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Temperature analysis of aortic repair with hypothermic circulatory arrest to quantify the injury by cooling

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Key question

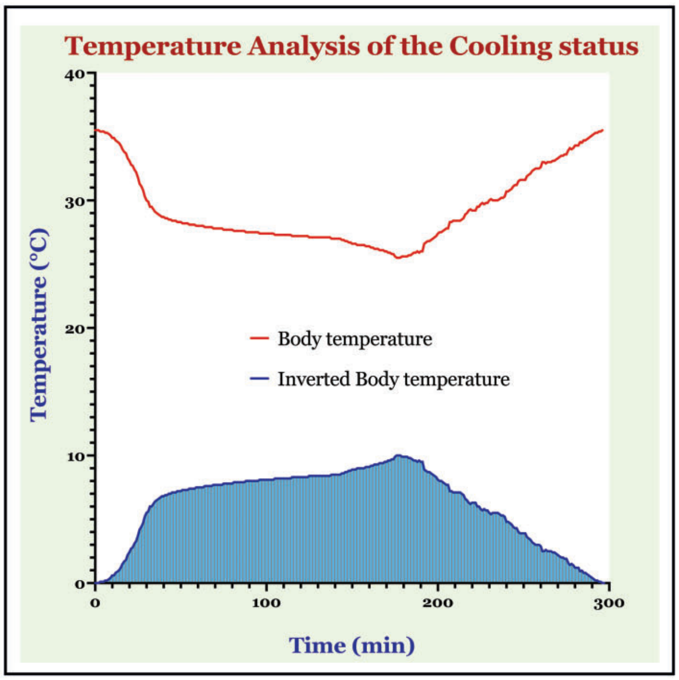
How can the cooling status affect the clinical outcome of aortic surgery with hypothermic circulatory arrest?

Key finding(s)

The cooling area, which indicated the degree of cooling, was significantly associated with the major adverse outcome.

Take-home message

The results of temperature analysis can be an important reference to determine an accurate temperature for proximal aortic repair.



Abstract

OBJECTIVES: We analyzed the temperature in proximal aortic repair with moderate hypothermic circulatory arrest (HCA) and evaluated the effect of the cooling status on postoperative outcomes.

METHODS: A total of 340 patients who underwent elective ascending aortic replacement or total arch replacement with moderate HCA from December 2006 to January 2021 were studied. The change in body temperature trends recorded during surgery was shown graphically. Several parameters, such as the nadir temperature, cooling speed and the degree of cooling (cooling area), which was the area under curve of inverted temperature trends from cooling to rewarming as calculated by the integral method, were analyzed. The relationships between these variables and a major adverse outcome (MAO) postoperatively defined as prolonged ventilation (>72 h), acute renal failure, stroke, reoperation for bleeding, deep sternal wound infection or in-hospital death were evaluated.

RESULTS: An MAO was observed in 68 patients (20%). The cooling area was larger in the MAO group than in the non-MAO group (1668.7 vs 1383.2°C min; $P < 0.0001$). A multivariate logistic model showed that old myocardial infarction, peripheral vascular disease, chronic renal dysfunction, cardiopulmonary bypass time and the cooling area were independent risk factors for an MAO (odds ratio = 1.1 per 100°C min; $P < 0.001$).

CONCLUSIONS: The cooling area, which indicates the degree of cooling, shows a significant relationship with an MAO after aortic repair. This finding indicates that the cooling status with HCA can affect clinical outcomes.

Keywords: Aortic repair • Hypothermic circulatory arrest • Temperature analysis • Clinical outcome

ABBREVIATIONS

AAR	Ascending aortic replacement
CPB	Cardiopulmonary bypass
HCA	Hypothermic circulatory arrest
MAO	Major adverse outcome
OR	Odds ratio
TAR	Total arch replacement

