Mild hypothermia versus normothermia in patients undergoing cardiac surgery

Valentino Bianco, DO, MPH, Arman Kilic, MD, Edgar Aranda-Michel, BS, Courtenay Dunn-Lewis, PhD, Derek Serna-Gallegos, MD, Shangzhen Chen, MPH, Valentino Bianco, DO, MPH, Arman Kilic, MD, Edgar Aranda-Michel, BS, Courtenay Dunn-Lewis, PhD, Derek Serna-Gallegos, MD, Shangzhen Chen, MPH, and Ibrahim Sultan, MD

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 2.4%; 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)

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. 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. The appropriate temperature for CPB is a topic of controversy in cardiac surgery, with proponents of both mild hypothermia and normothermia.
Although mild hypothermia has been shown to preserve myocardial function and reduce postoperative neurological dysfunction, hypothermic CPB bypass temperatures have been associated with numerous perioperative complications, including coagulopathy, slow postanesthesia recovery times, and impaired drug metabolism. Moreover, there is evidence that mild hypothermia during CPB does not offer any benefit regarding neuroprotective effects compared to normothermia.

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 CPB 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 χ² (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. After matching, a stratified Cox regression with robust variance estimator was used to determine the marginal effect of mortality.

**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).

**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 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.
| Variable                        | Temperature                          | SMD   | P value |
|--------------------------------|--------------------------------------|-------|---------|
|                                | 32°C-35°C (n = 1601)                 | 35°C  (n = 1601) |       |
| Age (y)                        | 67.0 (60.0-75.0)                     | 68.0 (60.0-75.0) | 0.003  |
| Men                            | 1151 (71.9)                         | 1142 (71.3)  | 0.012  |
| Women                          | 450 (28.1)                          | 459 (28.7)  | 0.012  |
| White race                     | 1512 (94.4)                         | 1504 (93.9) | 0.021  |
| Body mass index                | 29.3 (25.9-33.3)                    | 29.6 (25.8-33.8) | 0.038 |
| Body surface area (m²)         | 2.0 (1.9-2.2)                       | 2.1 (1.9-2.2) | 0.020  |
| Diabetes mellitus              | 674 (42.1)                          | 689 (43.0)  | 0.019  |
| Hypertension                   | 1407 (87.9)                         | 1403 (87.6) | 0.008  |
| 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   |
| Imunosuppression               | 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)
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%;
Mild Hypothermia versus Normothermia
in Patients Undergoing Cardiac Surgery

Methods

6525 Open Cardiac Cases
2011-2018

Results

Mortality

Propensity Matched

32-35 Celsius

0.8%

35 Celsius

2.0%

30-Day

2.6% vs 2.4% (P = .8)

Long-Term

18.1% vs 18.1% (P = 1.0)

Complications

Acute Renal Failure

3.7% vs 2.4% (P = .03)

ICU Stay Hours

46.5 vs 45.1 (P = .04)

Patients receiving mild hypothermia, while having increased postoperative complications, had similar long term mortality.

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

In a large meta-analysis, including 44 randomized controlled trials from 14 nations, Ho and colleagues 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. Other randomized prospective data 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

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 ≤ .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 the current study, 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. Other randomized prospective data 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) | 95% confidence interval | P value |
|-----------------------------------|------------------|-------------------------|---------|
|                                   | 32°C-35°C (n = 1601) | >35°C (n = 1601) |                   |         |
| 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.
increased blood loss and transfusion requirements, compared with patients with normothermia.\textsuperscript{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\textsuperscript{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.\textsuperscript{4,16}

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

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
Variable & Hazard ratio & 95\% confidence interval & \textit{P} value \\
\hline
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 & 0.576-1.015 & .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 \\
\hline
\end{tabular}
\caption{Shared frailty model for mortality (considering surgeon as random effect)}
\end{table}

\textit{NSTEMI}, Non-ST-elevated myocardial infarction; \textit{CABG}, coronary artery bypass grafting; \textit{AV}, aortic valve; \textit{MV}, mitral valve; \textit{CPB}, cardiopulmonary bypass.
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, despite accumulating evidence to the contrary. Existing evidence includes prospective randomized data showing increased subclinical cognitive impairment in patients who underwent mild hypothermia and noninferiority of normothermic bypass temperatures 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.

