Mild hypothermia versus normothermia in patients undergoing cardiac surgery

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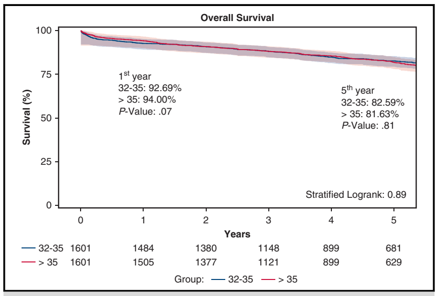
ABSTRACT

Objective: Temperature during cardiopulmonary bypass (CPB) for cardiac surgery has been controversial. The aim of the current study is to compare the outcomes for patients with mild hypothermia versus normothermic CPB temperatures.

Methods: All patients who underwent cardiac surgery with CPB and temperatures ≥32°C from 2011 to 2018 were included, which consisted of mild hypothermia (32°C-35°C) and normothermia (>35°C) cohorts. Propensity matching (1:1) was performed for risk adjustment. Primary outcomes included operative and long-term survival. Secondary outcomes included postoperative complications.

Results: A total of 6525 patients comprised 2 cohorts: mild hypothermia (32°C-35°C; n = 3148) versus normothermia (>35°C; n = 3377). Following adjustment for surgeon preference, there were 1601 propensity-matched patients who had similar baseline characteristics (standard mean difference, ≤0.10), including CPB time, crossclamp time, and intra-aortic balloon pump placement. Kaplan-Meier analysis showed no difference in long-term survival (82.6% vs 81.6%; *P* = .81). Over a median follow-up of 4.4 years, there were no differences in overall mortality (18.1% vs 18.1%; *P* = 1.1) or readmission (50.3% vs 48.3%; *P* = .2). Acute renal failure (3.7% vs 2.4%; *P* = .03) and intensive care unit hours (46.5 vs 45.1; *P* = .04) were significantly higher with hypothermia. There was no difference between cohorts for postoperative stroke (2.0% vs 2.0%; *P* = 1.0), reoperation (5.9% vs 6.0%; *P* = .9), or operative intra-aortic balloon pump placement (1.7% vs 1.8%; *P* = .9).

Conclusions: Patients with mild hypothermia during CPB had increased postoperative renal failure and length of intensive care unit stay. Although there was no difference in long-term survival, mild hypothermia does not appear to offer patients appreciable benefits, compared with normothermia. (JTCVS Open 2021;7:230-42)



Overall survival of patients after cardiac surgery under normothermia versus mild hypothermia.

CENTRAL MESSAGE

Following risk adjustment, use of mild hypothermia in cardiac surgery does not offer patients any substantial benefits and may increase postoperative complications.

PERSPECTIVE

Debate surrounds the appropriate core temperature during open heart surgery. Mild hypothermia can confer myocardial and end organ protection from ischemic insult. The current study shows that mild hypothermia is associated with increased postoperative events and minimal, if any, benefits. These findings support the use of normothermia in patients with similar preoperative risk.

See Commentaries on pages 243 and 245.

Cardiopulmonary bypass (CPB) is among the most significant medical advancements over the past century and its use has made modern cardiac surgery possible. However, CPB is associated with numerous perioperative complications, including renal dysfunction, coagulopathy, and neurologic decline.[1-3] Although no clear mechanism has been identified, some groups support the use of hypothermic CPB temperatures during bypass for myocardial and multiorgan protection from ischemic injury.[4] The appropriate temperature for CPB is a topic of controversy in cardiac surgery, with proponents of both mild hypothermia and normothermia.

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CIF = cumulative incidence functions
CPB = cardiopulmonary bypass

Although mild hypothermia has been shown to preserve myocardial function and reduce postoperative neurological dysfunction,[5] hypothermic CPB bypass temperatures have been associated with numerous perioperative complications, including coagulopathy, slow postanesthesia recovery times, and impaired drug metabolism.[4,6] Moreover, there is evidence that mild hypothermia during CPB does not offer any benefit regarding neuroprotective effects compared to normothermia.[7,8]

The objective of the current study was to provide a detailed analysis comparing outcomes for patients who underwent cardiac surgery with normothermic versus mildly hypothermic CBP temperatures. Primary outcomes included early and late survival. Secondary outcomes included postoperative complications and hospital readmission.

METHODS

Study Population

Patient outcomes were retrospectively gathered from our center's prospectively maintained cardiac surgical database. Use and analysis of the database was approved by the institutional review board and consent waived (STUDY18120143 approved and consent waived April 17, 2019). Patients from 2011 to 2018 were divided into 2 CPB temperature cohorts: mild hypothermia (32°C-35°C) and normothermia (>35°C). Core body temperature measurements were based on bladder probe temperatures.

Elective and urgent cases were included in the analysis; emergency cases were excluded. All Society of Thoracic Surgeons index cardiac surgery procedures were analyzed, including isolated coronary artery bypass grafting (CABG), isolated valve, and CABG with valve procedures. All hypothermic circulatory arrest cases and any patient who underwent cardiac surgery with CPB temperatures <32°C were excluded from primary analysis. The decision to cool a patient was based on a combination of surgeon preference and patient characteristics. Patients were weaned to 35.5°C to 36°C before ceasing CPB.

Statistical Analysis

Baseline patient characteristics. Baseline patient characteristics were compared between temperature cohorts. Wilcoxon rank-sum was used for continuous variables. The χ^2 (or Fisher exact test when 25% cell has expected number < 5) was used for categorical variables.

Propensity matching. Propensity score matching used logistic regression that included all baseline characteristics (Table 1) to reduce selection bias in a saturated manner. The individual surgeon and the effect of surgeon preference for CPB temperature was included in the propensity matching. Histograms comparing cohorts before and after matching can be found in Figures E1 and E2.

