Does moderate hypothermia really carry less bleeding risk than deep hypothermia for circulatory arrest? A propensity-matched comparison in hemiarch replacement

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ABSTRACT

Background: Moderate (MHCA) versus deep (DHCA) hypothermia for circulatory arrest in aortic arch surgery has been purported to reduce coagulopathy and bleeding complications, although there are limited data supporting this claim. This study aimed to compare bleeding-related events after aortic hemiarch replacement with MHCA versus DHCA.

Methods: Patients who underwent hemiarch replacement at a single institution from July 2005 to August 2014 were stratified into DHCA and MHCA groups (minimum systemic temperature $\leq 20^{\circ}\text{C}$ and $>20^{\circ}\text{C}$, respectively) and compared. Then, 1:1 propensity matching was performed to adjust for baseline differences.

Results: During the study period, 571 patients underwent hemiarch replacement: 401 (70.2%) with DHCA and 170 (29.8%) with MHCA. After propensity matching, 155 patients remained in each group. There were no significant differences between matched groups with regard to the proportion transfused with red blood cells, plasma, platelet concentrates, or cryoprecipitate on the operative day, the rate of reoperation for bleeding, or postoperative hematologic laboratory values. Among patients who received plasma, the median transfusion volume was statistically greater in the DHCA group (6 vs 5 units, $P = .01$). MHCA also resulted in a slight reduction in median volume of blood returned via cell saver (500 vs 472 mL, $P < .01$) and 12-hour postoperative chest tube output (440 vs 350, $P < .01$). Thirty-day mortality and morbidity did not differ significantly between groups.

Conclusions: MHCA compared with DHCA during hemiarch replacement may slightly reduce perioperative blood-loss and plasma transfusion requirement, although these differences do not translate into reduced reoperation for bleeding or postoperative mortality and morbidity. (J Thorac Cardiovasc Surg 2016;152:1559-69)

Comparing the effect of deep versus moderate hypothermic circulatory arrest on bleeding.

Central Message

Moderate hypothermic circulatory arrest compared with deep hypothermic circulatory arrest may slightly reduce perioperative blood-loss and plasma transfusion requirement, although transfusion of other products was similar.

Perspective

In this single-institution propensity matched analysis, moderate compared with deep hypothermia for circulatory arrest in hemiarch replacement led to slightly reduced perioperative blood-loss and plasma transfusion requirement. These differences did not translate into reduced transfusion of other blood products or differences in 30-day postoperative morbidity and mortality.

See Editorial Commentary page 1570.

The induction of hypothermia before circulatory arrest during aortic arch reconstruction has been used effectively as an organ-protection strategy for more than 4 decades¹; however,

the optimal degree of hypothermia at which adequate organ protection is achieved and hypothermia-associated complications are minimized remains uncertain and a topic of intense debate.² Because the nervous system is highly susceptible to injury with only brief periods of hypoxia, achieving adequate cerebral protection traditionally has been the driving concern during these procedures. Proponents of relatively deeper degrees of hypothermia have advocated that optimal cerebral

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Abbreviations and Acronyms

ASA	= American Society of Anesthesiologists
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
DUMC	= Duke University Medical Center
HCA	= hypothermic circulatory arrest
IQR	= interquartile range
MHCA	= moderate hypothermic circulatory arrest
PRBC	= packed red blood cells
rFVIIa	= recombinant activated factor VII

protection occurs with maximal suppression of cerebral metabolic activity or temperatures sufficient to produce electrocerebral inactivity on electroencephalography,³⁻⁹ usually 16°C or less.^{10,11} With the introduction of adjunctive regional cerebral perfusion strategies that provide continued perfusion and cooling of the brain after the initiation of systemic circulatory arrest,^{12,13} however, it is unclear whether cooling to the deep degrees of hypothermia required to reach electrocerebral inactivity is necessary. Indeed, advocates of more moderate degrees of hypothermic circulatory arrest (HCA) coupled with adjunctive cerebral perfusion have asserted that this approach provides comparable cerebral and visceral protection while potentially mitigating complications associated with deeper degrees of hypothermia.¹⁴⁻²¹

Coagulopathic bleeding is a common problem in surgery of the aortic arch with HCA and arises from a number of factors, including coagulation factor consumption caused by prolonged periods of cardiopulmonary bypass (CPB) support and hypothermia-related platelet dysfunction.²² Theoretically, deeper degrees of hypothermia may increase the severity of hypothermia-related coagulopathy and place the patient at risk for increased bleeding and blood product transfusion, which are known to lead to worse outcomes after cardiothoracic surgery.²³⁻²⁶ Currently, there is limited empirical evidence to support this claim. In this study, we sought to determine whether moderate hypothermic circulatory arrest (MHCA) compared with deep hypothermic circulatory arrest (DHCA) reduced the risk of bleeding and blood product transfusion in patients undergoing hemiarch replacement with circulatory arrest.

METHODS

Patient Selection

This retrospective cohort study was approved by the Duke University Medical Center (DUMC) institutional review board, which waived the need for individual patient consent. The study included all patients who underwent replacement of the aortic root or supracoronary ascending aorta (with or without aortic valve replacement) with concomitant hemiarch replacement using HCA at DUMC from July 2005 to August 2014. Patient and procedural characteristics as well as clinical outcomes data were obtained from the prospectively maintained Duke Thoracic Aortic Surgery

institutional database. The Society of Thoracic Surgeons definitions were used to define patient comorbidities and postoperative outcomes.²⁷ Transfusion data were obtained from a prospectively maintained registry of the DUMC Blood Bank and Transfusion Service. Laboratory values, chest tube output, and intraoperative autologous blood transfusion volumes were determined through additional review of the medical record.