INTRODUCTION

Ascending aortic replacement (AAR) and total arch replacement (TAR) with hypothermic circulatory arrest (HCA) for an aortic aneurysm are established surgeries and have favourable clinical results [1–3]. However, major postoperative complications still occur, such as neurological dysfunction, acute renal failure and respiratory failure. One of the causes of these complications is considered to be hypothermia, which is indispensable to AAR/TAR. Hypothermia is associated with coagulopathy, an increased inflammatory response and organ dysfunction [4–7]. Longer and deeper hypothermia causes greater injury by cooling and adverse outcomes more frequently. However, no previous studies have evaluated the temperature during surgery with HCA in detail or examined the relationships between HCA and clinical outcomes. Therefore, performing temperature analysis, which quantifies the degree of cooling and identifies factors related to temperature trends, may be clinically important. The results of this analysis may lead to an investigation of the optimal temperature and risk reduction for aortic surgery with HCA. In the present study, we analyzed body temperature trends in elective proximal aortic repair with moderate HCA during surgery to quantify the cooling status and evaluate its effect on the clinical outcome.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Institutional Review Board of Sapporo Medical University School of Medicine and Otaru General Hospital (332-1027, 2021-7-8). The need for informed consent was waived owing to the retrospective nature of the study.

Patients

From December 2006 to January 2021, 360 patients underwent elective AAR or TAR with moderate HCA for aortic aneurysm at our 2 referral institutions. Of these patients, we included 340 patients in the present study. Twenty patients were excluded because of insufficient recorded temperature data during surgery.

Study design and definition

The clinical data of the patients who underwent elective AAR/TAR at our referral institution were analyzed retrospectively, and the early outcomes were summarized. An analysis for temperature during surgery was performed as described below.

A major adverse outcome (MAO) was defined according to a previous study and the standard Society of Thoracic Surgeons database as follows: prolonged ventilation (>72 h), acute renal failure, stroke, reoperation for bleeding, deep sternal wound infection or in-hospital death [1]. Postoperative renal failure was defined as doubling of the serum creatinine concentration or the requirement for haemodialysis. A risk model for MAO was created using multivariate logistic regression analysis, including the results of temperature analysis. An estimation model was then established to investigate variables that are related to the cooling area.

Temperature analysis

Body temperatures used for analysis were extracted from anaesthesia records and cardiopulmonary bypass (CPB) data of the operation. Temperature trends from the beginning of cooling to achieving rewarming during the operation were plotted in a graph (Fig. 1). Furthermore, the change in temperature (per 1 min), which was inverted as a positive value based on the beginning of cooling, was also plotted (Fig. 1). The following variables were analyzed: the nadir temperature (°C), maximum change in temperature (°C), total cooling time (time from the start of cooling to achieving rewarming) (min) (Fig. 1A), cooling speed (maximum change in temperature/time from the start of cooling to reach the nadir temperature) (°C/min) (Fig. 1B), degree of cooling (cooling area [area under a plotted inverted temperature trends curve]) (°C/min) (Fig. 1C), warming time (time from the start of cooling to achieve rewarming) (min) and warming speed (change in temperature at the start of rewarming/warming time) (°C/min) (Fig. 1D). The cooling area was calculated by the integral method using Simpson's rule.

For body temperature, rectal, bladder and nasopharyngeal recorded temperatures were analyzed, and the mean of these values was used for the analysis. All temperature analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). Patients who had incorrect or irregularly recorded data were excluded from the analysis. All analyzed data