We used 1:1 greedy nearest neighbor matching, with specified caliper width (0.2) of the standard deviation of the logit of the propensity score. The difference in propensity score between groups was less than or equal to the caliper width. Finally, we checked the balance of the two cohorts using standardized mean difference (SMD). All SMD values were below 0.1, or well balanced.

After propensity score matching, because matched pairs were no longer independent, all calculations were based on matched pairs. McNemar tests were used for categorical variables. Paired *t* tests (or Wilcoxon signed-rank tests for nonnormal distributions) were used for continuous variables.

Mortality and survival. Long-term survival was compared for each group with the use of Kaplan-Meier curves. A cluster log rank test was used to compare mortality between the Kaplan-Meier curves of each group.

All baseline characteristics were assessed in the univariate Cox proportional hazard model to predict time to death. A shared frailty model for mortality was used to account for the effect of surgeon preference on CPB temperature. Significant covariables were adjusted in the multivariable models of time to death and readmission separately. After matching, a stratified Cox regression with robust variance estimator was used to determine the marginal effect of mortality.

Readmission. All readmissions to systemwide hospitals (>40 branches) were captured in our institution's database. In the event of multiple readmissions for the same patient, time to the first readmission was used in the model.

For readmission over time, cause-specific hazard was calculated using the cumulative incidence function (CIF) (death as a competing risk) in both univariate and multivariable models. CIF was used to generate a curve for long-term readmissions. A competing risk analysis with Fine and Gray regression was used to estimate the risk of readmission and account for the effect of surgeon preference on CPB temperature. After matching, a stratified Gray K-sample test was used to estimate the difference of CIF of readmissions between groups.

RESULTS

Baseline Characteristics

Figure 1 displays the patient flow diagram. We identified 6525 patients. There were differences between the 2 groups in baseline characteristics before matching (Table E1), including, but not limited to, body mass index, CPB time, and crossclamp time.

Following adjustment for surgeon preference for CPB temperature, there were 3202 propensity-matched patients (1601 each in the mild hypothermia and normothermia groups) (Table 1) well-matched (SMD, ≤0.10) for baseline characteristics and intraoperative variables, including CPB time (101 minutes vs 100 minutes; SMD, 0.036) and crossclamp time (75 minutes vs 74 minutes; SMD, 0.011). Propensity scores histograms before and after matching are in Figures E1 and E2.

In a comparison of the lowest median CPB temperature in the cohorts, the mild hypothermia cohort (median, 34.2°C; range, 33.4°C-34.8°C) was significantly lower than the normothermia cohort (median, 35.7°C; range, 35.4°C-36.0°C) ($P < .001$). There were similar proportions of patients that were elective (42.7% vs 42.9%; SMD, 0.034) and urgent (57.3% vs 57.1%; SMD, 0.034). The proportion of index case volume, including isolated valves, isolated CABG, and CABG + valve procedures, were similar between cohorts. There were no significant differences between cohorts in age (67.0 vs 68.0 years; $P = .7$). Patients were predominantly men (71.9% vs 71.3%; $P = .7$).

TABLE 1. Baseline characteristics after propensity score matching

	Temperature			
Variable	32°C-35°C (n = 1601)	>35°C (n = 1601)	SMD	*P* value
Age (y)	67.0 (60.0-75.0)	68.0 (60.0-75.0)	0.003	.7
Men	1151 (71.9)	1142 (71.3)	0.012	.7
Women	450 (28.1)	459 (28.7)	0.012	.7
White race	1512 (94.4)	1504 (93.9)	0.021	.5
Body mass index	29.3 (25.9-33.3)	29.6 (25.8-33.8)	0.038	.2
Body surface area (m^2)	2.0 (1.9-22)	2.1 (1.9-2.2)	0.020	.6
Diabetes mellitus	674 (42.1)	689 (43.0)	0.019	.6
Hypertension	1407 (87.9)	1403 (87.6)	0.008	.8
Chronic lung disease				
No	1271 (79.4)	1265 (79.0)	0.009	.8
Mild	158 (9.9)	146 (9.1)	0.025	.5
Moderate	83 (5.2)	81 (5.1)	0.005	.9
Severe	45 (2.8)	57 (3.6)	0.041	.2
Severity unknown	44 (2.8)	52 (3.3)	0.029	.4
Dialysis	38 (2.4)	41 (2.6)	0.013	.7
Immunosuppression	94 (5.9)	102 (6.4)	0.021	.6
Peripheral arterial disease	275 (17.2)	279 (17.4)	0.006	.9
Cerebrovascular disease	351 (21.9)	363 (22.7)	0.018	.6
Family history of CAD	351 (21.9)	339 (21.2)	0.018	.6
Previous heart failure	280 (17.5)	307 (19.2)	0.042	.2
Previous myocardial infarction	794 (49.6)	813 (50.8)	0.024	.5
Cardiac presentation				
No symptoms or angina	340 (21.2)	315 (19.7)	0.037	.3
Symptoms: Unlikely ischemia	60 (3.8)	70 (4.4)	0.029	.4
Stable angina	144 (9.0)	152 (9.5)	0.018	.6
Unstable angina	490 (30.6)	481 (30.0)	0.013	.7
NSTEMI	356 (22.2)	354 (22.1)	0.003	.9
STEMI	51 (3.2)	50 (3.1)	0.004	.9
Angina equivalent	17 (1.1)	16 (1.0)	0.006	.9
Other	143 (8.9)	163 (10.2)	0.039	.2
Arrhythmia	270 (16.9)	285 (17.8)	0.025	.5
No. of diseased vessels				
0	259 (16.2)	258 (16.1)	0.002	1.0
1	112 (7.0)	126 (7.9)	0.031	.3
2	294 (18.4)	325 (20.3)	0.051	.2
3	936 (58.5)	892 (55.7)	0.055	.1
Intra-aortic balloon pump	57 (3.6)	49 (3.1)	0.030	.4
Positive stress test	294 (18.4)	281 (17.6)	0.022	.5
Status				
Elective	684 (42.7)	687 (42.9)	0.034	.9
Urgent	917 (57.3)	914 (57.1)	0.034	.9
Surgery type				
Isolated CABG	996 (62.2)	962 (60.1)	0.043	.2
Isolated AV replacement	272 (17.0)	274 (17.1)	0.003	.9
Isolated MV replacement	30 (1.9)	37 (2.3)	0.030	.4
Isolated MV repair	54 (3.4)	54 (3.4)	0.000	1.0
CABG + AV replacement	179 (11.2)	192 (12.0)	0.023	.5