Conduct of Procedures

Anesthetic and surgical techniques for aortic hemiarch replacement at our institution have been described previously.^{5,9,10,28,29} Before July 2013, our institution predominately employed a practice of DHCA as described previously⁵; however, beginning in July 2013, our institution transitioned to a practice of MHCA with selective antegrade cerebral perfusion in these procedures, in which circulatory arrest was initiated after cooling to a temperature of no greater than 28°C.²⁹ The rationale behind this change in practice was based on the good outcomes reported by a number of centers that used an MCHA approach¹⁴⁻¹⁸ and the perceived potential to limit complications putatively associated with deeper degrees of hypothermia.

Transfusion Practices

Aspects of our institutional transfusion practices during aortic surgery have been published previously.^{22,30} Driven by societal perioperative transfusion guidelines,^{24,31} our approach to transfusion during aortic reconstruction with HCA has evolved into an algorithm, formally implemented in 2010, to allow for rapid and balanced blood product resuscitation during coagulopathic bleeding frequently encountered in these cases (Figure E1). Antifibrinolytic therapy with epsilon-aminocaproic acid is administered as a 5-g loading dose followed by a 1-g/h infusion and a cell saver (BRAT II blood cell salvage machine; Cobe Cardiovascular Inc, Arvada, Colo) is used for every case. Before separation from CPB, upon rewarming and reperfusion, the bypass reservoir is primed with 4 units of plasma with concomitant hemofiltration to ameliorate coagulation factor dilution, and a set of laboratory tests is obtained to help guide management. Protamine sulfate is then administered at a dose of 1 mg/100 units of initial heparin dosing, followed by additional 25- to 50-mg doses until activated clotting time is normalized or plateaus.

At the time of separation from CPB, a 0.3 µg/kg dose of desmopressin acetate is administered for platelet dysfunction and antifibrinolytic therapy with epsilon-aminocaproic acid is redosed as a 5-g bolus with continuation of the 1-g/h infusion until bleeding is minimal. If hemostasis is not immediately achieved, 1 unit of allogeneic, single-donor apheresis platelets is transfused followed by a second unit if bleeding persists. At this point, laboratory values are rechecked and if bleeding persists, an additional unit of platelets and 2 units of plasma are administered. In accordance with returning laboratory results, a unit of pooled (10 donor) cryoprecipitate (if fibrinogen level <200 mg/dL), platelets, and/or 2 plasma units are then transfused. If bleeding continues, recombinant activated factor VII (rFVIIa; 1-2 mg) is administered.³⁰ If hemostasis is still not obtained, packed red blood cells (PRBCs) and plasma are administered at a 1:1 ratio with additional cryoprecipitate, platelets, and hemostatic adjuncts administered at the clinical discretion of the attending physicians. With regard to red blood cell transfusion, serial hematocrits are drawn before and after separation from CPB. The return of washed, shed red blood cells (BRAT II blood cell salvage machine; Cobe Cardiovascular Inc) to the patient is used in all cases and additional red blood cell transfusion is avoided if the hematocrit is greater than 0.20.

Analysis

To assess the impact of the degree of hypothermia on bleeding and transfusion requirement, the cohort was stratified into DHCA and MHCA groups based on whether the minimum systemic temperature (measured in the urinary bladder) was ≤20°C or >20°C, respectively. Although a

FIGURE 1. A, Bar graph demonstrating the number of cases of hemiarch replacement per year from the total cohort with either deep (orange) or moderate (green) hypothermic circulatory arrest. Only patients up to August 2014 are included in that year. B, Bar graph demonstrating the number of cases of hemiarch replacement per year after propensity matching with either deep (orange) or moderate (green) hypothermic circulatory arrest. Only patients up to August 2014 are included in that year.

great deal of variability exists in the literature in terms of how DHCA and MCHA are defined,^{2,32} recently published expert consensus guidelines classify DHCA and MHCA by minimum nasopharyngeal temperature $\leq 20^{\circ}\text{C}$ or $>20^{\circ}\text{C}$.³³ These guidelines and much of the existing literature surrounding HCA in aortic arch surgery focus primarily on the cooling of the brain and neurologic outcomes. As such, selecting nasopharyngeal temperature, which is felt to be a better surrogate measure for brain temperature than systemic temperature, in relation to these considerations is appropriate. Because the primary focus of this study was bleeding-related outcomes, however, we chose to define our groups by minimum systemic temperature because we assessed this measurement to be the more appropriate surrogate for surgical field temperature and thus a more relevant predictor value for hypothermia-related coagulopathic bleeding within the surgical field.

Unadjusted patient and procedural characteristics as well as study outcomes were then summarized and compared between groups. For adjusted comparison, a 1:1 propensity-matched analysis using the nearest neighbor algorithm was performed using the following preoperative covariables that were determined a priori: age, sex, race, body mass index, hypertension, tobacco use, diabetes, coronary artery disease, congestive heart failure, history of stroke, chronic renal insufficiency (baseline creatinine $>1.5\text{ mg/dL}$), connective tissue disease, American Society of Anesthesiologists (ASA) class, bicuspid aortic valve, acute type A aortic dissection, chronic type A aortic dissection, preoperative malperfusion or shock, aortic rupture, procedural status, concomitant root replacement, redo sternotomy, adjunctive cerebral perfusion strategy (eg, antegrade cerebral perfusion or retrograde cerebral perfusion), and preoperative hemoglobin level, platelet count, international normalized ratio, and partial thromboplastin time.

