

Rapid cooling is a safe technique in patients undergoing circulatory arrest for aortic repair



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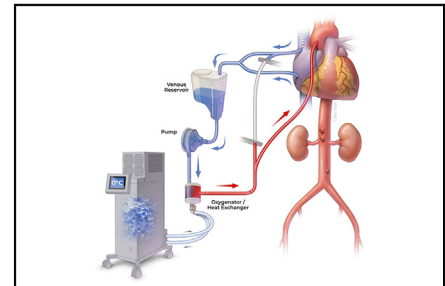
ABSTRACT

Objective: To evaluate our institutional experience with rapid cooling for hypothermic circulatory arrest in proximal aortic repair.

Methods: We retrospectively reviewed data from 2171 patients who underwent proximal aortic surgery requiring hypothermic circulatory arrest between 1991 and 2020. Cooling times were divided into quartiles and clinical outcome event rates were compared across quartiles using contingency table methods. Incremental effect of cooling time was assessed in the context of other perfusion time variables using multiple logistic regression analysis.

Results: Median age was 61 years (interquartile range, 49-70 years) and 34.1% of patients were women. The procedure was emergent in 33.5% of patients, 22.9% had a previous sternotomy. The median circulatory arrest time was 22 minutes, with retrograde cerebral perfusion used in 94% of cases. Median cardiopulmonary bypass time was 149 minutes, with an aortic crossclamp time of 90 minutes. Patients were cooled to deep hypothermia. The first quartile had cooling times ranging from 5 to 13 minutes, second 14 to 18 minutes, third 19-23 minutes, and fourth 24-81 minutes. Overall, 30-day mortality was 9.4%, and was not significantly different across quartiles. There was a statistically significant trend toward lower rates of postoperative encephalopathy, gastrointestinal complications, and respiratory failure with shorter cooling times ($P < .001$, $.006$, and $< .001$, respectively). There was no significant difference in rates of postoperative stroke or dialysis.

Conclusions: Rapid cooling can be performed safely in patients undergoing aortic surgery requiring circulatory arrest without increasing mortality or stroke. There were significantly lower rates of coagulopathy, respiratory failure, and postoperative encephalopathy with shorter cooling times. (JTCVS Techniques 2022;16:1-7)



Cardiopulmonary bypass setup to facilitate rapid cooling at a maximal temperature gradient.

CENTRAL MESSAGE

Rapid cooling is safe in patients undergoing aortic surgery requiring circulatory arrest.

PERSPECTIVE

Current guidelines to inform cooling rate on cardiopulmonary bypass are based on limited data. This study demonstrates that rapid cooling at gradients greater than 10 °C can be performed without an increase in mortality or morbidity.

▶ Video clip is available online.

To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

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The effects of cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) on neurologic outcomes have long been an important consideration in aortic surgery. Much attention has been given in the literature to methods for cerebral protection for cardiac cases involving circulatory arrest, including deep hypothermia, antegrade cerebral perfusion (ACP), and retrograde cerebral perfusion (RCP). Hypothermia is a critical aspect of cerebral protection, whether or not adjuncts are used.

Furthermore, many studies have suggested that temperature management while on CPB has a significant influence on rates of neurocognitive dysfunction following cardiac surgery. Rapid rewarming has repeatedly been demonstrated as a risk factor for postoperative cognitive impairment.¹⁻⁴ Based on these data, current guidelines state that temperature gradients between the arterial outflow and venous inflow should not exceed 10 °C, during both cooling and rewarming, to avoid creation of gaseous microemboli (Class 1, Level C).⁵ A narrow gradient results

Abbreviations and Acronyms

ACP	=	antegrade cerebral perfusion
BMI	=	body mass index
BSA	=	body surface area
CPB	=	cardiopulmonary bypass
GFR	=	glomerular filtration rate
GI	=	gastrointestinal
HCA	=	hypothermic circulatory arrest
RCP	=	retrograde cerebral perfusion

in longer cooling times. Therefore, in our study, cooling time will be used as a surrogate.

