Temperature Variation After Rewarming from Deep Hypothermic Circulatory Arrest Is Associated with Survival and Neurologic Outcome

Alessio Rungatscher, MD, PhD, FAHA,[1] Giovanni Battista Luciani, MD,[1]
Daniele Linardi, MD,[1] Elisabetta Milani, MD,[1] Leonardo Gottin, MD,[1]
Beat Walpoth, MD, PhD, FAHA,[2] and Giuseppe Faggian, MD[1]

Therapeutic hypothermia is recommended by international guidelines after cardio-circulatory arrest. However, the effects of different temperatures during the first 24 hours after deep hypothermic circulatory arrest (DHCA) for aortic arch surgery on survival and neurologic outcome are undefined. We hypothesize that temperature variation after aortic arch surgery is associated with survival and neurologic outcome. In the period 2010–2014, a total of 210 consecutive patients undergoing aortic arch surgery with DHCA were included. They were retrospectively divided into three groups by median nasopharyngeal temperature within 24 hours after rewarming: hypothermia (<36°C; $n = 65$), normothermia (36–37°C; $n = 110$), and hyperthermia (>37°C; $n = 35$). Multivariate stepwise logistic and linear regressions were performed to determine whether different temperature independently predicted 30-day mortality, stroke incidence, and neurologic outcome assessed by cerebral performance category (CPC) at hospital discharge. Compared with normothermia, hyperthermia was independently associated with a higher risk of 30-day mortality (28.6% vs. 10.9%; odds ratio [OR] 2.8; 95% confidence interval [CI], 1.1–8.6; $p = 0.005$), stroke incidence (64.3% vs. 9.1%; OR 9.1; 95% CI, 2.7–23.0; $p = 0.001$), and poor neurologic outcome (CPC 3–5) (68.8% vs. 39.6%; OR 4.8; 95% CI, 1.4–8.7; $p = 0.01$). No significant differences were demonstrated between hypothermia and normothermia. Postoperative hypothermia is not associated with a better outcome after aortic arch surgery with DHCA. However, postoperative hyperthermia (>37°C) is associated with high stroke incidence, poor neurologic outcome, and increased 30-day mortality. Target temperature management in the first 24 hours after surgery should be evaluated in prospective randomized trials.

Keywords: deep hypothermic circulatory arrest, aortic surgery, temperature management, hypothermia, neurologic outcome

Introduction

DEEP HYPOTHERMIC CIRCULATORY ARREST (DHCA) has been used for decades for cerebral protection during aortic arch surgery. Because DHCA dramatically reduces cerebral oxygen requirements, it enables the development of modern aortic surgery. However, the safe duration of arrest is limited by the risk of neurologic sequelae and recently, it has been only partially improved by the introduction of selective cerebral perfusion (SCP) (Linardi *et al.*, 2016).

Target temperature management has recently been demonstrated to be neuroprotective in cardiac arrest survivors (Dragancea *et al.*, 2015; Leary *et al.*, 2015). Therapeutic hypothermia and target temperature management are now recommended during the first 24 hours in postresuscitation care after cardiac arrest (Nunnally *et al.*, 2011; Nolan *et al.*, 2015).

However, a possible role for target temperature management during the first 24 hours after rewarming from DHCA has never been investigated.

On the other hand, although there is a general consensus that hyperthermia should be avoided during rewarming, the consequences of postrewarming hyperthermia remain unknown (Shum-Tim *et al.*, 1998). The development of hyperthermia in this setting is most frequently an adaptive response to cell damage, activation of inflammatory cascades, infections, or thermoregulatory dysregulation (Bar-Yosef *et al.*, 2004).

Although some clinical studies in comatose cardiac arrest survivors found a significant association between postresuscitation hyperthermia and worse outcome, the relationship between temperature after rewarming from DHCA and clinical outcomes remains largely unclear (Bro-Jeppesen *et al.*, 2013; Lee *et al.*, 2015).

We sought to evaluate the influence of hyperthermia and hypothermia during the first 24 hours after rewarming from DHCA and the association of temperature variation with survival and neurologic outcome.