TABLE 1. Unadjusted patient and procedural characteristics

Variable	Total	DHCA (n = 401)	MHCA (n = 170)	P value
Age, y	58 (48, 67)	58 (48, 67)	58 (51, 68)	.19
Female	175 (30.6%)	120 (29.9%)	55 (32.4%)	.62
White race	437 (76.5%)	313 (78.1%)	124 (72.9%)	.20
Body mass index	28.0 (24.9, 31.9)	27.7 (24.7, 31.9)	28.5 (25.4, 32.2)	.17
Hypertension	454 (79.5%)	318 (79.3%)	136 (80.0%)	.90
Hyperlipidemia	310 (54.3%)	215 (53.6%)	95 (55.9%)	.65
Smoker	244 (42.7%)	181 (45.1%)	63 (37.1%)	.08
Diabetes	54 (9.5%)	40 (10.0%)	14 (8.2%)	.64
Coronary artery disease	138 (24.2%)	98 (24.4%)	40 (23.5%)	.90
History of MI	41 (7.2%)	25 (6.3%)	16 (9.5%)	.20
CHF (NYHA ≥ 2)	190 (33.3%)	144 (36.2%)	46 (27.2%)	.04
History of stroke/TIA	37 (6.5%)	24 (6.0%)	13 (7.6%)	.46
COPD	67 (11.7%)	47 (11.7%)	20 (11.8%)	.99
Chronic kidney disease (baseline creatinine >1.5)	63 (11.0%)	38 (9.5%)	25 (14.7%)	.08
Peripheral artery disease	34 (6.0%)	22 (5.5%)	12 (7.1%)	.45
Connective tissue disease	20 (3.5%)	15 (3.7%)	5 (2.9%)	.80
Bicuspid aortic valve	246 (43.1%)	187 (46.6%)	59 (34.7%)	.01
Type A aortic dissection	156 (27.3%)	100 (24.9%)	56 (32.9%)	.05
Acute	118 (20.7%)	68 (68.0%)	50 (89.3%)	$<.01$
Chronic	39 (6.8%)	32 (32.0%)	7 (12.5%)	$<.01$
Aortic rupture	35 (6.1%)	20 (5.0%)	15 (8.9%)	.09
Malperfusion or Shock	31 (5.4%)	16 (4.0%)	15 (8.8%)	.03
Max aortic diameter	5.4 (5.0, 5.9)	5.5 (5.1, 6.0)	5.3 (5.0, 5.8)	.02
ASA class				$<.01$
2	50 (8.8%)	21 (5.2%)	29 (17.1%)	
3	358 (62.7%)	272 (67.8%)	86 (50.6%)	
4	163 (28.5%)	108 (26.9%)	55 (32.4%)	
Procedural status				$<.01$
Elective	418 (73.2%)	308 (71.1%)	110 (64.7%)	
Urgent	54 (9.5%)	40 (10.0%)	14 (8.2%)	
Emergent	99 (17.3%)	53 (13.2%)	46 (27.1%)	
Previous aortic surgery	96 (16.8%)	71 (17.7%)	25 (14.7%)	.46
Redo sternotomy	96 (16.8%)	70 (17.5%)	26 (15.3%)	.62
Root replacement	208 (36.4%)	154 (38.4%)	54 (31.8%)	.29
Preoperative laboratory values				
Hgb	13.6 (12.2, 14.8)	13.6 (12.3, 14.8)	13.5 (12.1, 14.7)	.12
INR	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	.84
Platelets	202 (170, 242)	203 (173, 242)	201 (165, 242)	.41
PTT	30.2 (28.0, 33.0)	30.0 (28.0, 33.2)	30.7 (28.0, 32.7)	.52
Creatinine	1.0 (0.8, 1.2)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)	.50
Adjunctive cerebral perfusion				
ACP	465 (81.4%)	306 (76.5%)	159 (93.5%)	$<.01$
RCP	111 (19.4%)	100 (25.0%)	11 (6.5%)	$<.01$
Both ACP and RCP	8 (1.4%)	8 (2.0%)	0	.11
Intraoperative EEG monitoring	457 (80.0%)	333 (83.3%)	124 (72.9%)	.006

Continuous variables are reported as the median value (Q1, Q3). *DHCA*, Deep hypothermic circulatory arrest; *MHCA*, moderate hypothermic circulatory arrest; *MI*, myocardial infarction; *CHF*, congestive heart failure; *NYHA*, New York Heart Association; *TIA*, transient ischemic attack; *COPD*, chronic obstructive pulmonary disease; *ASA*, American Society of Anesthesiologists; *Hgb*, hemoglobin; *INR*, international normalized ratio; *PTT*, partial thromboplastin time; *ACP*, antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *EEG*, electroencephalography.

The primary study outcome was the quantity of allogeneic blood product transfusion on the day of operation. Other bleeding-related outcomes assessed included the quantity of intraoperative autologous blood transfusion, 12-hour postoperative chest tube output, reoperation for bleeding, intraoperative and postoperative use of rFVIIa, and immediate postoperative

hematologic laboratory values. In addition, we evaluated a series of secondary outcomes that may not be directly related to bleeding but that are clinically relevant for patients undergoing surgery of the aortic arch and that may be affected by the degree of systemic hypothermia. These secondary outcomes included CPB time, aortic cross-clamp time, operative time,