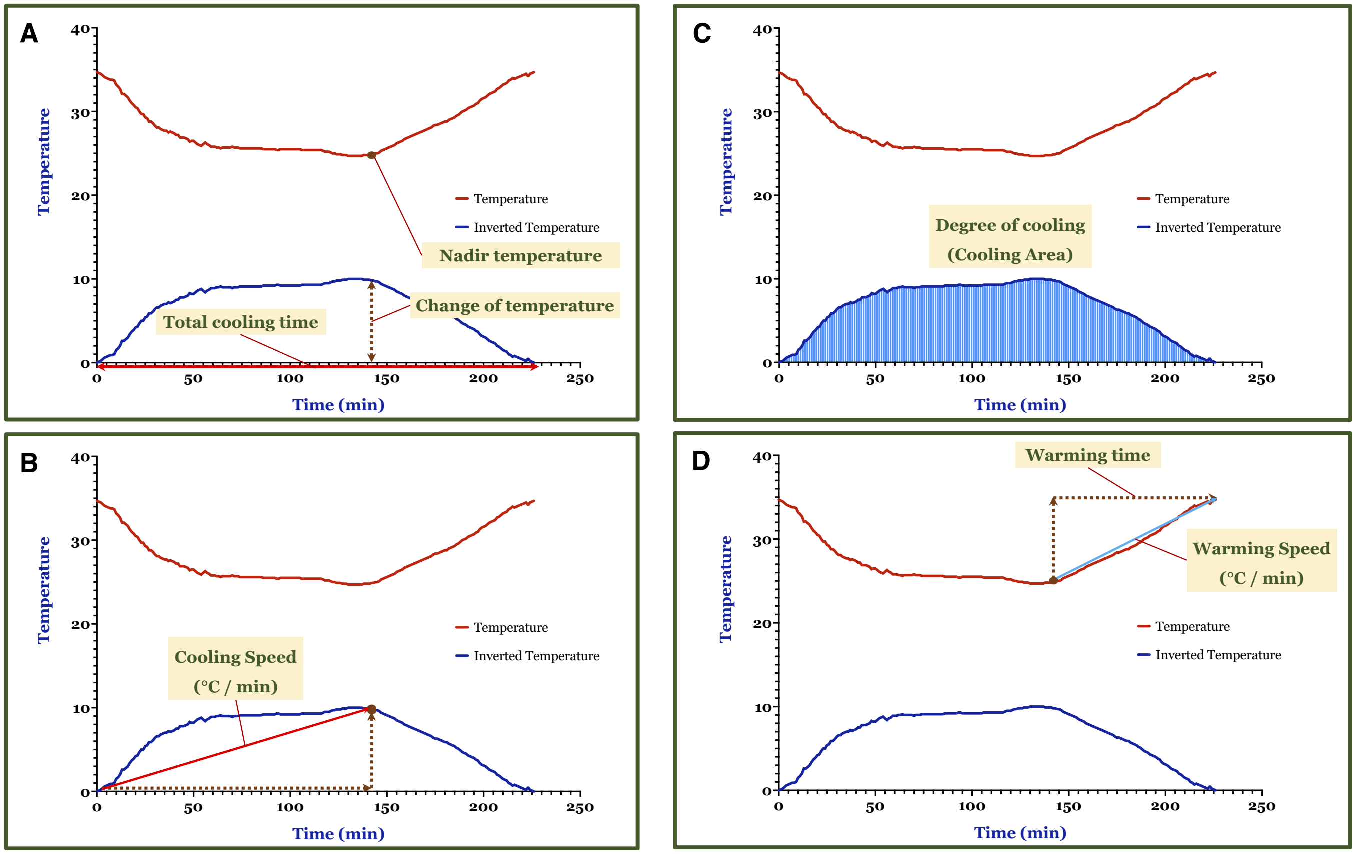


Figure 1: Temperature trends and inverted trends as positive values from cooling to rewarming and analyzed variables. (**A**) Nadir temperature (°C), maximum change in temperature (°C) and total cooling time (min). (**B**) Cooling speed (°C/min). (**C**) Degree of cooling = cooling area (°C min). (**D**) Warming time (min) and warming speed (°C/min).

were evaluated and assessed according to consensus between 2 investigators.

Surgical and cardiopulmonary techniques

The cannulation sites were selected from the ascending aorta, axillary artery and femoral arteries. CPB was established with bicaval drainage. Myocardial protection was achieved with the retrograde infusion of cold blood cardioplegia. Moderate HCA was performed when the body temperature was <25°C and the tympanic temperature was <20°C. Three antegrade selective cerebral perfusion cannulas were used for the brachiocephalic artery, left carotid artery and left subclavian artery in all cases. The tools used for cerebral monitoring included cerebral perfusion pressure, a radial arterial pressure line, electroencephalography and regional oxygen saturation in both frontal lobes as measured by near-infrared spectroscopy.

Temperature management for cooling and rewarming during CPB was performed in accordance with previous studies and guidelines [8–11]. The arterial outlet blood temperature was limited to <37°C to avoid cerebral hyperthermia. Temperature gradients between the arterial outlet and venous inflow on the oxygenator during cooling and rewarming did not exceed 10°C to avoid the generation of gaseous emboli and outgassing. A rewarming rate of 0.5°C/min was maintained to achieve the desired temperature for separation from bypass.

Statistical analysis

Statistical analysis was performed using the *t*-test for continuous variables and the χ^2 test and Fisher's exact test for categorical variables. A logistic regression model was used to identify the predominant predictors of an MAO. The estimation model for the cooling area was established using multiple linear regression analysis. The variables that showed significance in a univariate analysis were entered into a multivariate analysis. The best model of the logistic and linear regression models was obtained by backward stepdown selection using Akaike's information criterion. The cut-off values of the cooling area in Fig. 2 were detected using the K-mean clustering method. All data are expressed as mean ± standard deviation. Statistical significance was set at $P < 0.05$ (two-sided). All data analyses were performed using the statistical program R version 4.1.1 (R Foundation for Statistical Computing, http://www.r-project.org/).