Although there are ample data to support this recommendation for rewarming, the recommendation for peak cooling temperature gradient is based on 2 studies. In a study by Almond and colleagues,⁶ a canine model demonstrated extensive brain damage in 4 dogs that were cooled with a gradient >20 °C. The same changes were not observed in 6 dogs cooled with a gradient of 4 to 6 °C. This study was performed in 1964 with the use of a rotating disc oxygenator, which is no longer used in contemporary CPB circuits.⁷ Furthermore, the animals underwent a circulatory arrest period of 30 minutes, without cerebral perfusion at a core temperature of 10 °C or lower, which is not reflective of most modern practice. Geissler and colleagues⁸ used transesophageal echocardiography to detect gaseous emboli at the level of the aortic arch in a canine model. Their study demonstrated that temperature gradients of more than 10 °C, whereas cooling were associated with gaseous emboli formation. However, they also reported no gaseous microemboli formation in dogs undergoing rapid cooling through a heat exchanger at a water bath temperature of 4 °C. There is a paucity of data to support recommended cooling gradients in current guidelines.

At our institution, rapid cooling, with the widest possible gradient, enabled by our heater-cooler system, with the cooler temperature set at 0 °C, has been utilized in cases requiring HCA. In this study, we sought to evaluate the efficacy and safety of our technique in patients undergoing proximal aortic repair.

PATIENTS AND METHODS

Patients

The Committee for Protection of Human Subjects, the local institutional review board, approved this study (protocol HSC-MS-03-077) on August 10, 2014. This study utilized a historical cohort design, using risk factor and outcome data from our department's prospective cardiovascular surgery registry. We retrospectively reviewed the database from January 1, 1991, to December 31, 2020, to identify patients who underwent HCA for proximal aortic repair. Cooling times were divided into quartiles. Patients with missing values for cooling or warming times ($n = 227$) were

excluded from analysis. Emergency and elective patients were included because this technique is applicable across all aortic surgery patients.

Cooling and Surgical Techniques

Our technique to repair the proximal aorta with RCP has been reported.⁹ Briefly, in addition to the routine heart surgery monitoring techniques (eg, arterial pressure, Swan-Ganz catheter, myocardial temperature, and transesophageal echocardiography), regional cerebral oxygen saturation with near-infrared spectroscopy is used to assess cerebral perfusion. In the past, we used a 10-lead electroencephalogram, somatosensory evoked potentials, and a power mode transcranial Doppler for the neuromonitoring. As we gained more experience with near-infrared spectroscopy, we found that it is a simple and reliable method to monitor the adequacy of cooling and cerebral perfusion—and it alone provides sufficient information.⁹ Both nasopharyngeal and rectal/bladder temperatures are obtained for temperature monitoring. CPB, using bicaval venous drainage and arterial return, is established after systemic heparinization. In most cases, the ascending aorta was used for arterial return, including patients with aortic dissection. Earlier in the cohort, peripheral artery cannulation had been our preferred technique for acute dissection cases. However, we transitioned to central cannulation from the ascending aorta with Seldinger technique under transesophageal echocardiogram. Once CPB is established, the CardioQuip heater-cooler MCH 1000id (CardioQuip LLC) is used to cool arterial return using the widest possible temperature gradient (Figure 1 and Video 1). The cooler temperature is initially set at 0 °C. The rapid cooling technique is applied to all cases, regardless of the repair extent (hemiarch vs total arch), presence of aortic dissection, and urgency status (emergency vs elective). Once the nasopharyngeal temperature reaches the target temperature (below 20-25 °C), circulation is stopped, the snare around the superior vena cava is tightened, and the RCP is initiated through the superior vena cava cannula. RCP flow of 1500 mL/min and opening pressure at 25 to 32 mm Hg is targeted and then adjusted to <25 mm Hg, according to regional cerebral oxygenation saturation. A woven Dacron graft with a single side-arm for cannulation is used for proximal aortic repair. For patients requiring separate bypass to the arch vessels, a 4-vessel woven polyethylene terephthalate graft is used. After completion of the distal anastomosis, a clamp is placed proximal to the side-arm to restore the antegrade flow to the cerebral and systemic circulation, and flow is initiated with a low-flow of 2 L/min, which is then increased to the full-flow after 5 minutes. At this point, warming is initiated, the snare around the superior vena cava is released, and the cannula in the superior vena cava is redirected to the right atrium. After completing the remainder of the procedure, CPB is weaned in the usual fashion.