Materials and Methods

Study design

This was a retrospective observational cohort study of consecutive adult patients undergone aortic arch surgery with DHCA at the Division of Cardiac Surgery University Hospital of Verona in the period January 1, 2010 to December 31, 2014. Exclusion criteria were documented of suspected preoperative infections and signs of systemic inflammatory response syndrome.

Patients were divided into three groups by the median nasopharyngeal temperature within 24 hours after rewarming from DHCA: hypothermia (<36°C), normothermia (36–37°C), and hyperthermia (>37°C). The nasopharyngeal temperature was recorded hourly. There were no existing protocols on temperature management in the intensive care unit. Patients undergoing active rewarming in the intensive care unit were excluded.

Surgical and anesthetic technique

All patients underwent aortic arch replacement to treat aortic arch aneurysm or dissection. General anesthesia was performed in a standardized fashion with propofol, sufentanil, vecuronium, and isoflurane. The near-infrared spectroscopy was monitored throughout surgery. After systemic heparinization (300 IU/kg), cardiopulmonary bypass (CPB) and systemic cooling were initiated to the target temperature of 16–20°C. Acid-base management was based on pH-stat principles. Repeated administration of cold cardioplegia solution and topical cooling were used for myocardial protection. The arterial cannulation site was primarily the femoral artery, and venous cannulation was the right atrium.

On reaching the target temperature, 500 mg of thiopental was administered, the patient's head was packed in ice, and DHCA was initiated. An SCP was performed according to the surgeon's judgment (target flow, 10–20 mL/[kg·min] via bilateral carotid artery infusion).

After aortic arch repair, the aortic graft was cannulated for antegrade arterial perfusion; on commencement of CPB, the patient was warmed to 36.5°C (avoiding blood-bath gradients of >10°C) and weaned from CPB. Active rewarming was complete on reaching a nasopharyngeal temperature of 36.5°C. Perioperative blood products were transfused according to the attending physician's judgment, taking into account the patient's clinical status and available laboratory values.

Study outcome

Patient demographics and perioperative risk factors were abstracted by using medical records and recorded in an electronic database (Microsoft Access; Microsoft, Seattle, WA). The following end points were recorded for each patient: 30-day mortality, perioperative stroke incidence, and neurologic outcome assessed by the cerebral performance category (CPC) score. The CPC score reflects both mortality

TABLE 1. PREOPERATIVE VARIABLES AND RISK FACTORS

	Normothermia (n = 110)	Hypothermia (n = 65)	Hyperpyrexia (n = 35)	p
Age, years	65 ± 13	67 ± 11	59 ± 14	0.42
Male sex, %	68	65	69	0.37
Diabetes mellitus, %	8	9	7	0.35
Preop. serum creatinine level (mg/dL)	1.20 ± 1.05	1.25 ± 1.01	1.26 ± 0.98	0.90
Renal insufficiency, %	9	11	13	0.25
Hypertension, %	85	78	88	0.85
Carotid disease, %	18	15	12	0.48
Coronary artery disease, %	21	29	28	0.25
Congestive heart failure, %	10	12	15	0.70
History of stroke, %	5	6	9	0.18
WBC (10^9/L)	11.6 (9.8–14.2)	12.0 (10.2–13.9)	11.4 (8.2–13.6)	0.90
PCT (μg/L)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	0.90
Temperature (°C)	36.5 (35.5–37.5)	37.0 (36.5–37.5)	36.5 (36.0–37.0)	0.95
Hemiarch or partial arch surgery, %	94	91	89	0.65
Total arch surgery, %	6	9	11	0.65
Emergent surgery, %	42	38	41	0.87
Urgent surgery, %	13	16	18	0.67
Prior sternotomy, %	5	7	10	0.13
Acute aortic dissection, %	42	38	41	0.87
First open aortic surgery, %	73	67	65	0.18
CPB duration, min	185 ± 76	220 ± 65	190 ± 80	0.09
DHCA duration, min	34 ± 21	41 ± 28	39 ± 19	0.43
SCP, %	41	38	49	0.06

CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; PCT, procalcitonin; SCP, selective cerebral perfusion; WBC, white blood cells.