RESULTS

The patients' demographics are shown in Table 1. Among the 340 patients, the mean age was 68.9 ± 11.6 years and 222 (65.3%) were men.

The intraoperative and postoperative results are shown in Table 2. AAR was performed in 112 patients (32.9%) and TAR was performed in 228 (67.1%). The mean HCA time was 62.4 ± 25.3 min. Stroke occurred in 16 (4.7%) patients, acute renal

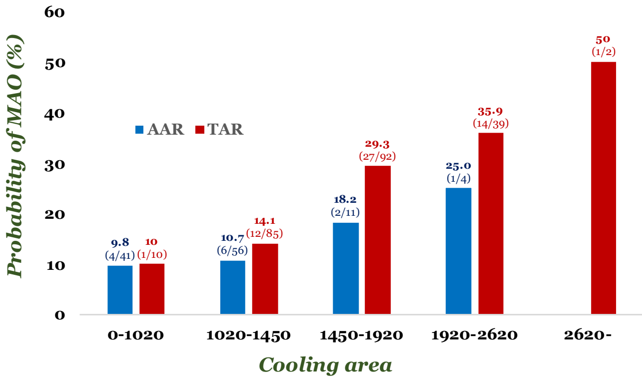


Figure 2: Relationship between the cooling area and the probability of an MAO in the AAR and TAR groups. AAR: ascending aortic replacement; MAO: major adverse outcome; TAR: total arch replacement.

Table 1: Patient demographic and clinical characteristics

Variable	
Patients	340
Age (years)	68.9 ± 11.6
Male sex	222 (65.3)
BMI (kg/m^2)	23.4 ± 3.31
BSA (m^2)	1.63 ± 0.19
Hypertension	126 (37.1)
Chronic obstructive pulmonary disease	138 (40.6)
Previous cardiac surgery	23 (6.8)
Diabetes mellitus	42 (12.4)
Coronary artery disease	38 (11.2)
Previous myocardial infarction	9 (2.6)
Cerebrovascular disease	46 (13.5)
Peripheral vascular disease	22 (6.5)
Chronic kidney disease	84 (24.7)
Haemodialysis	9 (2.6)
Congestive heart failure	55 (16.2)
Atrial fibrillation	20 (5.9)

Data are presented as the mean ± standard deviation or as the number (percentage) as appropriate.
BMI: body mass index; BSA: body surface area.

Table 2: Intraoperative and postoperative findings

Variable	
Operative procedure	
AAR	112 (32.9)
TAR	228 (67.1)
Concomitant procedure	93 (27.4)
Coronary artery bypass grafting	23 (6.8)
Valve	57 (16.8)
Aortic root (Bentall or David)	25 (7.4)
Cannulation site	
Ascending aorta	197 (57.9)
Axillary artery	118 (34.7)
CFA	11 (3.2)
Axillary artery + CFA	14 (4.1)
CPB time (min)	237.2 ± 7.76
SCP time (min)	111.5 ± 62.1
HCA time (min)	62.4 ± 25.3
Cardiac ischaemic time (min)	164.8 ± 54.9
Nadir temperature (°C)	23.93 ± 2.1
Transfusion requirements (U)	
Packed red blood cells	12.9 ± 6.4
Fresh-frozen plasma	11.7 ± 4.7
Platelets	22.7 ± 5.2
Postoperative outcome	
Stroke	16 (4.7)
Acute renal failure	11 (3.2)
Prolonged ventilation (>72 h)	27 (7.9)
Deep sternal wound infection	0 (0)
Reoperation for bleeding	13 (3.8)
In-hospital mortality	8 (2.4)

Data are presented as the mean ± standard deviation or as the number (percentage) as appropriate.
AAR: ascending aortic replacement; CFA: common femoral artery; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest; SCP: selective cerebral perfusion; TAR: total arch replacement.

failure in 11 (3.2%), prolonged ventilation (> 72 h) in 27 (7.9%), deep sternal wound infection in 0 (0%) and reoperation for bleeding in 13 (3.8%). MAO was observed in 68 patients (20%), and the in-hospital mortality rate was 2.4% (8/340).