End Points and Definition

The primary outcome was 30-day mortality. Secondary outcomes included postoperative stroke, postoperative respiratory failure, new dialysis, postoperative gastrointestinal (GI) complication, and intraoperative coagulopathy. Postoperative stroke was defined as confirmed neurological deficit of abrupt onset caused by disturbance in blood supply to the brain that did not resolve within 24 hours or confirmed with imaging (computed tomography scan or magnetic resonance imaging). Postoperative respiratory failure was defined as mechanical ventilation lasting longer than 48 hours or reintubation. Intraoperative coagulopathy was defined by need for delayed closure, factor VII administration, prothrombin complex concentrate administration, and requirement for transfusion >6 U platelet and/or >10 U cryoprecipitates. Postoperative GI complication was defined as ileus, GI bleeding, or mesenteric ischemia. Cooling time was defined as time from initiation of active cooling to targeted temperature, and warming time as time from resumption of CPB to a bladder temperature of 35.5 °C. Estimated glomerular filtration rate (eGFR) was calculated using Cockcroft-Gault equation. Body surface area (BSA) was calculated using Mosteller's formula.

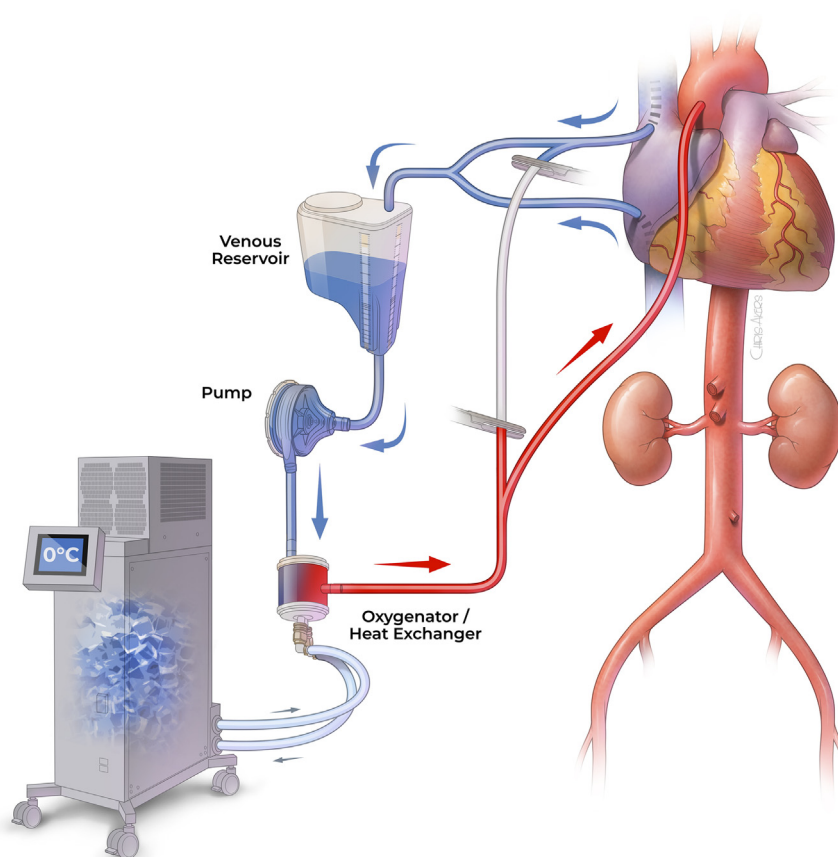


FIGURE 1. Cardiopulmonary bypass circuit setup to facilitate rapid cooling at a maximal temperature gradient. The cooler temperature is initially set at 0 °C.