TABLE 2. POSTOPERATIVE OUTCOMES IN PATIENTS (N=210) UNDERGOING AORTIC ARCH REPAIR
WITH DEEP HYPOTHERMIC CIRCULATORY ARREST AND DIFFERENT TEMPERATURE
DURING THE FIRST 24 HOURS AFTER REWARMING

Postoperative outcome	Normothermia (n=110)	Hypothermia (n=65)	Hyperthermia (n=35)	Hypothermia versus normothermia			Hyperthermia versus normothermia		
				p	OR	95% CI	p	OR	95% CI
30-day mortality, %	10.9	12.3	28.6	0.1	1.3	0.4–1.8	0.005	2.8	1.1–8.6
In-hospital death, %	8.2	9.2	25.7	0.1	1.1	0.3–1.9	0.004	3.5	1.8–7.5
Stroke, %	9.1	6.5	64.3	0.2	0.6	0.1–1.2	0.001	9.1	2.7–23
CPC (3–5), %	39.6	35.7	68.8	0.2	0.5	0.1–1.1	0.001	4.8	1.4–8.7
Reoperation for bleeding, %	11.4	12.1	10.9	0.1	1.1	0.2–2.0	0.1	0.9	0.2–1.8
Hospital stay, days	16±15	18±12	21±9	0.8	—	—	0.5	—	—

CI, confidence interval; CPC, cerebral performance category; OR, odds ratio.

and morbidity (Jacobs and Nadkarni, 2009); these score values were assessed at follow-up, which was performed at least 6 months after surgery. A favorable outcome was defined as a CPC score of 1 or 2, that is, alive with good cerebral performance or sufficient cerebral function for independent activities of daily life, with or without mild neurological or psychological deficits; ability to work in a sheltered environment was considered to indicate a CPC score of 2. The CPC scores 3 to 5 were recorded as unfavorable outcomes.

To assess the effect of different postoperative temperature on transfusion requirements, bleeding determining reoperation and blood components transfused within 48 hours of surgery were recorded.

Statistical analysis

All statistical analyses were performed by using PASW/SPSS statistical software version 18 (IBM, Inc., Chicago, IL). Continuous variables were expressed as the mean ± standard deviation, and categorical (frequency) variables were expressed as percentages. Univariate logistic regression analyses were initially conducted to test for between-groups differences in patient preoperative demographics, risk factors, and preoperative medications (Table 1). Categorical variables were analyzed with the χ^2 or Fisher exact tests. Continuous variables were first examined for normality of distribution: The t-test was used for those variables with normal distributions, and the nonparametric Wilcoxon rank-sum test was applied for the variables with skewed distributions. In all tests, two-tailed p-values were calculated.

To control for demographic factors, medications, and perioperative and operative risk factors, multivariate stepwise logistic regression was performed on all patient data to determine whether hypothermia and hyperthermia were independently associated with study outcomes than with normothermia. Multivariable Cox proportional hazards models were applied after checking for underlying assumptions of linearity, proportionality, and lack of interactions and odds ratio (OR) and 95% confidence interval (CI) are reported.

Results

A total of 210 consecutive patients underwent aortic arch surgery with DHCA and were considered for the present study. Normothermia characterized the first 24 hours in the

ICU in 110 patients; an additional, 65 patients were hypothermic and 35 more patients experienced hyperthermia.

Patient demographics and perioperative risk factors are presented in Table 1. Patients in the hyperthermia group had a marginally higher occurrence of SCP ($p=0.06$), whereas CPB duration tended to be higher in the hypothermia group ($p=0.09$). Of note, the groups did not significantly differ with respect to age, gender distribution, diabetes, history of smoking, and renal insufficiency.