TABLE 2. Patient and procedural characteristics after propensity matching

Variable	Total (n = 310)	DHCA (n = 155)	MHCA (n = 155)	Standardized difference	P value
Age	59 (51, 69)	60 (50,69)	58 (52, 68)	0%	.84
Female	99 (31.9%)	50 (32.3%)	49 (31.6%)	1.4%	.99
White race	239 (77%)	125 (80.6%)	114 (73.5%)	16.0%	.18
Body mass index	28.2 (25.0, 32.0)	27.9 (24.9, 31.8)	28.4 (25.3, 32.3)	13.4%	.35
Hypertension	247 (79.6%)	124 (80.0%)	123 (79.4%)	1.6%	.99
Hyperlipidemia	168 (54.1%)	82 (52.9%)	86 (55.5%)	5.2%	.73
Smoker	111 (35.8%)	56 (36.1%)	55 (35.5%)	1.3%	.99
Diabetes	27 (8.7%)	14 (9.0%)	13 (8.4%)	2.3%	.99
Coronary artery disease	76 (24.5%)	38 (24.5%)	38 (24.5%)	0%	.99
History of MI	24 (7.7%)	8 (5.2%)	16 (10.3%)	19.3%	.14
CHF (NYHA ≥ 2)	93 (30%)	50 (32.3%)	43 (27.7%)	10.1%	.45
History of stroke/TIA	21 (6.7%)	9 (5.8%)	12 (7.7%)	7.2%	.65
COPD	35 (11.2%)	18 (11.6%)	17 (11.0%)		.99
Chronic kidney disease (baseline creatinine >1.5)	42 (13.5%)	19 (12.3%)	23 (14.8%)	7.2%	.62
Peripheral artery disease	19 (6.1%)	8 (5.2%)	11 (7.1%)	8.1%	.64
Connective tissue disease	11 (3.5%)	6 (3.9%)	5 (3.2%)	3.6%	.99
Bicuspid aortic valve	115 (37%)	59 (38.1%)	56 (36.1%)	4.0%	.81
Ascending aortic dissection	87 (28%)	39 (25.2%)	48 (31.0%)	12.5%	.31
Acute	75 (24.1%)	33 (84.6%)	42 (87.5%)	12.9%	.76
Chronic	13 (4.1%)	6 (15.4%)	7 (14.6%)	3.1%	.99
Acute dissection with malperfusion or shock	18 (5.8%)	6 (3.9%)	12 (7.7%)	14.4%	.22
Max aortic diameter	5.3 (5.0, 5.8)	5.4 (5.0, 5.9)	5.3 (5.0, 5.8)	8.2%	.36
Aortic rupture	20 (6.4%)	11 (7.1%)	9 (5.8%)	5.5%	.82
ASA class					.01
2	39 (12.5%)	12 (7.7%)	27 (17.4%)	25.4%	
3	189 (60.9%)	106 (68.4%)	83 (53.5%)	29.7%	
4	82 (26.4%)	37 (23.9%)	45 (29.0%)	11.3%	
Procedural status					.36
Elective	217 (70%)	113 (72.9%)	104 (67.1%)	12.3%	
Urgent	29 (9.3%)	15 (9.7%)	14 (9.0%)	2.24%	
Emergent	64 (20.6%)	27 (17.4%)	37 (23.9%)	15.1%	
Previous aortic surgery	43 (13.8%)	21 (13.5%)	22 (14.2%)	1.8%	.99
Redo sternotomy	50 (16.1%)	25 (16.1%)	25 (16.1%)	0	.99
Root replacement	105 (33.8%)	56 (36.1%)	49 (31.6%)	11.1%	.64
Preoperative laboratory values					
Hgb	13.6 (12.2, 14.8)	13.7 (12.3, 14.9)	13.5 (12.1, 14.7)	4.9%	.62
INR	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	11.3%	.53
Platelets	201 (168, 240)	201 (172, 237)	197 (165, 242)	1.0%	.58
PTT	30.4 (28.0, 33.0)	30.4 (28.1, 33.3)	30.5 (28.0, 32.7)	5.0%	.80
Creatinine	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	7.1%	.62
Adjunctive cerebral perfusion	309 (99.7%)	154 (99.4%)	155 (100%)	11.4%	.99
ACP	292 (94.1%)	145 (93.5%)	147 (94.8%)	2.9%	.81
RCP	17 (5.4%)	9 (5.8%)	8 (5.2%)	5.8%	.99
Both ACP and RCP	0	0	0	0	NA
Intraoperative EEG monitoring	238 (76.7%)	121 (78.1%)	117 (75.5%)	6.1%	.69

Continuous variables are reported as median value (Q1, Q3). *DHCA*, Deep hypothermic circulatory arrest; *MHCA*, moderate hypothermic circulatory arrest; *MI*, myocardial infarction; *CHF*, congestive heart failure; *NYHA*, New York Heart Association; *TIA*, transient ischemic attack; *COPD*, chronic obstructive pulmonary disease; *ASA*, American Society of Anesthesiologists; *Hgb*, hemoglobin; *INR*, international normalized ratio; *PTT*, partial thromboplastin time; *ACP*, antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *NA*, not available; *EEG*, electroencephalography.

and circulatory arrest time as well as 30-day mortality, acute kidney injury, peak postoperative creatinine, new-onset dialysis, stroke, transient ischemic attack, prolonged postoperative ventilation (>24 hours), length of hospitalization, rate of 30-day readmission, and discharge to a location other than home.

Baseline characteristics, procedural characteristics, and outcomes were summarized with the median value and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. Wilcoxon rank sum test was used to compare continuous variables, whereas the Fisher exact test (cell counts <5) or Pearson χ^2 test was

used to compare categorical variables. A $P < .05$ was used to indicate statistical significance. All statistical analyses were performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 571 patients underwent aortic hemiarch replacement: 401 (70.2%) with DHCA and 170 (29.8%) with MHCA. Consistent with the change in institutional approach towards the management of HCA during the study period, DHCA predominated before 2013, whereas MHCA became predominate thereafter (Figure 1). There were several statistically significant differences in the baseline and procedural characteristics between the DHCA and MHCA groups (Table 1). Most notably, compared with the DHCA group, there was a greater incidence of type A aortic dissection in the MHCA group (32.9% vs 24.9%, $P = .048$). There was also a greater incidence of preoperative malperfusion or shock (8.8% vs 4.0%, $P = .03$) as well as a greater proportion of emergent procedures (27.1% vs 13.2%, $P < .01$).