(Continued)

TABLE 1. Continued

Variable	Temperature 32°C-35°C (n = 1601)	>35°C (n = 1601)	SMD	*P* value
CABG + MV replacement	18 (1.1)	17 (1.1)	0.006	.9
CABG + MV repair	52 (3.3)	65 (4.1)	0.041	.2
BITA use	148 (9.2)	141 (8.8)	0.017	.7
CPB type				
Combination	6 (0.4)	6 (0.4)	0.000	1.0
Full	1595 (99.6)	1595 (99.6)	0.000	1.0
Serum creatinine	1.0 (0.8-1.2)	1.0 (0.8-1.2)	0.008	.8
Albumin	3.6 (3.3-3.9)	3.6 (3.3-3.9)	0.021	1.0
Total bilirubin (mg/dL)	0.6 (0.4-0.8)	0.6 (0.4-0.8)	0.053	.1
Ejection fraction (%)	55.0 (45.0-60.0)	55.0 (45.0-60.0)	0.002	.9
STS risk score (%)	1.5 (0.8-3.1)	1.6 (0.7-3.4)	0.053	.5
Previous valve procedure	18 (1.1)	18 (1.1)	0.000	1.0
Previous CABG	73 (4.6)	85 (5.3)	0.034	.3
Previous PCI	389 (24.3)	423 (26.4)	0.056	.2
CPB time (min)	101.0 (83.0-126.0)	100.0 (79.0-125.0)	0.036	.04
Crossclamp time (min)	75.0 (57.0-97.0)	74.0 (56.0-95.0)	0.011	.2

Values are presented as n (%) or median (interquartile range 1-3) for categorical and continuous variables, respectively. Propensity score matching includes matching for surgeon preference of CPB temperature. *SMD*, Standardized mean difference; *CAD*, coronary artery disease; *NSTEMI*, non-ST-elevated myocardial infarction; *CABG*, coronary artery bypass grafting; *AV*, aortic valve; *MV*, mitral valve; *BITA*, bilateral internal thoracic artery; *CPB*, cardiopulmonary bypass; *STS*, Society of Thoracic Surgeons; *PCI*, percutaneous coronary intervention.

Postoperative Outcomes

Following matching for surgeon preference (Figure 2), acute renal failure (3.7% vs 2.4%; $P = .030$) and total intensive care unit hours (46.5 vs 45.1; $P = .04$) were significantly higher for the mild hypothermia cohort (Table 2). Blood transfusion (33.8% vs 31.0%; $P = .089$) was not statistically different. There was no difference between cohorts for postoperative stroke (2.0% vs 2.0%;

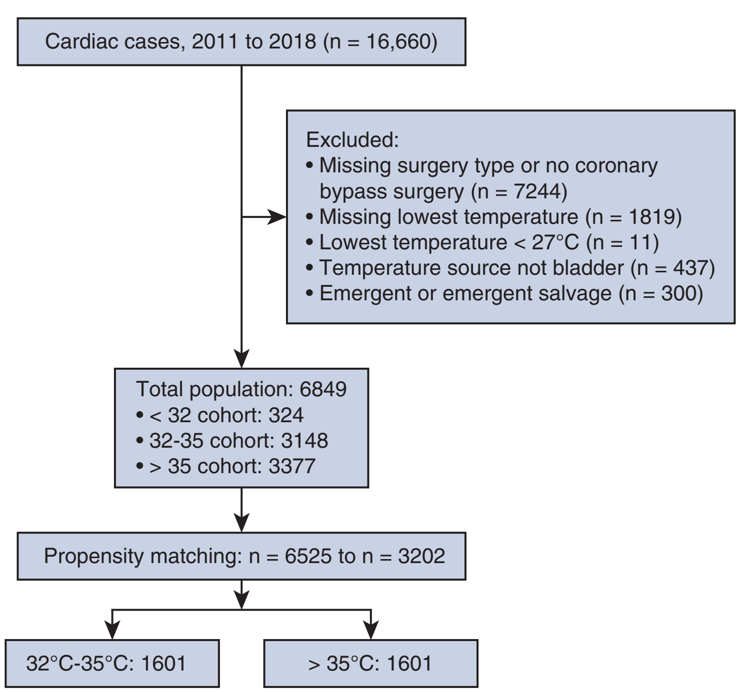

FIGURE 1. Consolidated Standards of Reporting Trials patient flow diagram.