The results of temperature analysis in the non-MAO and MAO groups when divided according to whether AAR or TAR was performed are shown in Table 3. MAO was observed in 13 patients (11.6%) in the AAR group and in 55 (24.1%) in the TAR group. There was no significant difference in the nadir temperature, change in temperature, cooling speed, warming time or warming speed between the MAO and non-MAO groups according to whether AAR or TAR was performed. The total cooling time was significantly longer in the MAO group than in the non-MAO group ($P < 0.0001$), and the cooling area was significantly higher in the MAO group than in the non-MAO group ($P < 0.0001$) regardless of whether AAR or TAR was performed. The relationship between the cooling area and the probability of an MAO in the AAR and TAR groups is shown in Fig. 2. There was a proportional relationship, which indicated that a large cooling area led to a high incidence rate of an MAO.

The results of univariate and multivariate logistic analyses for MAO are shown in Table 4. In the univariate analysis, surgical procedures, such as TAR, coronary artery bypass grafting and valve and aortic root surgery, were not detected as risk factors for MAO. Multivariate logistic analyses showed that previous myocardial infarction [P = 0.029; odds ratio (OR) = 5.32], peripheral vascular disease (P = 0.072; OR = 2.63), chronic kidney disease (P = 0.002; OR = 2.68), CPB time (per min) (P = 0.004; OR = 1.01) and the cooling area of body temperature (per 100°C min) (P = 0.006; OR = 1.1) were independent factors associated with an MAO (Table 4). TAR as the operative procedure, cardiac ischaemic time (per min) and HCA time were not identified to be predictors of MAO in multivariate analysis. The area under the receiver-operating characteristic curve of this model was 0.77. The variance inflation factor for all independent variables in this model showed low scores of <2.0.

To investigate variables related to the cooling area of the body temperature, an estimation model was established using multiple regression linear analysis. The patients' characteristics and operative factors, including the cannulation site, were introduced into this model. The model showed the following: cooling area = 2486.7 - 3.5 × age + 93.9 × congestive heart failure - 163.9 × peripheral vascular disease + 87.6 × TAR - 70.9 × nadir temperature + 12.1 × HCA time. The cannulation site was not an independent variable. The results of the parameter estimates of this model are shown in Table 5. The model showed a significant correlation (adjusted R^2 = 0.62 and P < 0.0001). The variance

Table 3: Comparison of temperature data between the non-major adverse outcome and major adverse outcome groups according to whether ascending aortic replacement or total arch replacement was performed

Variable	AAR group (*n* = 112)			TAR group (*n* = 228)		
	Non-MAO (*n* = 99)	MAO (*n* = 13)	*P*-Value	Non-MAO (*n* = 173)	MAO (*n* = 55)	*P*-Value
Nadir temperature (°C)	24.3 ± 2.5	24.9 ± 1.79	0.41	23.8 ± 1.65	23.6 ± 2.24	0.52
Change in temperature (°C)	11.2 ± 2.39	10.9 ± 1.88	0.76	11.8 ± 1.86	11.6 ± 2.22	0.41
Total cooling time (min)	156.6 ± 57.6	193.2 ± 72.9	0.04	187.8 ± 40.1	203.4 ± 41.0	0.013
Cooling speed (°C/min)	0.32 ± 0.23	0.25 ± 0.12	0.32	0.20 ± 0.18	0.17 ± 0.15	0.25
Cooling area (°C min)	1073.6 ± 377.4	1344.2 ± 746.2	0.037	1528.0 ± 382.8	1749.9 ± 509.2	0.001
Warming time (min)	92.3 ± 53.2	98.4 ± 35.9	0.69	81.4 ± 28.7	81.6 ± 30.1	0.97
Warming speed (°C/min)	0.17 ± 0.13	0.12 ± 0.06)	0.24	0.17 ± 0.06	0.19 ± 0.09	0.14

Data are presented as the mean ± standard deviation or as the number (percentage) as appropriate.
AAR: ascending aortic replacement; MAO: major adverse outcome; TAR: total arch replacement.