Statistical Analysis

Continuous variables are shown as medians and interquartile ranges. Cooling times were divided into quartiles and categorical clinical outcome event occurrences were compared across quartiles using contingency table methods. One-way analysis of variance was used to compare the continuous variables among the four quartiles. Cochran-Armitage trend test was used to test for significant trends across quartiles. To assess effect of cooling time on selected clinical outcomes (end points), and to separate cooling time from other perfusion time variables (ie, CPB time, RCP

time, aortic crossclamp time, circulatory arrest time, and rewarming time), with which it should be correlated, we developed multiple logistic regression models with clinical outcomes as the dependent variable. We also included clinical variables that may be correlated with both clinical outcome and cooling time (eg, age, emergency status, eGFR, body mass index [BMI], BSA, cooling rate, nadir nasopharyngeal temperature, and date of surgery) in these models. Candidate clinical variables were screened by Spearman rank correlation with outcomes, and models were constructed using stepwise selection followed by purposeful final model review and model diagnostics. Linear regression models were used to assess influence of clinical and perfusion-related factors on cooling time. All computations were performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

In all, 2171 patients underwent aortic surgery requiring HCA during the study time period. Median age was 61 years (interquartile range, 49-70 years) and 34.1% of patients were women. The procedure performed was classified as emergency in 33.5% of patients and 22.9% of patients had a prior sternotomy. Additional baseline characteristics of the group are summarized in [Table 1](#). Hemiarch replacement was performed in 78.4% of cases with total arch in 21.6%. Concomitant procedures and intraoperative characteristics are summarized in [Table 2](#). The median circulatory arrest time was 22 minutes. RCP was utilized as cerebral



VIDEO 1. Video of our cardiopulmonary bypass circuit setup for rapid cooling and retrograde cerebral perfusion in a representative case. Video available at: [https://www.jtcvs.org/article/S2666-2507\(22\)00532-6/fulltext](https://www.jtcvs.org/article/S2666-2507(22)00532-6/fulltext).

TABLE 1. Baseline patient characteristics (N = 2171)

Patient variable	Result
Age (y)	61 (49-70)
Female	740 (34.1)
Body surface area* (m ²)	2.04 (1.84-2.25)
Body mass index	28.0 (24.4-32.5)
Hypertension	1362 (62.7)
Diabetes mellitus	200 (9.2)
CAD	490 (22.6)
COPD	547 (25.2)
Cerebrovascular	270 (12.4)
eGFR (mL/min/1.83 m ²)	81.5 (59.3-111.1)
HAD/CTD	415 (19.1)
Prior sternotomy	498 (22.9)
Rupture	55 (2.5)
Emergency/urgent	728 (33.5)

Continuous variables are expressed median (interquartile range) and categorical variables are expressed as n (%). CAD, Coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate, calculated using Cockcroft-Gault equation; HAD, heritable aortic disease; CTD, connective tissue disorder. *Body surface area was calculated using Mosteller's formula.

protection in addition to hypothermia in 94% of cases. The median RCP time was 21 minutes. In the remainder, ACP was utilized in 3%, and 2% did not have cerebral perfusion during HCA. Median CPB time was 149 minutes, with an aortic crossclamp time of 90 minutes. The patients were grouped into quartiles based on cooling time. The first quartile had cooling times ranging from 5 to 13 minutes, second 14 to 18 minutes, third 19 to 23 minutes, and fourth 24 to 81 minutes (Table 3). Nadir nasopharyngeal temperature was higher in the group with the shortest cooling time, which was associated with shorter time spent rewarming. A shorter cooling time was also associated with shorter total CPB time, although cooling time only accounted for approximately 3% of the variance in CPB time (regression R^2). BMI was not associated with cooling time (linear