After propensity matching, 155 patients remained in each group. The median minimum systemic temperature was 17.0°C (IQR, 15.7°C–18.0°C) and 24.0°C (IQR, 21.3°C–26.2°C) for the DHCA and MHCA groups, respectively. The median minimum nasopharyngeal temperatures for the matched DHCA and MHCA groups were 14.2°C (IQR, 13.1°C–15.4°C) and 18.1°C (IQR, 15.2°C–21.1°C), respectively. The matched groups were not significantly

different with respect to all covariables included in the propensity match with the exception of ASA class (Table 2, Figure E2). Specifically, there was a greater proportion of ASA class 2 patients in the MHCA group (17.4% vs 7.7%, standardized difference 25.4%) and conversely a greater proportion of ASA class 3 patients in the DHCA group (68.4% vs 53.5%, standardized difference 29.7%). A total of 4 surgeons performed all the procedures in the cohort, with a similar proportion of patients in the matched DHCA and MHCA cohorts operated on the by our institution's senior aortic surgeon (G.C.H.) (78.7% DHCA vs 75.5% MHCA, $P = .30$).

With regard to bleeding-related outcomes, there were no significant differences between the matched groups in the proportion of patients transfused with PRBC, plasma, pooled platelets, or cryoprecipitate (Table 3). Among patients transfused with plasma, the median number of units transfused was statistically greater in the DHCA group (6 [IQR, 4–9] vs 5 [IQR, 4–8] units, $P = .01$). In contrast, among patients who received cryoprecipitate, the amount transfused was statistically lower in the DHCA group (1 [IQR, 1–1] vs 1 [IQR, 1–2], $P < .01$). The DHCA group had a significantly greater median volume of autologous washed blood returned via the cell saver device (500 [IQR, 250–738] vs 472 [IQR, 250–700] mL, $P < .01$) and a greater chest tube output 12 hours postoperatively (440 [IQR, 300–735] vs 360 [IQR, 230–633] mL, $P < .01$) compared with the MHCA group. In contrast, a greater

TABLE 3. Primary bleeding-related outcomes after propensity matching

Variable	Total (n = 310)	DHCA (n = 155)	MHCA (n = 155)	P value
Intraoperative PRBC				
Number of patients transfused (%)	208 (67.1%)	103 (66.5%)	105 (67.7%)	.90
Median (IQR) units among patients transfused	3 (2, 5)	3 (2, 5)	3 (2, 5)	.65
Intraoperative plasma				
Number of patients transfused (%)	281 (90.6%)	138 (89.0%)	143 (92.3%)	.44
Median (IQR) units among patients transfused	6 (4, 8)	6 (4, 9)	5 (4, 8)	.01
Intraoperative platelets				
Number of patients transfused (%)	271 (87.4%)	133 (85.8%)	138 (89.0%)	.49
Median (IQR) units among patients transfused	2 (2, 3)	2 (2, 3)	2 (2, 3)	.12
Intraoperative cryoprecipitate				
Number of patients transfused (%)	126 (40.6%)	57 (36.8%)	69 (44.5%)	.20
Median (IQR) units among patients transfused	1 (1, 1.75)	1 (1, 1)	1 (1, 2)	<.01
Cell saver, mL	500 (250, 718)	500 (250, 738)	472 (250, 700)	<.01
Intraoperative rFVIIa	86 (27.7%)	34 (21.9%)	52 (33.5%)	.03
Postoperative rFVIIa	13 (4.1%)	8 (5.2%)	5 (3.2%)	.57
12-h chest tube output, mL	400 (250, 699)	440 (300, 735)	360 (230, 633)	<.01
Reoperation for bleeding	10 (3.2%)	5 (3.2%)	5 (3.2%)	.99
Postoperative laboratory values				
Hemoglobin, g/dL	9.9 (9.3, 10.6)	9.9 (9.2, 10.6)	10.0 (9.4, 10.6)	.52
Platelets, $10^9/L$	145 (123, 172)	140 (120, 169)	147 (127, 173)	.09
INR	1.1 (0.9, 1.2)	1.1 (1.0, 1.2)	1.1 (0.9, 1.2)	.02
Partial thromboplastin time, s	28.5 (26.0, 32.2)	28.5 (25.8, 33.9)	28.6 (26.3, 31.4)	.51

Continuous variables are reported as median value (Q1, Q3). DHCA, Deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest; PRBCs, packed red blood cells; IQR, interquartile range; rFVIIa, recombinant activated factor VII; INR, international normalized ratio.

TABLE 4. Secondary outcomes after propensity matching

Variable	Total (n = 310)	DHCA (n = 155)	MHCA (n = 155)	P value
Cardiopulmonary bypass time	195 (171, 224)	205 (185, 228)	182 (150, 215)	<.01
Cross-clamp time	123 (103, 153)	133 (109, 155)	117 (95, 147)	.005
Circulatory arrest time	16 (14, 21)	16 (14, 21)	16.5 (13, 20)	.26
Operative time	330 (294, 383)	334 (301, 385)	320 (281, 367)	.02
30-d/in-hospital mortality	7 (2.3%)	2 (1.3%)	5 (3.2%)	.45
AKI (creatinine >2.0 and 2× baseline)	27 (8.7%)	11 (7.1%)	16 (10.3%)	.42
Delayed sternal closure	7 (2.3%)	3 (1.9%)	4 (2.6%)	.99
New-onset dialysis	8 (2.5%)	1 (0.6%)	7 (4.5%)	.07
Peak postoperative creatinine	1.3 (1.1, 1.7)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	.41
Stroke	4 (1.3%)	3 (1.9%)	1 (0.6%)	.62
Transient ischemic attack	3 (1.0%)	3 (1.9%)	0	.25
Prolonged ventilation (>24 h)	34 (11.0%)	21 (13.5%)	13 (8.4%)	.20
Length of stay, d	6 (5, 8)	6 (5, 9)	6 (5, 7)	.22
30-d readmission	37 (8.7%)	21 (13.5%)	16 (10.3%)	.48
Discharge to location other than home	6 (1.9%)	3 (1.9%)	3 (1.9%)	.99

