommendations is sparse, and reveals a need for target temperature and cooling mode data in age-appropriate animal models. Accordingly, we determined cardiac function and hemodynamic indices in immature piglets (< 28 days) undergoing graded and rapid central cooling from 36°C to 20 °C over 20 minutes by directing cardiac output through an extracorporeal circuit. Functional parameters were recorded continuously using aortic flow probes and left ventricular (LV) pressure capacitance catheters. Stroke volume and work increased during temperature reduction, peaking at 29°C, while systemic vascular resistance did not change. Although, heart rate decreased steadily, cardiac output, power, and LV dp/dt_{max} was maintained until 29°C. All function parameters decreased below 29°C, implying a critical threshold had been exceeded at lower temperatures. These data show that the temperature range 30 ± 1 °C maintains cardiac function and that this target should be further evaluated as a target for therapeutic hypothermia.

INTRODUCTION

The role of therapeutic hypothermia in infants and children following cardiac arrest remains controversial. The International Liaison Committee on Resuscitation (ILCOR) recently published a consensus statement including specific recommendations and guidelines for therapeutic hypothermia in infants and children ¹. The committee acknowledged that these guidelines were based primarily on data from studies in adults and adult animal models of asphyxia and arrest, as well as a few neonatal studies employing surface cooling. Randomized clinical trials in adults have shown that mild hypothermia (33–34°C) after cardiac arrest provides possible benefit to survivors ². Results of these studies in part prompted an earlier ILCOR statement, advising cooling to 32 to 34°C in unconscious adult patients with spontaneous circulation, when the initial rhythm was ventricular fibrillation ². However, the advisory statement also emphasized the very narrow indication for treatment with hypothermia using this temperature range. This committee stressed that numerous factors, which might determine therapeutic benefit or risks, required definition. Prominent among these factors is

Address: Michael A. Portman, MD, Children's Hospital and Regional Medical Center, 4800 Sand Point Way NE M/S G0035, Seattle WA 98105, Michael.Portman@Seattlechildrens.org.

Conflict of Interest Statement.

There is no conflict of interest to disclose for any of the authors.

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target temperature, as some human and animal studies have shown either limited benefit by mild hypothermia or the various adverse effects of more profound temperature drops.

Review of the literature shows relatively few studies, which define the temperature threshold separating myocardial benefit from dysfunction at any developmental stage. Studies in isolated perfused rabbit hearts, emulating cardiac arrest and reperfusion, have shown that 30° C provides far superior preservation of cardiac function and metabolic energy stores than did 34° C^{3–5}. In an adult swine model, when ventricular fibrillation was induced at temperatures 30–33°C, resuscitative measures were facilitated with significantly improved defibrillation success and resuscitation outcome, when compared to 35°C or normothermic (37 °C) conditions⁶. These data cast some doubts on the adequacy of the higher range of the recommended temperature for providing tissue protection. However, some concern exists regarding the immature heart's ability at the lower temperature range to provide adequate cardiac output and maintenance of systemic blood pressure.

The primary objective of this study was to define in an immature or juvenile model, the affects of rapid central cooling on cardiac function and determine the relationship between temperature and cardiac function. The study was performed under conditions of an extracorporeal circuit and assisted circulation in a juvenile pig model.