TABLE 2. Operative characteristics (N = 2171)

Patient variable	Result
Extent of aortic arch repair	
Hemiarch replacement	1703 (78.4)
Total arch replacement	468 (21.6)
Concomitant procedures	
Aortic valve replacement	518 (23.9)
Aortic root replacement	398 (18.3)
Coronary artery bypass grafting	63 (2.9)
Nadir nasopharyngeal temperature (° C)	17.7 (16.2-19.5)
Aortic crossclamp time (min)	90 (67-116)
Cardiopulmonary bypass time (min)	149 (120-182)
Retrograde cerebral perfusion time (min)	21 (14-33)

Continuous variables are expressed as median (interquartile range), categorical variables are expressed as n (%).

regression $P = .683$), whereas longer cooling time quartiles had larger BSAs ($P < .001$) (Table 3).

Overall, 30-day mortality was 9.4%, and was not significantly different across groups (Table 4). Multiple variable logistic regression analyses demonstrated that 30-day mortality were more highly associated with emergency cases (odds ratio, 2.12, 95% confidence interval 1.39-3.22, $P < .001$), longer CPB time (odds ratio [OR], 1.02/min; 95% CI, 1.01-1.02; $P < .001$), and lower eGFR (OR, 0.98/mL/min/1.73 m²; 95% CI, 0.98-0.99; $P < .001$), and higher BMI (OR, 1.02; 95% CI, 1.01-1.03; $P < .021$). There was no significant difference in rates of postoperative stroke or new dialysis in univariable analysis across groups. Similarly, the multiple variable logistic regression analyses demonstrated that risks for stroke in overall group were emergency cases (OR, 2.24; 95% CI, 1.57-3.21; $P < .001$), longer CPB time (OR, 1.01/min; 95% CI, 1.00-1.01; $P < .001$), longer circulatory arrest time (OR, 1.02/min; 95% CI, 1.01-1.03; $P = .007$), lower eGFR (OR, .99/mL/min/1.73 m²; 95% CI, .98-0.99; $P = .004$), and more recent date of surgery (OR, 1.00/year; 95% CI, 1.00-1.00; $P = .001$) but more rapid cooling rate (lowest temperature/cooling time) (OR, 0.60/°/min; 95% CI, 0.39-0.95; $P < .029$) was protective and shorter circulatory arrest time (OR, 1.03 min; 95% CI, 1.01-1.04; $P < .001$). Patients with the shortest cooling time had significantly lower rates of intraoperative coagulopathy in univariate analysis. However, there was no significant difference in multivariable analysis. There was a statistically significant trend toward lower rates of postoperative encephalopathy and respiratory failure associated with shorter cooling times. There was a statistically significant trend toward lower rates of postoperative GI complications and respiratory failure associated with shorter cooling times.

DISCUSSION

This retrospective cohort study demonstrates that rapid cooling can be safely utilized without a significant increase in major adverse events, such as mortality or stroke. The rates of mortality and other major complications observed in this cohort are similar to those reported in other large studies.¹⁰ The results of this study also point to potential benefits of rapid cooling, such as lower rates of postoperative encephalopathy, GI complications, and respiratory failure. Complex aortic surgery is associated with long CPB times due to the need for cooling and circulatory arrest. Adjuncts, such as ACP and RCP, have resulted in wider use of moderate hypothermia. However, significant CPB time is still spent cooling and rewarming. The adverse effects of CPB are well recognized, including postoperative neurological and renal dysfunction, as well as coagulopathy and bleeding.¹¹⁻¹³ A shorter cooling duration and, therefore, total CPB time, may improve patient outcomes for operations involving HCA.