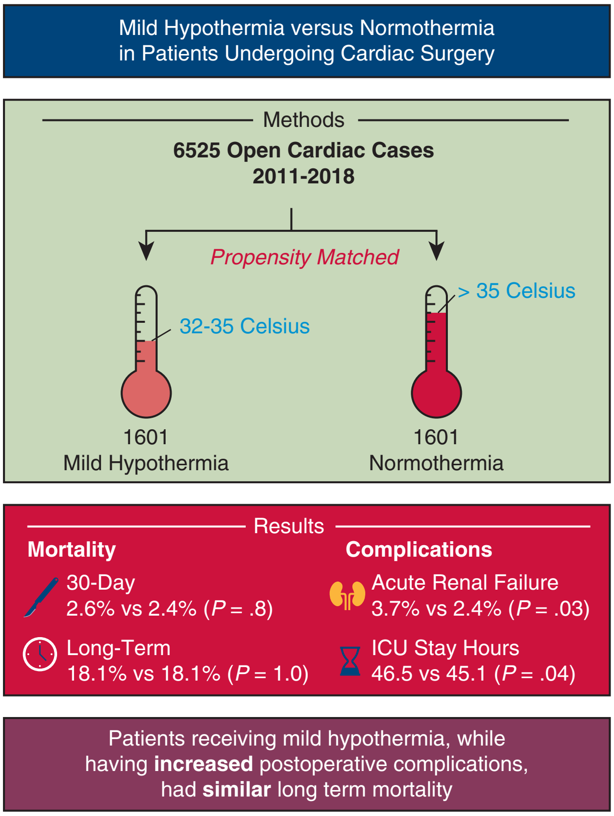

FIGURE 2. Following propensity matching for surgeon preference, postoperative acute renal failure was significantly higher in the normothermia cohort. *ICU*, Intensive care unit.

$P = 1.0$), reoperation (5.9% vs 6.0%; $P = .9$), or intra-aortic balloon pump placement (1.7% vs 1.8%; $P = .9$). There was no difference in prolonged ventilatory requirements (8.3% vs 8.0%; $P = .7$), sternal wound infection (0.3% vs 0.2%; $P = 1.0$), sepsis (1.3% vs 0.8%; $P = .2$), pneumonia (3.4% vs 2.6%; $P = .2$), atrial fibrillation (34.5% vs 33.7%; $P = .6$), and length of stay (8.0 days vs 8.0 days; $P = .2$).

Survival and Hospital Readmission

Kaplan-Meier survival showed that there was no difference between mild hypothermia and normothermia cohorts (82.6% vs 81.63%; $P = .81$) for long-term survival (Figure 3).

Over a mean follow-up period of 4.4 years (range, 2.79-6.11 years), there was no difference between cohorts for overall mortality (18.1% vs 18.1%; $P = 1.0$) or overall hospital readmission (50.3% vs 48.3%; $P = .2$) with propensity matching (Table 2). There was no difference between cohorts for 30-day mortality (2.6% vs 2.4%; $P = .8$) or 1-year mortality (7.3% vs 6.0%; $P = .1$).

On multivariable analysis, mild hypothermia was not a predictor of mortality (hazard ratio [HR], 1.02; 95% confidence interval, 0.89-1.16; $P = .8$) (Table 3). The most significant preoperative predictors of mortality included a history of dialysis (HR, 1.77; 95% confidence interval [CI], 1.23-2.56; $P = .002$), severe chronic obstructive pulmonary disease (HR, 1.69; 95% CI, 1.33-2.15; $P < .001$), peripheral artery disease (HR, 1.57; 95% CI, 1.37-1.79; $P < .001$), and immunosuppression (HR, 1.55; 95% CI, 1.26-1.92; $P \leq .001$).

Cumulative incidence of long-term hospital readmission was not different between cohorts (50.12% vs 49.4%; $P = .46$) (Figure 4). The Fine and Gray model for risk of readmission showed that mild hypothermia was not a predictor of hospital readmission (HR, 1.04; 95% CI, 0.96-1.11; $P = .3$) (Table 4). Severe lung disease (HR, 1.30; 95% CI, 1.070-1.58; $P = .008$), immunosuppression (HR, 1.36; 95% CI, 1.18-1.57; $P < .001$), and isolated mitral valve replacement (HR, 1.49; 95% CI, 1.19-1.86; $P < .001$) were among the most significant predictors of hospital readmission.

DISCUSSION

To our knowledge, the current study is among the largest single-center analyses comparing propensity-matched outcomes for CPB temperature cohorts. For cardiac surgery patients who underwent mild hypothermia (32°C-35°C) versus normothermia (>35°C), we reported no significant differences for short- or long-term survival and hospital readmission. Although long-term survival was not different between CPB temperature cohorts in this study, the increased risks associated with heightened acute postoperative renal failure, calls for close examination of the potential risks versus benefits of mild hypothermia.

In a large meta-analysis, including 44 randomized controlled trials from 14 nations, Ho and colleagues[4] compared the relative risks of normothermic (>34°C) versus hypothermic (≤34°C) CPB temperatures in adult cardiac surgery. Mortality between bypass temperature cohorts was not significantly different. Likewise, there was no difference in the risk of postoperative stroke and infections, which is consistent with the current study's results. Furthermore, the meta-analysis did indicate a significantly increased risk of requiring blood transfusions, including fresh frozen plasma, red blood cells, and platelets; whereas the current study did not find a statistically significant difference [33.8% vs 31.0%; $P = .089$]. However, the importance of increased blood transfusions should not be understated, as substantial literature has shown an impact on patient morbidity and mortality.[9-15] Other randomized prospective data[16] found a reduced need for blood products in patients who had cardiac operations with normothermic CPB temperatures. This is not surprising, given that well-established data have shown that even very mild perioperative hypothermia (<1°C below normal temperatures) in patients undergoing surgery is associated with significantly