Postoperative outcomes are summarized in Table 2. In-hospital mortality was 8% (9/110) in the normothermia group, 9% (6/65) in the hypothermia group, and 26% (9/35) in the hyperthermia group. Multiorgan system failure was the most common cause of death. There were five additional 30-day all-cause of death (three in normothermia, two in hypothermia, and one in hyperthermia). To determine whether hypothermia and hyperthermia were independently associated with a significantly higher risk of in-hospital death and 30-day all-cause mortality, multivariate stepwise logistic analysis was performed, controlling for patients' demographics, preoperative risk factors, and intraoperative variables (Figs. 1 and 2). Hyperthermia was independently associated with a higher risk of in-hospital death ($p=0.001$) and 30-day all-cause mortality ($p=0.005$) than normothermia. Hypothermia was not different from normothermia for in-hospital mortality ($p=0.2$) and 30-day all-cause mortality ($p=0.1$).

The incidence of stroke in the hyperthermia group was ninefold higher than in the normothermia group (64.3% vs. 9.1%; $p=0.001$; OR, 9.1; 95% CI, 2.7–23.0). Hypothermia had a lower incidence of stroke compared with normothermia, but the difference was not significant (6.5% vs. 9.1%; $p=0.02$).
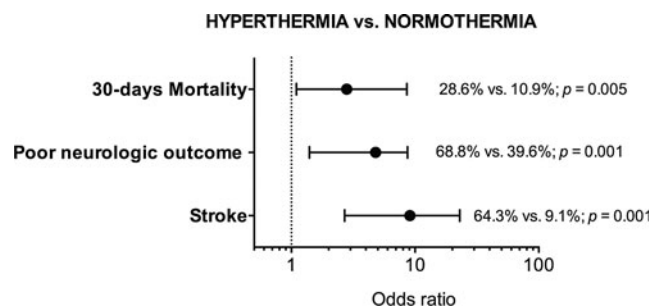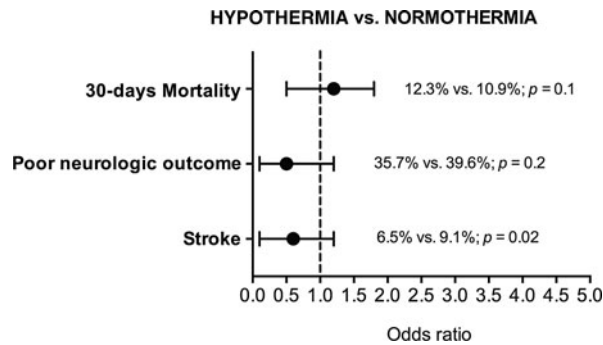

FIG. 1. Hyperthermia group compared with normothermia group. Odds ratio and rates of the primary end points.

HYPOTHERMIA vs. NORMOTHERMIA

FIG. 2. Hypothermia group compared with normothermia group. Odds ratio and rates of the primary end points.

Poor neurologic outcome defined as a CPC score between 3 and 5 was higher in the hyperthermia group than in the normothermia group (68.8% vs. 39.6%; $p = 0.001$; OR 4.8; 95% CI, 1.4–8.7.). Indeed, hypothermia was demonstrated to be neither detrimental nor preventive on poor neurological outcome compared with normothermia (35.7% vs. 39.6%; $p = 0.2$; OR 0.5; 95% CI, 0.1–1.3).

No significant difference was observed between groups in the amount of transfused packed red blood cells, fresh-frozen plasma, and pooled platelets (Table 3).

Discussion

Cerebral ischemia is the major pathogenic factor leading to neuronal dysfunction and death after aortic arch surgery (Shimizu et al., 2013). Since the introduction of aortic arch replacement in the 1950s by DeBakey and Cooley, the two main methods of brain protection during this procedure have been different degrees of hypothermia and adjuncts for cerebral perfusion (Tsai et al., 2013). The ideal temperature during hypothermic circulatory arrest remains unclear, and the introduction of SCP has generated a debate on whether deep hypothermia or moderate hypothermia is preferable (Linardi et al., 2016).

Most of the efforts to improve neuroprotection and general outcome in aortic arch surgery are limited to the ischemic phase. However, it is reasonable to identify at least two additional critical phases for neuroprotection. The first is reperfusion with consequent rewarming. Any neuroprotection afforded by hypothermia is counterbalanced by damage occurring during the rewarming process (Grigore et al., 2002). Indeed, brain temperature, as measured in the jugular bulb, frequently exceeds 38°C during rewarming (Cook et al., 1994). In addition, rewarming is associated with jugular bulb desaturation, which, in turn, has been associated with neurocognitive dysfunction (Croughwell et al., 1994; Kadoi et al., 2001).