TABLE 3. Intraoperative outcomes by cooling time

Outcome	First quartile: 5-13 min (n = 593)	Second quartile: 14-18 min (n = 601)	Third quartile: 19-23 min (n = 471)	Fourth quartile: 24-81 min (n = 506)	P value*
Age (y)	60 (47-70)	61 (50-71)	61 (49-71)	62 (50-70)	.714
Body surface area (m ²)	1.99 (1.79-2.20)	2.05 (1.83-2.27)	2.06 (1.88-2.27)	2.14 (1.96-2.34)	<.001
Body mass index	27.4 (23.7-31.7)	27.9 (24.3-32.5)	28.0 (25.1-32.8)	28.7 (25.9-33.3)	.683
Emergency (%)	106 (17.9)	138 (23.0)	122 (25.9)	137 (27.1)	<.001
Warming time (min)	69 (55-83)	75 (60-90)	80 (62-91)	82 (67-100)	<.001
Nadir nasopharyngeal temperature (° C)	19.2 (17.5-21.4)	17.8 (16.4-19.3)	17.1 (15.8-18.7)	16.7 (15.3-18.0)	<.001
Circulatory arrest time (min)	17 (11-28)	22 (16-35)	24 (17-38)	26 (18-40)	<.001
RCP time (min)	17 (10-26)	21 (15-33)	23 (16-33)	25 (17-38)	<.001
Aortic crossclamp time (min)	92 (70-122)	90 (66-116)	89 (65-114)	89 (67-112)	.027
Cardiopulmonary bypass time (min)	139 (114-172)	144 (119-182)	149 (124-183)	162 (135-193)	<.001
Concomitant aortic valve/aortic root/coronary procedures	277 (46.7)	273 (45.4)	197 (41.8)	207 (40.9)	.163

Continuous variables are expressed as median (interquartile range), categorical variables are expressed as n (%). *P values for categorical values and continuous variables were derived from the χ^2 test and 1-way analysis of variance, respectively.

In this study, shorter cooling time resulted in a higher minimum temperature. Moderate HCA has demonstrated improved neurological and renal outcomes when compared with deep HCA.^{12,13} Moderate HCA has also been associated with improved survival compared with deep HCA when adjunctive cerebral perfusion was used in both groups.¹⁴ A higher minimum temperature, coupled with a shorter CPB time, may have contributed to a trend toward improved outcomes in this study.

The primary method of cerebral protection in this study was hypothermia plus RCP. Only 2% of patients were managed with deep HCA alone and, therefore, these results may not be applicable to centers where deep HCA is the preferred method of cerebral protection. Many authors have demonstrated similar results with the use of ACP and RCP for cases involving HCA.^{13,15,16} Adjunctive

cerebral protection has gained favor due to superior outcomes compared to deep HCA alone.¹⁰ However, there remains a wide degree of variability among centers, particularly in North America, where deep HCA alone is still utilized in a significant proportion of aortic cases.

In this study, the use of RCP with cold blood almost certainly contributed to a lower nadir nasopharyngeal temperature than the temperature at time of circulatory arrest. Other groups have noted that bladder temperature tends to lag behind nasopharyngeal temperature while cooling.¹⁷ Our protocol for temperature monitoring involves nasopharyngeal and bladder or rectal temperature monitoring. The decision to initiate circulatory arrest is based on nasopharyngeal temperature, which is representative of the brain temperature.¹⁸ The brain is then cooled further with RCP, whereas the body temperature has a higher nadir.

TABLE 4. Postoperative outcomes by cooling time

Outcome	First quartile: 5-13 min (n = 593)	Second quartile: 14-18 min (n = 601)	Third quartile: 19-23 min (n = 471)	Fourth quartile: 24-81 min (n = 506)	P value*
30-d mortality	47 (7.9)	58 (9.7)	48 (10.2)	52 (10.3)	.170
Postoperative stroke	39 (6.6)	42 (7.0)	36 (7.6)	29 (5.7)	.710
Postoperative GI complication†	50 (8.4)	89 (14.8)	69 (14.7)	72 (14.2)	.006
Intraoperative coagulopathy	84 (14.2)	115 (19.1)	91 (19.3)	100 (25.6)	.019
Postoperative respiratory failure‡	108 (18.2)	139 (23.1)	132 (28.0)	150 (29.6)	<.001
Postoperative new dialysis	49 (8.3)	42 (7.0)	34 (7.2)	33 (6.5)	.310

Values are presented as n (%). GI, Gastrointestinal. *P values were derived from the Cochran-Armitage trend test. †Including ileus, bleed, and ischemia. ‡Respiratory failure = ventilation hours >48 hours, reintubation, or tracheostomy.