TABLE 2. Outcomes after propensity score matching*

Variables	Temperature (°C) 32°C-35°C (n = 1601)	>35°C (n = 1601)	95% confidence interval	P value
Blood product transfusion	541 (33.8)	496 (31.0)	–0.02 to 0.07	.09
Prolonged ventilation	133 (8.3)	128 (8.0)	–0.06 to 0.02	.7
Deep sternal wound infection	4 (0.3)	3 (0.2)	–0.004 to 0.00	.7
Acute renal failure	59 (3.7)	38 (2.4)	–0.02 to 0.13	.030
Sepsis	20 (1.3)	13 (0.8)	–0.01 to 0.00	.2
Pneumonia	54 (3.4)	42 (2.6)	–0.05 to 0.03	.2
Permanent stroke	32 (2.0)	32 (2.0)	–0.05 to 0.07	1.0
Operative IABP	27 (1.7)	28 (1.8)	–0.05 to 0.89	.9
Reoperation	94 (5.9)	96 (6.0)	–0.03 to 0.08	.9
New-onset atrial fibrillation	553 (34.5)	540 (33.7)	–0.08 to 0.12	.6
Length of stay (d)	8.0 (6.0-11.0)	8.0 (6.0-11.0)	NA	.2
Total ICU time (h)	46.5 (26.0-74.0)	45.1 (26.0-71.0)	NA	.04
Follow-up years	4.4 (2.8-6.4)	4.3 (2.7-6.0)	NA	.082
Mortality				
30 d	42 (2.6)	29 (2.4)	–0.02 to –0.01	.8
1 y	117 (7.3)	96 (6.0)	–0.04 to 0.05	.1
5 y	246 (15.4)	251 (15.7)	–0.04, to 0.06	.8
Overall	289 (18.1)	290 (18.1)	–0.03 to 0.06	1.0
Readmission				
30 d	195 (12.2)	186 (11.6)	–0.01 to 0.09	.6
1 y	447 (27.9)	428 (26.7)	–0.04 to 0.05	.5
5 y	748 (46.7)	733 (45.8)	–0.05 to 0.04	.6
Overall	806 (50.3)	773 (48.3)	–0.05 to 0.04	.2
Cardiac readmission	689 (43.0)	651 (40.7)	–0.05 to 0.04	.2
Heart failure readmission	291 (18.2)	317 (19.8)	–0.05 to 0.06	.2

Values are presented at n (%) or median (interquartile range 1-3) for categorical and continuous variables, respectively. *IABP*, Intra-aortic balloon pump; *NA*, not applicable; *ICU*, intensive care unit. *Propensity score matching, including matching for surgeon preference of cardiopulmonary bypass temperature.

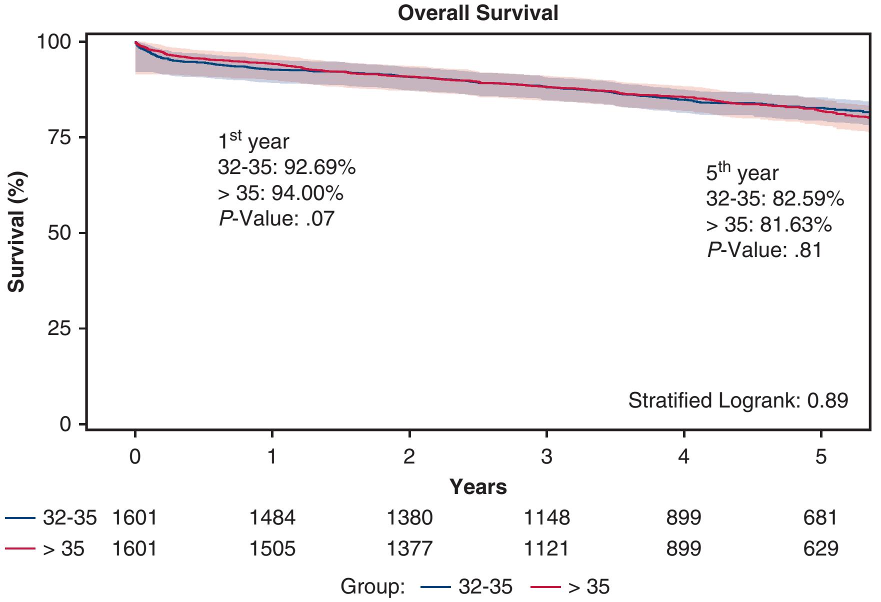

FIGURE 3. Kaplan-Meier survival curve showing no difference in long-term survival between cardiopulmonary bypass temperature cohorts.

TABLE 3. Shared frailty model for mortality (considering surgeon as random effect)

Variable	Hazard ratio	95% confidence interval	*P* value
32°C-35°C (ref: >35°C)	1.018	0.895-1.159	.8
Diabetes	1.367	1.211-1.542	<.001
Chronic lung disease (ref: none)			
Mild	1.223	1.018-1.468	.031
Moderate	1.575	1.299-1.910	<.001
Severe	1.689	1.329-2.148	<.001
Severity unknown	1.678	1.219-2.309	.001
Dialysis	1.773	1.227-2.562	.002
Immunosuppression	1.556	1.263-1.916	<.001
Peripheral vascular disease	1.570	1.374-1.794	<.001
Cerebrovascular disease	1.258	1.103-1.434	<.001
Prior heart failure	1.269	1.098-1.467	.001
Cardiac presentation (ref: none)			
Symptoms: unlikely ischemia	1.247	0.989-1.571	.062
Stable angina	1.093	0.865-1.382	.5
Unstable angina	0.838	0.692-1.015	.070
NSTEMI	1.010	0.825-1.237	.9
STEMI	1.160	0.802-1.677	.4
Angina equivalent	0.769	0.376-1.571	.5
Other	1.155	0.921-1.448	.2
Arrhythmia	1.309	1.142-1.500	<.001
Surgery type (ref: isolated CABG)			
Isolated AV replacement	1.130	0.923-1.385	.2
Isolated MV replacement	1.417	0.966-2.079	.07
Isolated MV repair	0.887	0.611-1.289	.5
CABG + AV replacement	1.461	1.202-1.777	<.001
CABG + MV replacement	1.097	0.651-1.847	.7
CABG + MV repair	1.154	0.875-1.521	.3
Full CPB (ref: combination)	0.385	0.190-0.780	.008
Prior CABG procedure	1.350	1.097-1.662	.005
Age	1.041	1.035-1.048	<.001
Serum creatinine	1.124	1.062-1.189	<.001
Albumin	0.516	0.456-0.584	<.001
Ejection fraction	0.993	0.988-0.998	.005
CPB time	1.010	1.007-1.013	<.001
Crossclamp time	0.990	0.987-0.994	<.001
Surgeon (random effect)	–	–	.1