The second additional critical phase of neuroprotection is the early postoperative period. The concept of target temperature management, which is nowadays recommended during the first 24 hours after cardiac arrest, has not been considered after circulatory arrest induced for aortic arch surgery.

Numerous studies, both in experimental models of cerebral ischemia and in stroke in humans, have repeatedly demonstrated the deleterious effects of hyperthermia and the protective effects of hypothermia (Chen et al., 1991; Kim et al., 1996; Rungatscher et al., 2012, 2013). The pathophysiological explanation for this deleterious effect relates to the existence of zones of ischemic but potentially viable tissue known as the penumbra. This area is vulnerable to secondary insults, and its fate greatly influences the ultimate neurological outcome (Bar-Yosef et al., 2004). Increased temperature is associated with an increased metabolic rate, potentially worsening the delicate balance between oxygen supply and demand existing in the ischemic penumbra (Wang et al., 2009). Hyperthermia is also linked with other potentially harmful effects, including accentuated release of toxic excitatory neurotransmitters, increased oxygen free-radical formation, blood-brain barrier disruption, cytoskeleton destruction, increased number of ischemic depolarizations, and increased neural intracellular lactic acidosis (Karaszewski et al., 2009; Wang et al., 2009). Even mild degrees of hyperthermia might be harmful; animal models of cerebral ischemia found that a temperature increase of as small as 1–2°C was enough to increase damage (Saini et al., 2009).

Against this background, it is plausible that cerebral hyperthermia, often accompanying the rewarming stage or the first hours after intervention, may exacerbate neurological damage after DHCA.

Theoretically, two approaches can be pursued to try to prevent rewarming-induced cerebral hyperthermia. One approach is to slow the rate of rewarming by limiting the difference between blood temperature and the water temperature in the CPB heat-exchanger apparatus. This approach reduced the incidence of jugular bulb desaturation and postoperative neurocognitive dysfunction (Grigore et al., 2009; Gordan et al., 2010). A possible disadvantage of this approach is prolongation of the rewarming stage, which may increase overall CPB time.

The second approach to prevent cerebral hyperthermia is to limit the target rewarming temperature. Traditionally, separation from bypass is attempted after normothermia has been accomplished. Although this separation temperature varies among institutions, a nasopharyngeal temperature of 36–37°C would likely be a common temperature goal. However, brain temperature during the rewarming phase has been shown to be ∼1–3°C higher than the nasopharyngeal temperature and a significant discrepancy remains well into the postoperative period (Bar-Yosef et al., 2004). Limiting the rewarming nasopharyngeal temperature to 34–35°C

TABLE 3. POSTOPERATIVE TRANSFUSION REQUIREMENTS (48 HOURS) IN PATIENTS ($N = 210$) UNDERGOING SURGICAL AORTIC ARCH REPAIR WITH DEEP HYPOTHERMIC CIRCULATORY ARREST AND WITH DIFFERENT TEMPERATURE DURING THE FIRST 24 HOURS AFTER REWARMING

Postoperative transfusion	Normothermia (n = 110)	Hypothermia (n = 65)	Hyperthermia (n = 35)	p
Packed red blood cells, units	6.5 ± 4.0	8.0 ± 3.5	5.0 ± 2.0	0.1
Fresh-frozen plasma, units	8.0 ± 5.5	7.0 ± 6.5	7.0 ± 4.0	0.8
Pooled platelets, units	4.0 ± 3.0	8.5 ± 6.0	4.5 ± 5.0	0.3

should, therefore, prevent cerebral hyperthermia. In fact, this approach was used in a randomized, controlled trial with a demonstrable improvement in neurocognitive function after coronary artery bypass surgery (Nathan *et al.*, 2001). The obvious drawback with this approach is the occurrence of mild hypothermia in the first several hours after separation from CPB, especially because separation from CPB is usually accompanied by a continued decrease in temperature (referred to as after-drop) of at least 0.5°C.