Table 4: Risk factors for major adverse outcomes identified by univariate and multivariate analyses

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Operative procedure				
Ascending aortic replacement	1.0 (reference)			
Total arch replacement	2.42 (1.26–4.65)	0.008		
Previous myocardial infarction	8.51 (2.07–34.9)	0.003	5.44 (1.22–24.3)	0.027
Peripheral vascular disease	2.41 (1.01–6.0)	0.049	2.63 (0.92–7.49)	0.071
Chronic kidney disease	2.85 (1.62–5.0)	<0.001	2.75 (1.48–5.12)	0.001
CPB time (per min)	1.01 (1.01–1.01)	<0.0001	1.01 (1.0–1.01)	0.004
HCA time (per min)	1.04 (1.02–1.05)	<0.0001		
Cardiac ischaemic time (per min)	1.01 (1.01–1.02)	<0.0001		
Cooling area of body temperature (per 100°C min)	1.14 (1.08–1.21)	<0.0001	1.09 (1.02–1.17)	0.012

CI: confidence interval; CPB: cardiopulmonary bypass; HCA, hypothermic circulatory arrest; OR: odds ratio.

Table 5: Parameter estimates of the best multiple linear regression models for the cooling area

Variable	Estimate	Standard error	*t* value	*P*-Value
(Intercept)	2486.7	227.8	10.9	<0.0001
Age (years)	-3.5	1.38	-2.52	0.012
Congestive heart failure	93.9	47.2	1.99	0.047
Peripheral vascular disease	-163.9	64.9	-2.53	0.012
Total arch replacement	87.6	42.8	2.05	0.042
Nadir temperature (°C)	-70.9	8.20	-8.65	<0.0001
HCA time (min)	12.1	0.76	16.0	<0.0001

HCA: hypothermic circulatory arrest.

inflation factor for all independent variables in this estimation model showed low scores of <1.5.

DISCUSSION

Proximal aortic repair by AAR/TAR with HCA for aortic aneurysm is an established surgery, which shows an excellent clinical outcome. The early operative mortality rate, including emergent surgery, was reported to be 6.7–9.0% in several previous studies [1–3]. For proximal aortic diseases, selecting AAR and TAR properly depending on the patient's characteristics, such as aortic anatomical factors, can achieve favourable results.

However, postoperative major complications with AAR/TAR can still occur. In a previous study, adverse outcomes, including neurological dysfunction, acute renal injury, respiratory failure and bleeding events, were recognized in 1.8–21.0% of patients [2, 5, 12–15]. Surgical invasion that can cause these complications is strongly related to hypothermia, which is indispensable for AAR/TAR. A longer and deeper hypothermia can cause adverse clinical outcomes. However, these relationships have not been evaluated and objectively described in a previous study. Therefore, this study aimed to quantify the degree of cooling in intentional hypothermia by temperature analysis and to evaluate the relationships of cooling with clinical outcomes. We also investigated the variables that affect cooling. We considered that the results of this analysis might be useful for reducing the surgical risk.

A multivariate logistic model showed that the cooling area of the body temperature was an independent risk factor for an MAO. The cooling area was the area under the curve of inverted temperature trends from cooling to rewarming as calculated by the integral method. Therefore, this variable indicates the degree of cooling, which can evaluate the depth and length of cooling. The cooling area can be interpreted as injury due to cooling because this also showed a proportional correlation with the incidence of an MAO (Fig. 2). Furthermore, in logistic multivariate analysis, the cooling area and the CPB time were included in the model and detected independently. This result indicated that there was an injury due to not only CPB but also the change in temperature itself. For example, in our series, cases in which the cooling time was longer and the cooling area was greater had complicated cardiac features such as a distal arch aneurysm needing a deeper distal anastomosis site or resternotomy with adhesions. The surgical procedures in these cases needed a longer HCA time, which led to prolonged CPB and cooling times. In such complicated surgical cases, longer and deeper cooling is often required as well as a prolonged CPB time, and all of these variables can be independently associated with surgical injury and lead directly to adverse clinical outcomes.

We have performed AAR with cooling of body temperature to below 25°C in the same way as for TAR. This surgical procedure has been performed for the reliable prevention of organ ischaemia. Cases that underwent AAR using the same temperature management method as that used for TAR were also included in our study. As in the TAR group, we found a strong relationship between the cooling area and postoperative adverse outcomes in the AAR group. Therefore, over-cooling in a case that is expected to have a shorter HCA time, such as a simple AAR, may lead to an adverse outcome instead of conferring organ protection.