METHODS

Surgical procedures

Use of pigs in our research was approved by Children's Hospital and Regional Medical Center Animal Care Committee. All research adhered to *APS Guiding Principles in the Care and Use of Animals*. Piglets (age 12–20 days, 9–13 kg, male, n=13) received intramuscular injection with ketamine (33 mg/kg), atropine (0.02 mg/kg), and xylazine (2 mg/kg) for sedation. Under propofol anesthesia (3mg/kg intravenous loading, followed by 3mg/kg/hr for maintenance), the animals were intubated and ventilated with 40% oxygen. The femoral artery and venous were cannulated separately to monitor blood pressure, collect blood samples and infuse propofol and 5% dextrose-9% NaCl solution. Blood oxygen level, pH, and CO₂ level was measured by Radiometer ABL 820. Following performance of a median sternotomy, a flow probe was placed around the ascending aorta to measure cardiac output (TS420, Transonic Systems, Inc). A Millar high-fidelity micromanometer was passed into left ventricle via the apex to measure left ventricular pressure. The aorta and right appendage were cannulated. Sterile cannulae were connected to a cardiopulmonary bypass circuit with a Stockert-Shiley roller pump and a hollow fiber oxygenator (Minimax X Plus, Medtronic) and the animal given heparin (350 units per kg). The circuit was primed with 10% Dextran 40- 0.9% sodium chloride solution 500 ml. The circuit exchanger and a heating pad maintained temperature at 37°C. The esophagus and radial temperature were monitored with thermo probes. A PowerLab 16/30 recorder (AD Instruments) with on-line computer continuously recorded data. Baseline data was recorded before initiating the extracorporeal circuit. The pump rate was constant throughout the protocol and the left ventricular end pressure (LVEDP) was controlled in a stable condition in each animal within the physiological range (<12 mmHg). The levels of hemodynamic parameters were controlled to approximate baseline. After achieving 10 minutes of stable parameters, the hypothermia protocol was initiated and data was recorded continuously.

Hypothermia protocol

Hypothermia is generally considered as the core temperature $\leq 35^{\circ}\text{C}$ ⁷. Accordingly, the baseline temperature was taken at 36°C. The roll pump temperature was progressively reduced in order to reach 20°C of esophageal temperature steadily in approximately 20 min and then

kept stable for 5 minutes, prior to re-warming back to 36°C in 25 min. Arterial blood samples were collected at baseline 30, 26, and 20 °C, respectively after equilibration for 3 minutes at these temperature. As hypothermia influences vascular responses in addition to cardiac contractility, five forms of hemodynamic indices were measured: cardiac contractility, rate, power, after-load, and pre-load with the extracorporeal circuit.

Statistical Analysis

The reported values are means $\pm$ standard error (SE) in the text, tables, and figures. The S-PLUS Version 6.2 Program (Insightful Corp., 2003) was used for statistical analysis. Data were evaluated with repeated measure analyses of variance within groups and single factor analysis of variance across groups. When significant F values were obtained, individual group means were tested for differences. The criterion for significance was $p < 0.05$ for all comparisons.

RESULTS

Relationship between cardiac function and temperature

Baseline hemodynamic indices at 36 °C while attached to the circuit are shown in Table 1. Variability in these parameters primarily reflects the heterogeneity caused by differences in size and age even across the narrow age range studied in these piglets. We were not able to accurately assess body surface area in these piglets to correct for these differences, particularly for cardiac output. As we were interested in investigating relative changes in hemodynamic and functional parameters for each individual pig, these are summarized and plotted during continuous temperature reduction as values relative to baseline (Figure 1). Cardiac contractility was indexed as the maximum of left ventricular pressure first derivative ($dP/dt_{\max}$), which remained constant as the esophageal temperature decreased from 36°C to 29°C. The $dP/dt_{\max}$ decreased progressively between 28°C and 24°C ($P < 0.05$, with slightly less drop between 23°C and 20°C. The stroke volume and stroke work curves show a steady climb as temperature slowly decreases, peaking at 29°C ($p < 0.05$), followed by a descending limb starting at 28°C. The ascending limb for stroke volume and work occurs independently of systemic vascular resistance, which does not change during this period.. Thus, the data support the notion that cardiac contractile function increases as temperature declines to 29°C. Changes in stroke volume are balances somewhat by the negative chronotropy caused by hypothermia. Accordingly, cardiac output, and cardiac power (product of the left ventricular peak pressure and the maximum of cardiac output), which are time and heart rate dependent indices, are steady throughout the temperature range as stroke volume increases. The negative effect of increasing systemic peripheral resistance on cardiac work parameters is apparent, as these all decrease steadily as temperature declines below 28°C. Diastolic function or ventricular relaxation, indexed through $dP/dt_{\min}$, demonstrated sensitivity to hypothermia, and steadily decreased throughout the entire temperature range.