In addition, hypothermia is known to reduce the activity of enzymes that are involved in platelet activation pathways and clotting factors, both of which can increase transfusion requirements after surgical intervention (Insler *et al.*, 2000). In the present study, transfusion requirement did not differ significantly between hypothermia and normothermia groups. Similarly, there was no observed difference in the incidence of surgical re-exploration.

It should be noted that to date no recommendation for a guideline is provided regarding optimal temperature for weaning from CPB due to insufficient evidence (Engelman *et al.*, 2015).

Excessive rewarming after DHCA may induce cerebral hyperthermia, negating the beneficial effect of the previous hypothermic period. Limiting the rewarming temperature may, thus, allow the full realization of the theoretical benefits of DHCA. Although the present study fails to demonstrate a positive association with mild hypothermia during 24 hours after intervention, hyperthermia was demonstrated to be associated with higher mortality, higher stroke incidence, and poor neurologic outcome. Mild postoperative hypothermia was not associated with increased transfusion requirements; however, it may have at least a preventive role in the insidious onset of hyperthermia.

This study was limited in that it was a retrospective cohort study from a single institution. In addition, despite the use of logistic regression models to adjust for potential confounders that may have affected outcomes, other immeasurable factors, nonetheless, may have biased the results.

To define the temperature course and to compare groups, we considered median nasopharyngeal temperature within 24 hours after rewarming and not peak values. The threshold temperature between normothermia and hyperthermia was considered to be 37°C (Zeiner *et al.*, 2001).

From the present study, it is not possible to determine whether hyperthermia is the consequence and not a possible cause of neurologic damage. However, the aim of our study was not to focus on causes of hyperthermia after circulatory arrest but to demonstrate the association with temperature variation and outcome.

Although the cause and effect of elevated temperature on survival and neurologic recovery were not proved, it seems prudent to rigorously control temperature in the first 24 hours after rewarming.

Conclusions

Postoperative hyperthermia is independently associated with higher mortality and neurologic morbidity after aortic arch surgery with DHCA. Postoperative hypothermia is not associated with better outcome compared with normothermia. Clinical trials evaluating the efficacy of target temperature management after rewarming are needed.

References

Bar-Yosef S, Mathew JP, Newman MF, Landolfo KP, Grocott HP; Neurological Outcome Research Group, *et al.* Prevention of cerebral hyperthermia during cardiac surgery by limiting on-bypass rewarming in combination with post-bypass body surface warming: a feasibility study. Anesth Analg 2004;99:641–646.

Bro-Jeppesen J, Hassager C, Wanscher M, Søholm H, Thomsen JH, Lippert FK, *et al.* Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation 2013;84:1734–1740.

Chen H, Chopp M, Welch KM. Effect of mild hyperthermia on the ischemic infarct volume after middle cerebral artery occlusion in the rat. Neurology 1991;41:1133–1135.

Cook DJ, Oliver WC, Jr., Orszulak TA, Daly RC. A prospective, randomized comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994;107:1020–1028.

Croughwell ND, Newman MF, Blumenthal JA, White WD, Lewis JB, Frasco PE, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. Ann Thorac Surg 1994;58:1702–1708.

Dragancea I, Horn J, Kuiper M, Friberg H, Ullén S, Wetterslev J, *et al.* Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: results from a randomised controlled clinical trial. Resuscitation 2015;93:164–170.

Engelman R, Baker RA, Likosky DS, Grigore A, Dickinson TA, Shore-Lesserson L, *et al.* The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical Practice Guidelines for Cardiopulmonary Bypass—temperature management during cardiopulmonary bypass. Ann Thorac Surg 2015;100:748–757.

Gordan ML, Kellermann K, Blobner M, Nollert G, Kochs EF, Jungwirth B. Fast rewarming after deep hypothermic circulatory arrest in rats impairs histologic outcome and increases NFκB expression in the brain. Perfusion 2010;25:349–354.