Continuous variables are reported as median value (Q1, Q3). DHCA, Deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest; AKI, acute kidney injury.

proportion of patients undergoing MHCA received intraoperative rFVIIa (33.5% vs 21.9%, $P = .03$), whereas there was no significant difference between groups in postoperative rFVIIa administration. Postoperative hematologic values were similar between groups.

The median time on CPB was significantly shorter in the MHCA group (182 [IQR, 150-215] vs 205 [IQR, 185-228] minutes, $P < .01$). The cross-clamp time (117 [IQR, 95-147] vs 133 [IQR, 109-155] minutes, $P < .01$) and operative times (320 [IQR, 281-367] vs 334 [IQR, 301-385] minutes, $P < .01$) were also shorter in the MHCA group, whereas the circulatory arrest times did not differ significantly between groups. The 30-day/in-hospital mortality did not differ significantly between the DHCA and MHCA groups (1.3% vs 3.2%, $P = .45$) (Table 4). There were likewise no statistically significant differences between groups in regard to organ-specific complications such as stroke and acute kidney injury, although there was a trend towards increased new onset dialysis in the MHCA group (4.5% vs 0.6%, $P = .07$).

DISCUSSION

In this study, we conducted a comparison of patients managed with MHCA versus DHCA during hemiarach replacement to determine whether a lesser degree of hypothermia leads to a reduction in the extent of bleeding and blood product transfusion associated with this procedure. After propensity matching to control for a number of potentially confounding variables, there were no significant differences in the proportion of DHCA and MHCA patients who were transfused with PRBC, plasma, platelets, and cryoprecipitate. Among patients who received transfusion, there was a slight statistical increase in the volume of plasma transfused in the DHCA compared with the

MHCA group. We also found that the volume of intraoperative autologous blood transfused via the cell saver device and the postoperative chest tube output were statistically greater in the DHCA group, which suggests that DHCA may lead to greater perioperative blood loss compared with MHCA. It should be noted, however, that the magnitude of change between the MHCA and DHCA groups with respect to these outcomes was small and unlikely to be clinically significant. We also observed that the MHCA group had a slight statistical increase in the amount of allogeneic cryoprecipitate transfused and rFVIIa received. This may have contributed to the slight reduction in cell saver transfusion and postoperative chest tube output in patients undergoing MHCA and likely reflects the incorporation of relatively early cryoprecipitate administration and rFVIIa use into our institutional transfusion algorithm in 2010.³⁰ Together, the findings of this study suggest that although MHCA compared with DHCA may result in a slight reduction in perioperative blood loss and plasma transfusion volume, these differences do not clearly translate into clinically meaningful benefit as it pertains to reduced transfusion of other allogeneic blood products or the need for reoperation as a result of bleeding.

To our knowledge, 2 previous single-institution studies have directly compared the effect of DHCA versus MHCA on transfusion requirement in aortic arch replacement.¹⁹ In 2013, Tsai and colleagues²⁰ reported no significant difference in transfusion requirement between patients who underwent any type of aortic arch replacement with a minimum nasopharyngeal temperature <20.0°C ($n = 78$) versus >20.0°C ($n = 143$). In 2015, Vallabhajosyula and colleagues¹⁹ compared patients who underwent elective hemiarach replacement for aortic aneurysm disease with either MHCA ($n = 75$) or DHCA ($n = 301$), including

patients with a minimum systemic temperature $\geq 25^{\circ}\text{C}$ or $< 20.0^{\circ}\text{C}$, respectively. They demonstrated similar unadjusted 30-day mortality and morbidity between these groups and also found a significant reduction in the unadjusted rate of intraoperative blood transfusion in the MHCA group.

Several factors complicate the comparison of the results from the present study to these previous studies. Perhaps most important is the discrepancy in the definitions of DHCA and MHCA. This discrepancy is not surprising because there is considerable variability in the literature regarding these definitions.^{2,32,33} In this study, we chose to stratify patients in reference to the minimum systemic temperature as opposed to nasopharyngeal temperature because we assessed that systemic temperature is the more relevant predictor for bleeding and coagulopathy encountered in the surgical field. Because minimum nasopharyngeal temperature often is several degrees lower than minimum systemic temperature, in large part due to the continued cooling of the head by the regional cerebral perfusion used during systemic circulatory arrest, we have included some patients in the moderate hypothermia group that might be classified as deep hypothermia patients had they been stratified by nasopharyngeal temperature or by alternative definitions. It is possible that our inclusion of relatively cooler patients in the MHCA group limited the ability to detect a benefit with regard to reduced transfusion that may be present at milder temperatures in the MHCA range. Lastly, neither the present study nor the previous studies accounted for nadir blood temperature as a predictor of bleeding and coagulopathy. This temperature corresponds to the lowest temperature of blood in the cooling circuit and is dependent on a number of factors including the temperature of the cooling bath (12°C for all cases at our institution) and the duration cooling. It is possible that the nadir blood temperature corresponds with the extent of functional coagulation factor and platelet depletion and therefore may be an important predictor of coagulopathic bleeding in these procedures.