NSTEMI, Non-ST-elevated myocardial infarction; *CABG*, coronary artery bypass grafting; *AV*, aortic valve; *MV*, mitral valve; *CPB*, cardiopulmonary bypass.

increased blood loss and transfusion requirements, compared with patients with normothermia.[17]

Important findings in the current study include increased blood product use and significantly increased postoperative acute renal failure in the mild hypothermia cohort. Although intraoperative decision making is hard to delineate, it may be that surgeons chose to use mild hypothermia to increase multisystemic organ protection from ischemic injury and myocardial tissue preservation[18] in cases with concerning perioperative patient characteristics or intraoperative factors. If intraoperative protection from cardiac ischemia was improved by hypothermia, we could see an increased need for IABP placement in the normothermia group. However, there is no difference in IABP requirements between temperature cohorts in this investigation, consistent with prior work.[4,16]

Although not the primary focus of the current study, it is important to address the often-touted neuroprotective

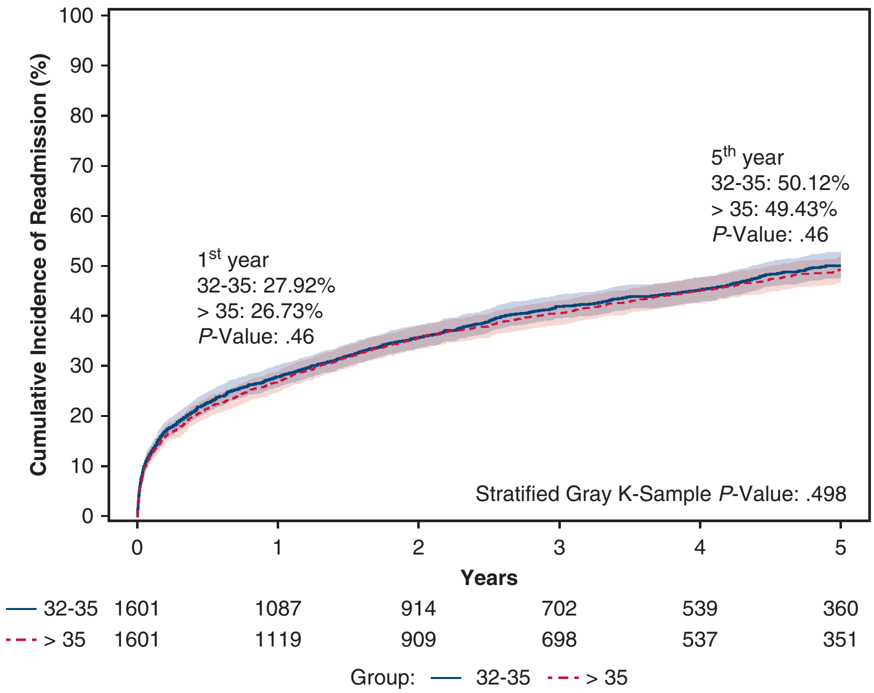

FIGURE 4. Cumulative incidence of hospital readmission was not significantly different between normothermia and mild hypothermia cohorts.

TABLE 4. Fine and Gray model for readmission (considering surgeon as random effect)

Variable	Hazard ratio	95% confidence interval	*P* value
32°C-35°C (ref: >35°C)	1.035	0.964-1.111	.3
Woman	1.254	1.148-1.370	<.001
Diabetes	1.161	1.078-1.251	<.001
Chronic lung disease (ref: none)			
Mild	1.311	1.170-1.469	<.001
Moderate	1.291	1.120-1.488	<.001
Severe	1.301	1.070-1.582	.008
Severity unknown	1.129	0.923-1.381	.2
Immunosuppression	1.364	1.184-1.571	<.001
Peripheral vascular disease	1.251	1.141-1.372	<.001
Cerebrovascular disease	1.253	1.150-1.364	<.001
Prior heart failure	1.164	1.061-1.276	.001
Arrhythmia	1.149	1.044-1.265	.004
Surgery type (ref: isolated CABG)			
Isolated AV replacement	1.001	0.907-1.104	1.0
Isolated MV replacement	1.487	1.187-1.863	<.001
Isolated MV repair	0.876	0.714-1.074	.2
CABG + AV replacement	1.120	1.001-1.253	.048
CABG + MV Replacement	1.366	0.961-1.944	.083
CABG + MV repair	1.195	0.991-1.442	.063
Age	1.007	1.003-1.011	<.001
Body surface area	1.212	1.030-1.427	.021
Serum creatinine	1.123	1.090-1.158	<.001
Albumin	0.782	0.724-0.844	<.001
STS risk score	0.977	0.965-0.990	<.001

CABG, Coronary artery bypass grafting; *AV*, aortic valve; *MV*, mitral valve; *STS*, Society of Thoracic Surgeons.

benefits of mildly hypothermic CPB temperatures,[5,19,20] despite accumulating evidence to the contrary.[7,8,21,22] Existing evidence includes prospective randomized data showing increased subclinical cognitive impairment in patients who underwent mild hypothermia[21] and noninferiority of normothermic bypass temperatures[7] in terms of neuroprotection. Indeed, we did not find any difference between CPB temperature cohorts regarding clinically apparent neurologic complications, indicated by similar postoperative stroke. Nonetheless, subclinical neurological deficits are potentially influential to patients' postoperative quality of life and merit further investigation.