Grigore AM, Grocott HP, Mathew JP, Phillips-Bute B, Stanley TO, Butler A, *et al.* The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. Anesth Analg 2002;94:4–10.

Grigore AM, Murray CF, Ramakrishna H, Djaiani G. A core review of temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg 2009;109:1741–1751.

Insler SR, O'Connor MS, Leventhal MJ, Nelson DR, Starr NJ. Association between postoperative hypothermia and adverse outcome after coronary artery bypass surgery. Ann Thorac Surg 2000;70:175–181.

Jacobs I, Nadkarni V. Utstein cardiac arrest outcome reports. Resuscitation 2009;80:290.

Kadoi Y, Saito S, Goto F, Fujita N. Decrease in jugular venous oxygen saturation during normothermic cardiopulmonary bypass predicts short-term postoperative neurologic dysfunction in elderly patients. J Am Coll Cardiol 2001;38:1450–1455.

Karaszewski B, Wardlaw JM, Marshall I, Cvoro V, Warto-lowska K, Haga K, et al. Early brain temperature elevation and anaerobic metabolism in human acute ischaemic stroke. Brain 2009;132:955–964.

Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. Stroke 1996;27:2274–2280.

Leary M, Blewer AL, Delfin G, Abella BS. Variability in postarrest targeted temperature management practice: implications of the 2015 guidelines. Ther Hypothermia Temp Manag 2015;5:184–187.

Lee BK, Song KH, Jung YH, Lee DH, Youn CS, Lee SM, et al. The influence of post-rewarming temperature management on post-rewarming fever development after cardiac arrest. Resuscitation 2015;97:20–26.

Linardi D, Faggian G, Rungatscher A. Temperature management during circulatory arrest in cardiac surgery. Ther Hypothermia Temp Manag 2016;6:9–16.

Nathan HJ, Wells GA, Munson JL, Wozny D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. Circulation 2001;104:85–91.

Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 2015;41:2039–2056.

Nunnally ME, Jaeschke R, Bellingan GJ, Lacroix J, Mourvillier B, Rodriguez-Vega GM, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. Crit Care Med 2011;39:1113–1125.

Rungatscher A, Linardi D, Giacomazzi A, Tessari M, Menon T, Mazzucco A, et al. Cardioprotective effect of δ-opioid receptor agonist vs. mild therapeutic hypothermia in a rat model of cardiac arrest with extracorporeal life support. Resuscitation 2013;84:244–248.

Rungatscher A, Linardi D, Tessari M, Menon T, Luciani GB, Mazzucco A, et al. Levosimendan is superior to epinephrine in improving myocardial function after cardiopulmonary bypass with deep hypothermic circulatory arrest in rats. J Thorac Cardiovasc Surg 2012;143:209–214.

Saini M, Saqqur M, Kamruzzaman A, Lees KR, Shuaib A; VISTA Investigators. Effect of hyperthermia on prognosis after acute ischemic stroke. Stroke 2009;40:3051–3059.

Shimizu H, Matayoshi T, Morita M, Ueda T, Yozu R. Total arch replacement under flow monitoring during selective cerebral perfusion using a single pump. Ann Thorac Surg 2013;95:29–34.

Shum-Tim D, Nagashima M, Shinoka T, Bucerius J, Nollert G, Lidov HG, et al. Postischemic hyperthermia exacerbates neurologic injury after deep hypothermic circulatory arrest. J Thorac Cardiovasc Surg 1998;116:780–792.

Tsai JY, Pan W, Lemaire SA, Pisklak P, Lee VV, Bracey AW, et al. Moderate hypothermia during aortic arch surgery is associated with reduced risk of early mortality. J Thorac Cardiovasc Surg 2013;146:662–667.

Wang CX, Stroink A, Casto JM, Kattner K. Hyperthermia exacerbates ischaemic brain injury. Int J Stroke 2009;4:274–284.

Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007–2012.

Address correspondence to:
Alessio Rungatscher, MD, PhD, FAHA
Department of Surgery
Division of Cardiac Surgery
University of Verona
Piazzale Stefani 1
Verona 37126
Italy

E-mail: alessio.rungatscher@univr.it