Measurement of temperature in the nasopharynx may also help to explain the lack of influence of body mass on cooling time. These factors may contribute to shorter body re-warming times when circulation is resumed.

Unsurprisingly, the cooling time inversely correlated with a patient's BSA (ie, patients with larger BSA required longer cooling time to reach the target temperature), whereas BMI did not correlate with cooling time. Of note, multivariable logistic regression analysis demonstrated the 30-day mortality was not affected by BSA but higher BMI was a risk of mortality. These results prove that cooling time itself was not the surrogate of outcomes relative to the BSA or BMI.

Avoidance of cerebral hyperthermia remains paramount because this has been associated with adverse patient outcomes.^{11,19} At our institution, it is standard practice to follow guideline directed temperature gradients of no more than 10 °C while rewarming. Furthermore, we subscribe to the belief that rewarming should not be initiated immediately after CPB is resumed.¹⁸ Concomitant valve or aortic root procedure would affect the time to complete rewarming time, but as shown in Table 3, the frequency of concomitant procedures was similar among the all quartiles. However, in our study, a shorter cooling time was associated with a shorter warming time. Again, a shorter total CPB time may contribute to beneficial patient effects.

The cooling time had wide range in this study, which may be attributed to multiple factors. First, the cooling duration became progressively shorter as we gained experience with its use. Second, we transitioned from peripheral to central cannulation in aortic dissection cases, which likely resulted in faster drop in nasopharyngeal temperature. The majority of cases with cooling time ≥ 19 minutes in our series were performed before 2012. The multivariable analyses demonstrated the date of surgery. The era did not affect 30-day mortality but more recent cases had higher stroke rate. We were unable to explain these findings but they may be attributable to the involvement of low-volume surgeons in the recent cases, higher incidence of more urgent and redo cases.

The data that inform current guidelines around cooling come from small trials involving animal models. To our knowledge, this is the first study to examine rapid cooling in the contemporary literature. This study reinforces that rapid cooling is not associated with adverse outcomes when performed with contemporary CPB circuits, and when using adjunctive cerebral protection measures.

Study Limitations

This study has several limitations. First, it is a single-center, retrospective experience using a prospective database. Although there were significant trends toward improved secondary outcome measures with rapid cooling, these should be considered hypothesis generating. Second,

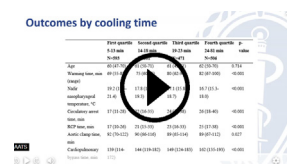
this cohort involves patients primarily managed with RCP. Multiple studies have demonstrated comparable outcomes of ACP and RCP, and the principles of temperature management have not been demonstrated to differ with the use of either method. Rapid cooling safety was not tested in patients managed solely with deep HCA without cerebral perfusion and may not be applicable to this patient cohort. Finally, these results are reflective of a high-volume aortic surgical center and may not be applicable, or practical, across all centers.

CONCLUSIONS

Rapid cooling with times as short as 5 minutes can be performed safely in patients undergoing aortic surgery requiring circulatory arrest. Further study may be warranted to determine optimal temperature management strategies for cases involving HCA in contemporary cardiac surgery.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: <https://www.aats.org/resources/1887>.



Conflict of Interest Statement

Dr Sandhyu is a consultant for WL Gore. Dr Estrera is a consultant for WL Gore, CryoLife, Edwards Lifescience, and Terumo Aortic. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: rapid cooling, aortic surgery, cardiopulmonary bypass, hypothermic circulatory arrest