Differences in blood product transfusion practices also may have contributed to the different transfusion rates observed between the current and previously published single institution studies. There is little detail, however, provided on institutional transfusion practices during HCA in either the studies of Tsai or Vallabhajosyula. Therefore, it is not known to what extent these differences may have impacted their findings. At our institution, we have adopted an aggressive approach towards the management of intraoperative bleeding and coagulopathy in aortic arch surgery with HCA.^{22,30} Specifically, our transfusion algorithm calls for the repletion of coagulation factors by plasma transfusion before separation from CPB and subsequent early transfusion of platelets and cryoprecipitate if hemostasis is not rapidly obtained thereafter. Additional

blood products and rFVIIa are administered in cases of refractory bleeding. This approach generally has provided for excellent hemostasis intraoperatively and has helped to minimize postoperative bleeding and bleeding related complications.³⁰ Because our transfusion algorithm was developed for the management of coagulopathy associated with DHCA, however, it is possible that application of this algorithm with MHCA has led to overtransfusion in these cases and consequently limited the ability to detect the benefit MHCA may provide relating to reduced severity of coagulopathy and bleeding. This possibility is one that we are carefully considering going forward as we continue to balance the need to control bleeding in these cases with the effort to keep blood product transfusion to a minimum.

Despite the fact that our study does not demonstrate substantial clinical benefit of MHCA over DHCA in regard to reduced bleeding and transfusion, our results nevertheless support the apparent safety of MHCA in comparison with DHCA. Among the panel of nonbleeding-related clinical outcomes assessed, there were no significant differences in mortality or organ-specific morbidity between the MHCA and the DHCA group. Interestingly, however, we did note a trend towards increased incidence of new-onset dialysis in the MHCA group (4.5% vs 0.6%, $P = .07$), raising the possibility that the visceral organs are at increased risk of ischemic injury with MHCA compared with DHCA. Regardless, the comparable outcomes observed between MHCA and DHCA support that clinical equipoise exists between these 2 organ-protection strategies and add weight to the argument that a well-designed randomized trial is needed to definitively determine the optimal strategy for HCA during aortic arch reconstruction.

There are a number of limitations to the current study. First, as with any retrospective study, there is potential confounding from unmeasured variables that could not be accounted for in the adjusted analysis. Second, it is important to note that operative and transfusion practices were not standardized over the entirety of the study period. Because patients in the DHCA and MHCA groups were disproportionately represented in the cohort with respect to time, we could not include year of surgery in our propensity match. Study findings may therefore have been affected to some degree by changes in practice over time that could not be completely accounted for in the adjusted analysis, most notably the implementation of our transfusion algorithm in 2010. This limitation further underscores the need for a prospective randomized clinical trial comparing MHCA and DHCA in which clinical practices are standardized to alleviate the potential sources of confounding and bias inherent to any retrospective comparison. Lastly, although we have reported a robust panel of clinically relevant bleeding-related outcomes, estimated blood loss could not be reported because of the difficulty in obtaining an accurate measurement of blood loss in these cases. We also

could not report the effect of the degree of hypothermia on functional coagulation assessments, such as thromboelastography or thromboelastometry, because of the inconsistent use of such tests and the inability to reliably abstract meaningful information related to these tests from the medical record.

In summary, the findings presented herein suggest that although perioperative bleeding and plasma transfusion volume may be slightly increased in DHCA compared with MHCA patients, these differences did not correspond to a clinically significant change in the rate of transfusion of other blood products or the need for reoperation due to bleeding. Additional study will be needed to determine whether cooling to milder temperatures within the MHCA temperature range leads to clinically significant benefit with regard to bleeding-related outcomes in comparison to DHCA. Nevertheless, the comparable bleeding-related outcomes, as well as similar other major morbidity and mortality rates, observed between the DHCA and MHCA groups in this study further confirms the current clinical equipoise between these strategies and supports that a prospective randomized trial would be useful for the determination of the optimal degree of hypothermia during aortic arch reconstruction with circulatory arrest.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Tuesday/04-28-15_612_1550_Keenan.mp4.

Conflict of Interest Statement

Dr Levy has received consulting fees from CSL Behring, Grifols, and Medco. All other authors have nothing to disclose with regard to commercial support.

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Key Words: deep hypothermia, moderate hypothermia, circulatory arrest, coagulopathy, transfusion, hemiarch replacement, aortic arch surgery

Discussion

Dr E. Chen (Atlanta, Ga). Thanks very much. Congratulations, Dr Keenan, on a fabulous presentation. I'd like to commend you and your co-authors for helping us to gain a better understanding of the differences in bleeding risk and blood transfusion requirements between deep and moderate hypothermic circulatory arrest at the time of arch reconstruction.

As the use of moderate hypothermia becomes more widespread, studies such as yours are critical in affording us better understanding of the true differences between this technique and the more traditional technique of deep hypothermia. Thanks again for sending all your presentation materials and manuscript well in advance of the meeting.

I've got 3 questions. The first is, although it meets the definition of moderate hypothermia by recent consensus definition, the median temperature of 24°C in the moderate group is probably a little lower than some of the average temperatures reported in more recent publications. I wonder if you guys were able to look at potential differences when spreading out the differences in temperature, or are the numbers still low given that your group only recently changed circulation management strategy in 2013?

Dr Keenan (Durham, NC). Thank you for the question, Dr Chen.

You've raised an issue relating to the challenge of doing comparative research on a continuous variable. Ultimately our cohort in the moderate group was made up of patients that probably were lower than some of the recent reports composed of patients at relatively milder temperatures in the moderate hypothermia temperature range. This speaks to the fact that there is a fairly wide range in moderate hypothermia from 20 to 28°C as currently defined in the literature.