Arterial blood oxygen saturation was maintained at 100% throughout the protocol in each animal. The CO₂ partial pressure, and temperature corrected pH did not change over the temperature range of these protocols (Table 2), indicating that these factors did not influence the hemodynamics. Cardiopulmonary bypass decreased hemoglobin and systemic oxygen delivery from baseline. However, hemoglobin did not decrease further with a temperature drop. Systemic oxygen delivery was maintained at 30°C but was significantly reduced at 26°C and 20°C compared with 36°C on pump.

DISCUSSION

The therapeutic target temperatures for hypothermia, applied for brain or heart protection after insult in adults, are poorly defined. Data in children are even more limited although

extracorporeal life support is used for various indications. Graded or continuous temperature studies defining cardiac function and hemodynamics at multiple time points are few at any developmental level^{8,9}. Target temperature recommendations have been influenced by results from studies, which showed that hypothermia alters hemodynamic function in biphasic mode, increasing heart rate and blood pressure as temperature declines to 33°C, and then decreasing both with further temperature drop⁹. These studies in baboons implicated cycles in circulating catecholamines as the primary etiology for these hemodynamic phases.

We could not find a comparable published study, which investigated progressive cooling in an immature model. Two studies in neonatal pigs showed that cardiac output was decreased at specific temperatures such as 32°C, although other left ventricular performance parameters were not measured^{10,11}. Results from these prior studies are consistent with a recent clinical investigation, showing decreased stroke volume and cardiac output in neonates undergoing cooling to 33°C following perinatal asphyxia¹². Diminished heart rates in all these studies apparently caused reductions in cardiac output as stroke volume was maintained during mild or moderate hypothermia. Paradoxically, hypothermia is used regularly and effectively as a treatment for postoperative junctional ectopic tachycardia (JET) in infants and children^{13–15}. Several investigators noted that systemic hypothermia (32–34°C) led to a reduction in heart rate and automaticity in these patients with rises in systolic blood pressure^{13,14}.

The cited studies in infants and children all employed surface cooling supported by low ambient air temperature, and few clearly defined the time required for reaching target temperature^{10–12}. External surface temperature reduction methods used for clinical trials in adults after cardiac arrest have shown extremely slow cooling rates¹⁶. These methods, which include ice, cooling blankets, and drops in ambient air temperature, diminish therapeutic potential, as delayed cooling appears to adversely affect cardiac function. Central cooling as used in our study is highly efficient, but invasive and difficult to implement in certain scenarios such as the prehospital environment or emergency room. Endovascular cooling using catheters holds potential, but have not been specifically tested in children^{16–20}. Cooling using a veno-venous circuit for extracorporeal membrane oxygenation has been performed as a pilot study in human neonates, although only heart rate and blood pressure data are available²¹. Additionally, neonates included in the study were treated with pharmacological agents, such as dopamine, which can complicate interpretation with respect to hypothermia's hemodynamic effects. Therefore, limited data exist regarding rapid central cooling and cardiac function.

The paucity of data and the anticipation of technical advances in rapid cooling for infants and children prompted evaluation of the hemodynamic responses in this immature porcine model. The data indicate that cardiac output, power, and dp/dt_{max} are maintained until temperature drops below 29°C. Weisser et al using similar techniques, but somewhat older and larger pigs, also showed that stroke volume increased during transition from 37° to 31°C in pigs⁸. Although, minor discrepancies in addition to age exist between the two studies, they both reinforce the tenet that mild but rapidly induced hypothermia maintains or even increases cardiac systolic function and output during temperature transitions in this range. Diastolic function, indexed by $-dp/dt$, is adversely affected by decreasing temperature to 34°C. This finding is consistent with previous studies in older swine⁸, and diastolic dysfunction at this temperature can be exacerbated by pacing²².

Propofol was used as anesthesia throughout these protocols, and could have influenced cardiac function parameters. Several investigators have shown that this anesthetic inhibits contractile function in isolated cardiomyocytes^{23,24}. Additionally, propofol depression of contractile function in isolated perfused rat heart decreases with temperature²⁵. Leslie et al showed that hypothermia to 34°C increases propofol blood concentrations 28% in humans, and reduces compartmental clearance²⁶. However, Graham et al elegantly showed that propofol at

substantially higher doses (7.5 mg/kg/hr) than used in our study depresses $dP/dt_{\max}$ and $dP/dt_{\min}$ but did not affect load independent indices of systolic function in neonatal pigs²⁷. Furthermore no systolic or diastolic indices were further depressed by increasing doses up to 30 mg/kg/hr. Therefore, it is unlikely that the comparatively mild compartmental shifts and increases in blood concentration induced by hypothermia would affect the indices during the temperature reduction in this protocol.