The cooling area was evaluated in detail by multiple linear regression analysis to investigate factors related to the cooling status during surgery. We found that age, congestive heart failure and peripheral vascular disease were the predominant variables related to the cooling status among the patients' characteristics. Age and peripheral vascular disease were likely related to difficulty in cooling due to distal vascular resistance. In addition, congestive heart failure was related to easier cooling because of lower cardiac output. The variable TAR was identified because of taking a longer cooling time than AAR for reconstruction of the left subclavian artery.

The HCA time and nadir temperature, which were factors of cooling length and depth, showed a strong correlation with the cooling area. In a complicated case requiring a longer HCA time, the cooling area indicating cooling injury was necessarily greater. These results suggested that if a smaller cooling area leads to reduction in surgical invasiveness, shortening the HCA time and raising the nadir temperature could be useful for reducing the surgical risk. The HCA time can be made shorter by the conversion of the distal anastomosis site or the use of the frozen elephant trunk technique as shown by our previous study, which showed that variables such as anatomical factors or the surgical procedure were correlated with the length of the HCA time [16]. Although a change in the surgical procedure only to shorten the HCA time and improve early clinical outcomes is not necessarily appropriate for the long-term outcome, it can be an alternative for a reduction in surgical risk. With regard to other means of reducing the cooling area, raising the nadir temperature can be achieved by a change in the target body temperature for circulatory arrest. Therefore, this approach suggests that mild HCA has a lower surgical risk than that with moderate HCA. In recent years, several studies have shown good clinical outcomes with an elevated target body temperature for circulatory arrest, and this finding may be because of less injury by cooling [14, 17–19]. Dong *et al.* [19] reported that mild HCA had a lower incidence of postoperative major adverse events than moderate HCA. Mild HCA with less effects of cooling can be considered to be more optimal, if a decline in ischaemic tolerance due to an elevation in the target temperature for HCA is acceptable. However, to make this conclusion, a detailed comparison between surgeries with different target body temperatures is required. The reason for this requirement is that severe complications due to lower body circulatory arrest under mild hypothermia can occur, particularly in complicated surgical cases requiring a prolonged HCA time. Therefore, temperature analysis of a larger dataset, including mild and moderate HCA, is required. In such a future investigation to detect the optimal temperature for aortic repair with HCA, the risk model including the cooling area in the present study could be an important reference. The present study is important because injury from cooling was evaluated and quantified as the cooling area by temperature analysis, and the possibility of a reduction in surgical risk was objectively indicated by this variable.

In this study, a detailed evaluation of the relationship between neurological dysfunction and tympanic temperature was not performed. This complication may be associated with the cooling and rewarming status of tympanic temperature [10, 11, 20]. Further investigation to determine this association is required for total evaluation of proximal aortic repair with HCA.

Limitations

There are several limitations to the present study. The recorded data during surgery could have included inaccurate body temperatures because of the presence of urine in the bladder or faecal impaction in the rectum. Although temperature management during CPB was in accordance with a guideline, there could have been a difference in the method of cooling and rewarming depending on the perfusionist. Although an MAO was defined from a general clinical adverse outcome of proximal aortic repair, several factors in this definition cannot be caused by cooling. Therefore, how can adapt our risk model with the cooling area to other cohorts is unclear. Our results need to be validated by the accumulation of more data, including mild and moderate HCA, from multicentre, prospective studies.

CONCLUSION

We performed temperature analysis for elective proximal aortic surgery, including AAR and TAR, with moderate HCA to quantify the degree of cooling and evaluate its relationships with the clinical outcome. The cooling area, which represents the degree of cooling, showed a strong association with a postoperative adverse outcome also in the AAR group. The cooling area could be an important reference to detect the optimum temperature during aortic surgery in the future. A raised target temperature may be preferable for a patient in whom the HCA time is expected to be shorter.

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Conflict of interest: none declared.

Data availability

The data underpinning this article will be shared on reasonable request to the corresponding author.

Author contributions

Hiroshi Sato: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Writing – original draft; Writing – review & editing. **Yutaka Iba:** Investigation. **Nobuyoshi Kawaharada:** Investigation. **Joji Fukada:** Investigation. **Yuu Iwashiro:** Investigation. **Shingo Tsushima:** Investigation. **Itaru Hosaka:** Investigation. **Akihito Okawa:** Investigation. **Tsuyoshi Shibata:** Investigation. **Jyunji Nakazawa:** Investigation. **Tomohiro Nakajima:** Investigation. **Takeo Hasegawa:** Investigation. **Yukihiko Tamiya:** Investigation.

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