We made the decision to divide our cohort to allow for a clinically useful comparison between deep and moderate hypothermia based on existing definitions, but indeed we have included a fair number of patients that are on the lower end of the moderate hypothermia spectrum, and that may have limited our ability to detect a difference between outcomes in the deep and moderate hypothermia patients.

We did not do a subanalysis of patients in the more mild range of moderate hypothermia. Of note, there was a recent study published from the Penn group that also compared deep and moderate hypothermia. Their moderate patients were all 25°C and greater, and they did see a difference.

Therefore, we acknowledge that there is a possibility that our inclusion of patients in the lower end of the moderate hypothermia range patients may be a masking an effect present if only patients on the higher end of the moderate range had been considered.

Dr Chen. Second: despite the fact that, and I commend you for this, propensity matching was used to eliminate selection bias, I still wonder if there is a chance that inclusion of emergent type A cases in both groups may have added a clinical variable that statistical analysis could not completely tease out given that about a third of the patients were emergent with type A dissection.

Did you do any analysis looking at the isolated elective cases only to try to eliminate any further variables?

Dr Keenan. Thank you for this question.

To start, in our matched groups we did have balance in terms of the proportion of emergent and acute type A dissection cases. So for the validity of this comparison, at least on that level, we think there was balance. Certainly, there could be unmeasured potentially confounding factors that can affect the analysis. But you do raise the question of whether you introduce a certain degree of heterogeneity including elective and nonelective cases that ultimately limits your ability to detect a difference that may be present in one subset or another, and so some people may argue that elective and emergent cases should be studied separately altogether.

In this study, we wanted to include all patients, so that was our prespecified hypothesis, and that's what we started with. We did not look specifically at elective or nonelective cases, but that may be an area for future study.

Dr Chen. And, last, I think we all clearly recognize that coagulopathy after circulatory arrest is multifactorial, temperature being just one of the many factors. But there was little mention of cannulation and cerebral protection strategies in your presentation, and I wonder if you could just comment on the differences in strategy between the two groups, and did they evolve over time as your temperature changed?

Dr Keenan. Sure. Thank you.

With our transition to moderate hypothermia, we have used essentially exclusively unilateral selective antegrade cerebral perfusion through the right axillary artery. And when we do that, we target a flow of 5 to 15 mL per kilogram to a mean arterial pressure of 50 to 60 mm Hg with a 12° perfusate.

In situations in which it seems like for anatomical reasons or otherwise that cannulation through the axillary artery for perfusion may not be possible, the practice based on surgeon preference has been to cool to deep temperatures and then use retrograde cerebral perfusion.

In the deep cohort, still generally we do selective antegrade cerebral perfusion, but about a quarter were retrograde. Our group published a study last year where we compared those two strategies and didn't see any clinical differences. So we use either/or but about 25% was retrograde.

Dr Chen. Great job. Thank you.

Dr A. Estrera (*Houston, Tex*). Dr Keenan, I have really 2 questions. The first question relates to your temperature. How did you measure temperature? There is a lot of studies out there, and we know the difference between nasopharyngeal, tympanic, and bladder and rectal for core body temperature. How did you specifically measure temperature during your cases?

Dr Keenan. During our cases, we measure nasopharyngeal temperature as well as bladder or systemic measurements.

For this study, we divided our cohort based on systemic temperature rather than nasopharyngeal temperature because we felt the systemic temperature would be more important for our primary outcomes of bleeding-related outcomes or systemic coagulopathy.

But it raises a good point that there is heterogeneity in the way those things are reported, and nasopharyngeal temperature may be more relevant to a neurologic or other outcomes.

Dr Estrera. And I commend you for your consistency, but the reality is we all know that the bladder temperature oftentimes lags behind the nasopharyngeal temperature, and thus, at a 24° bladder temperature, you're probably less than 20° nasopharyngeal, at least from my experience. Just a comment.

The last question I have relates to your study period and pharmacological adjuncts. Your study period started in 2005. We all know that aprotinin, which we used extensively for these kinds of cases up to 2008, was discontinued. Was that factored in? And also comment about if you use the fibrinogen concentrate in your study.

Dr Keenan. Thank you for the question.

So this is, as I noted, a limitation in the study that there was evolving transfusion and adjunct management over the course of the study. Earlier on in the series, aprotinin was used. Now we use AMICAR (Akorn, Inc, Lake Forest, Ill) for antifibrinolytic therapy. We use this in conjunction also with a protocolized method for delivery of blood products. As part of this protocol, factor VII in cases of refractory bleeding and there was a small group of about 20 patients in this cohort that did receive fibrinogen concentrate as part of a prospective pilot study looking at the efficacy of that adjunct. Recently, we've also used prothrombin complex concentrate as an adjunctive agent for coagulopathy management in aortic cases, but none of the patients in this study received this agent. It's all part of an effort to be very aggressive in managing the coagulopathy that comes about in these cases.

However, aside from the factors that we mentioned in the propensity match, these adjuncts weren't not accounted for in the analysis.

Dr Estrera. Thank you.

FIGURE E1. Institutional transfusion algorithm schematic. CPB, Cardiopulmonary bypass; FFP, fresh-frozen plasma; TEG, thromboelastogram; HCA, hypothermic circulatory arrest; rFVIIa, recombinant activated Factor VII; PRBC, packed red blood cells; ICU, intensive care unit.

FIGURE E2. Standardized differences between the DHCA and MHCA groups before and after matching. *DHCA*, Deep hypothermic circulatory arrest; *MHCA*, moderate hypothermic circulatory arrest.