As the cardiopulmonary bypass circuit was not primed with blood, the experimental conditions caused some hemodilution and normovolumic anemia. However, hemoglobin values were stable throughout the cooling procedure. Studies in somewhat larger pigs, than used in this study, have shown that hemoglobin does not significantly alter cardiac index or oxygen consumption at 38°C or 32°C until it drops below 4 gm/dl (23). As our experiments operated at hemoglobin values greater than 4.0, we believe that this degree of anemia minimally influenced our results. Nevertheless, the low hemoglobin does represent a limitation of our methods.

In summary, we have shown that rapid cooling to temperatures as low as 29°C does not depress systolic function or cardiac work in the immature heart. This data should be considered when developing target temperatures and ILCOR guidelines for the therapeutic use of hypothermia in children. We should note that these studies were performed in piglets which had not undergone hypoxic or ischemic insult. Conceivably the myocardium and vascular circuits respond differently to hypothermia after injury. Nevertheless, this study challenges existing paradigms that cardiac work is suppressed by moderate hypothermia in immature organisms, and serves as a template for further investigations for determining target therapeutic temperatures after global or focal ischemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cardiac function and hemodynamic parameters are shown as a percentile of baseline during rapid cooling induced by extracorporeal circuit. (*, $P \leq 0.05$ versus 36°C). Absolute baseline parameters are shown in Table I.

Table 1

Baseline Hemodynamics at 36°C

	MEAN	SE
LVP (mmHg)	111.14	10.87
LVEDP (mmHg)	6.42	1.25
CO (L/min)	1.51	0.2
CI (L/min/M ²)	4.87	0.65
HR (BPM)	128.37	10.6
dP/dt_{max} (mmHg/sec)	2637.4	337.65
Power_{max} (Watts)	1.156	0.265
SV (ml)	11.74	1.37
Work (Joules)	0.164	0.021
-dp/dt_{max} (mmHg/sec)	-1757.13	344.58
Resistance (dyne/cm/sec)	1.664	0.319

CO_{mean}, Mean value of cardiac output; DP, developed pressure; $\pm$ dP/dt_{max}, maximum of the positive or negative first derivative of left ventricular pressure; HR, heart rate; CI, cardiac index; Power_{max}, Maximum of cardiac power.

Table 2

Blood gas parameters and hemoglobin values during hypothermic protocol

	BASELINE (36°C)	On-pump (36°C)	30°C	26°C	20°C
SysO ₂ del (mM/min/M ²)	224.7 ±17.6	111.3 ±4.7 [*]	93.3 ±6.7 [*]	57.3±4.3 ^{*,+}	33.1±1.5 ^{*,+}
PCO ₂ a (mmHg)	41.6 ±4.2	40.1 ±3.9	45.3 ±6.1	46.5 ±5.3	42.9 ±2.3
pHa	7.41 ±0.04	7.41 ±0.04 [*]	7.39 ±0.08 [*]	7.39 ±0.07 [*]	7.39 ±0.05 [*]
Hgb (g/100ml)	10.7 ±0.38	5.1 ±0.40 [*]	4.9 ±0.30 [*]	4.9 ±0.20 [*]	4.5±0.15 [*]

Values are mean ± standard error. The arterial blood indices were determined at 36°C during baseline and with extracorporeal circulation, at 36°C, 30°C, 26°C and 20°C as described in Methods. The abbreviations used are: **SysO₂del**, systemic oxygen delivery (O₂ content × cardiac index); PCO₂a, arterial blood CO₂ partial pressure; pHa, arterial blood pH (

^{*} p < 0.05 versus baseline,
⁺ p < 0.05 versus On-pump 36°C).