The decision to offer mild systemic hypothermia during CPB should be based on the available evidence of risks versus benefits. Although prior literature has established the potential efficacy of normothermic temperatures for CPB, in the contemporary era there remains debate as to the appropriate temperature for routine cardiac surgery. The current study provides a large, propensity-matched sample. After accounting for surgeon preference, these outcomes may hold relevance for future decision making regarding CPB temperature. Our results indicate that mild hypothermia does not offer sufficient benefits and may increase patient risk. Therefore, we do not routinely use mild hypothermia for CPB during cardiac surgery.

Limitations

The study is limited in that it was designed based on retrospective data and is influenced by potential confounding and selection bias, which was somewhat controlled for by propensity matching of baseline characteristics. There is a chance that some of the patients were lost to follow-up or were readmitted to out-of-system centers. There may be inherent differences in patients who underwent mild hypothermia that are not accounted for in the study risk adjustment. Variability in surgeon preference for when and if they cooled patients to mild hypothermia is an additional potential source of selection bias. Factors such as transient regional wall motion abnormalities, including concern for poor protection or heightened ischemia risk may have influenced the surgeon's preference for hypothermia. As a retrospective investigation, these data can detect associations but not a causal relationship between hypothermia and outcomes.

CONCLUSIONS

Patients who had mild hypothermic temperatures during CPB had increased postoperative renal failure and length of intensive care unit stay. There was no difference between cohorts for the incidence of postoperative stroke, long-term overall mortality, and readmissions. Moreover, in prior subgroup analysis, we found no significant difference for operative mortality and survival for a comparison between cohorts with hypothermic CPB temperatures (<32°C) and normothermia. This may suggest that normothermia can be appropriate even in patients that some surgeons may cool to lower temperatures. Given these data, there are risks associated with the use of mild hypothermia for cardiac surgery and no clear benefits over normothermia, indicating that patients may fare better with the routine use of normothermia.

Conflict of Interest Statement

Dr Kilic serves on the Medtronic Advisory Board and receives personal fees. Dr Sultan receives institutional research support from AtriCure and Medtronic. 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: normothermia, mild hypothermia, cardiopulmonary bypass

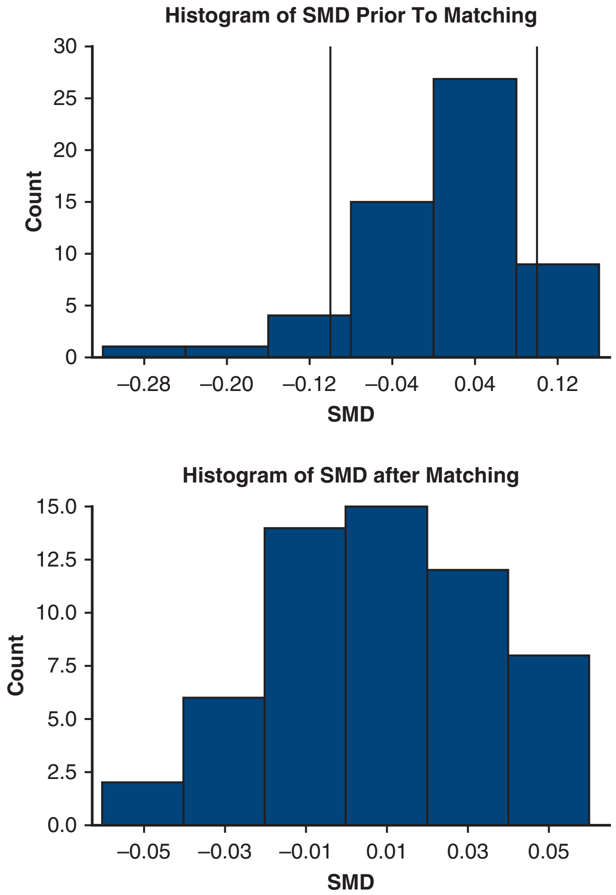

FIGURE E1. Propensity scores before matching. Group refers to cardiac surgery patients undergoing mild hypothermia (32°C-35°C) compared with normothermia (>35°C). *SMD*, Standardized mean difference.

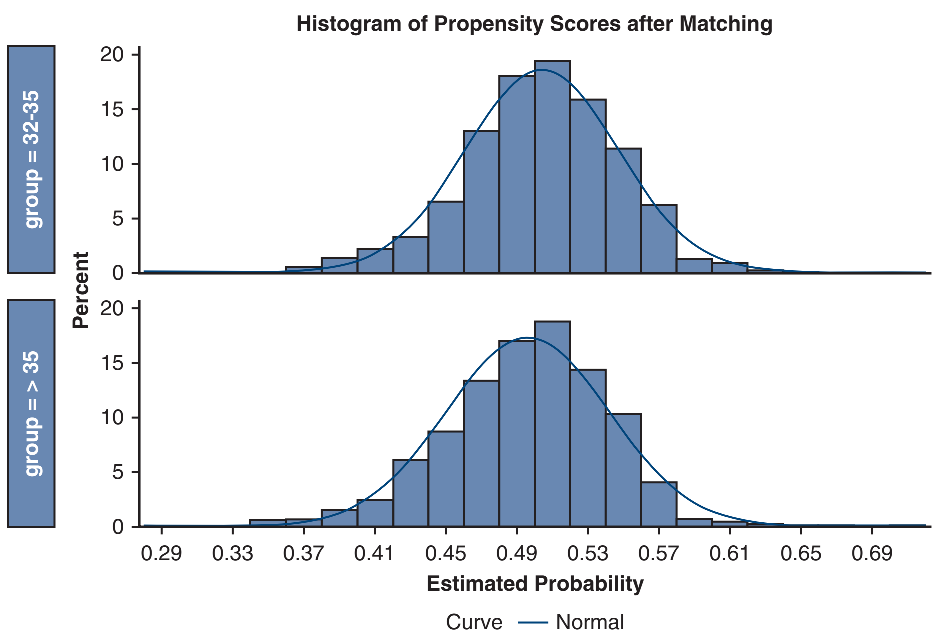

FIGURE E2. Propensity scores after matching. Group refers to cardiac surgery patients undergoing mild hypothermia (32°C-35°C) compared with normothermia (>35°C).

TABLE E1. Baseline characteristics before propensity score matching

Variable	Temperature 32°C-35°C (n = 3148)	>35°C (n = 3377)	*P* value	SMD
Age	68.0 (60.0-75.0)	68.0 (60.0-76.0)	.068	0.046
Male	2217 (70.4)	2329 (69.0)	.2	0.032
Female	931 (29.6)	1048 (31.0)	.2	0.032
White race	2982 (94.7)	3140 (93.0)	.003	0.073
Black race	113 (3.6)	160 (4.7)	.021	0.058
BMI	28.7 (25.5-32.8)	29.7 (26.0-34.0)	<.001	0.146
BSA	2.0 (1.9-2.2)	2.0 (1.9-2.2)	<.001	0.096
Diabetes mellitus	1264 (40.2)	1501 (44.5)	<.001	0.087
Hypertension	2755 (87.5)	2923 (86.6)	.2	0.029
Chronic lung disease			.1	
No	2488 (79.1)	2599 (77.0)		0.050
Mild	299 (9.5)	322 (9.5)		0.001
Moderate	157 (5.0)	223 (6.6)		0.069
Severe	108 (3.4)	122 (3.6)		0.010
Severity unknown	95 (3.0)	109 (3.2)		0.012
Dialysis	62 (2.0)	87 (2.6)	.1	0.041
Immunosuppression	176 (5.6)	201 (6.0)	.5	0.016
Peripheral arterial disease	549 (17.4)	657 (19.5)	.036	0.052
Cerebrovascular disease	718 (22.8)	739 (21.9)	.4	0.022
Family history of CAD	633 (20.1)	749 (22.2)	.041	0.051
Previous heart failure	609 (19.4)	710 (21.0)	.092	0.042
Previous MI	1508 (47.9)	1625 (48.1)	.9	0.004
Cardiac presentation			<.001	
No symptoms or angina	773 (24.6)	755 (22.4)		0.052
Symptoms unlikely to be ischemia	121 (3.8)	197 (5.8)		0.093
Stable angina	287 (9.1)	278 (8.2)		0.031
Unstable angina	890 (28.3)	932 (27.6)		0.015
NSTEMI	613 (19.5)	650 (19.3)		0.006
STEMI	83 (2.6)	120 (3.6)		0.053
Angina equivalent	34 (1.1)	28 (0.8)		0.026
Other	347 (11.0)	417 (12.4)		0.041
Arrhythmia	536 (17.0)	638 (18.9)	.050	0.047
No. of diseased vessels			.4	
0	495 (19.1)	503 (19.4)		0.008
1	209 (8.1)	242 (9.4)		0.045
2	455 (17.6)	456 (17.6)		0.001
3	1430 (55.2)	1388 (53.6)		0.033
Intra-aortic balloon pump	69 (2.7)	70 (2.7)	.9	0.002
Positive stress test	434 (16.8)	416 (16.1)	.5	0.019
Status			1.0	
Elective	1243 (48.0)	1242 (48.0)		<.001
Urgent	1346 (52.0)	1347 (52.0)		<.001
Surgery type			.7	
Isolated CABG	1426 (55.1)	1380 (53.3)		0.036
Isolated AV replacement	499 (19.3)	545 (21.1)		0.044
Isolated MV replacement	58 (2.2)	56 (2.2)		0.005
Isolated MV repair	118 (4.6)	113 (4.4)		0.009

(Continued)

TABLE E1. Continued

Variable	Temperature 32°C-35°C (n = 3148)	>35°C (n = 3377)	*P* value	SMD
CABG + AV replacement	353 (13.6)	360 (13.9)		0.008
CABG + MV replacement	32 (1.2)	26 (1.0)		0.022
CABG + MV repair	103 (4.0)	109 (4.2)		0.012
BITA utilization	193 (7.5)	196 (7.6)	.9	0.004
CPB type			.8	
Combination	8 (0.3)	9 (0.35)		0.006
Full	2581 (99.7)	2580 (99.7)		0.021
Serum creatinine	1.0 (0.8-1.2)	1.0 (0.8-1.2)	<.001	0.077
Albumin	3.7 (3.4-4.0)	3.7 (3.3-3.9)	.048	0.041
Total bilirubin	0.6 (0.4-0.8)	0.6 (0.5-0.8)	<.001	0.092
Ejection fraction	55.0 (45.0-60.0)	55.0 (45.0-60.0)	.5	0.008
STS risk score	1.5 (0.7-3.2)	1.7 (0.9-3.6)	<.001	0.090
Previous valve procedure	41 (1.3)	60 (1.8)	.1	0.039
Previous CABG	151 (4.8)	204 (6.0)	.027	0.055
Previous PCI	743 (23.6)	891 (26.4)	.010	0.064
CPB time	109.0 (87.0-135.5)	97.0 (75.0-122.0)	<.001	0.308
Crossclamp time	79.0 (61.0-103.0)	73.0 (54.0-95.0)	<.001	0.207

Values are presented as n (%) or median (interquartile range 1-3) for categorical and continuous variables, respectively. *SMD*, Standardized mean difference; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *MI*, myocardial infarction; *NSTEMI*, non-ST elevated myocardial infarction; *CABG*, Coronary Artery Bypass Grafting; *AV*, aortic valve; *MV*, mitral valve; *BITA*, bilateral internal thoracic artery; *CPB*, cardiopulmonary bypass; *STS*, Society of Thoracic Surgeons; *PCI*, percutaneous coronary intervention.