References
1. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Paczynski AD. Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1983;86:845-57.
2. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg. 2002;21:232-44.
3. Taggart DP, Westaby S. Neurological and cognitive disorders after coronary artery bypass grafting. Curr Opin Cardiol. 2001;16:271-6.
4. Ho KM, Tan JA. Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: a systematic review. Cardiovasc Ther. 2011;29:260-79.
5. Nathan HJ, Rodriguez R, Wozny D, Dupuis JY, Rubens FD, Bryson GL, et al. Neurprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. J Thorac Cardiovasc Surg. 2007;133:1206-11.
6. Insler SR, Sessler DI. Perioperative thermoregulation and temperature monitoring. Anesthesiol Clin. 2006;24:823-37.
7. Fakir R, Zimpfer D, Sodeck GH, Rajek A, Mora B, Dumfart J, et al. Influence of temperature management on neurocognitive function in biological aortic valve replacement. A prospective randomized trial. J Cardiovasc Surg (Torino). 2012;53:107-12.
8. Heyer EJ, Adams DC, Delphin E, McMahon DJ, Steneck SD, Oz MC, et al. Cerebral dysfunction after coronary artery bypass grafting done with mild or moderate hypothermia. J Thorac Cardiovasc Surg. 1997;114:270-7.
9. Engoren M, Schwann TA, Habib RH, Neill SN, Vance JL, Likosky DS. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97:514-20.
10. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg. 2002;74:1180-6.
11. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Callford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation. 2007;116:2544-52.
12. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellek FW, Likosky DS, et al. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg. 2009;108:1741-6.
13. Koch CG, Li L, Duncan AI, Mihaljevic T, Covgrove DM, Loop FD, et al. Morbidity and mortality risk associated with red blood cell and blood component transfusion in isolated coronary artery bypass grafting. Crit Care Med. 2006;34:1608-16.
14. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg. 2006;81:1650-7.
15. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. *Transfusion*. 1994;34:471-7.
16. Birdi I, Regragui I, Izzat MB, Bryan AJ, Angelini GD. Influence of normothermic systemic perfusion during coronary artery bypass operations: a randomized prospective study. *J Thorac Cardiovasc Surg*. 1997;114:475-81.
17. Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. *Anesthesiology*. 2008;108:71-7.
18. Kelly FE, Nolan JP. The effects of mild induced hypothermia on the myocardium: a systematic review. *Anesthesia*. 2010;65:505-15.
19. Nathan HJ, Wells GA, Munson JL, Wozny D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. *Circulation*. 2001;104:I85-91.
20. Okano N, Owada R, Fujita N, Kadoi Y, Saito S, Goto F. Cerebral oxygenation is better during mild hypothermic than normothermic cardiopulmonary bypass. *Can J Anesth*. 2000;47:131-6.
21. Grinn M, Czerny M, Baumer H, Kilo J, Madl C, Kramer L, et al. Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting—a prospective randomized trial. *Eur J Cardiothorac Surg*. 2000;18:270-5.
22. Rees K, Beranek-Stanley M, Burke M, Ebrahim S. Hypothermia to reduce neurological damage following coronary artery bypass surgery. *Cochrane Database Syst Rev*. 2001:Cd002138.

**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).
| Variable | Temperature | \(32^\circ \text{C} - 35^\circ \text{C} (n = 3148)\) | \(>35^\circ \text{C} (n = 3377)\) | \(P\) 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 |
| Variable                      | Temperature | P value | SMD |
|-------------------------------|-------------|---------|-----|
|                              | 32°C-35°C (n = 3148) | >35°C (n = 3377) |     |
| 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   |
| CPB type                      |             |         |     |
| Combination                   | 8 (0.3)     | 9 (0.35)  | .8   |
| Full                          | 2581 (99.7) | 2580 (99.7) | 0.006 |
| Serum creatinine              | 1.0 (0.8-1.2) | 1.0 (0.8-1.2) | <.001 |
| Albumin                       | 3.7 (3.4-4.0) | 3.7 (3.3-3.9) | .048 |
| Total bilirubin               | 0.6 (0.4-0.8) | 0.6 (0.5-0.8) | <.001 |
| Ejection fraction             | 55.0 (45.0-60.0) | 55.0 (45.0-60.0) | .5   |
| STS risk score                | 1.5 (0.7-3.2) | 1.7 (0.9-3.6) | <.001 |
| Previous valve procedure      | 41 (1.3)    | 60 (1.8)   | .1   |
| Previous CABG                 | 151 (4.8)   | 204 (6.0)  | .027 |
| Previous PCI                  | 743 (23.6)  | 891 (26.4) | .010 |
| CPB time                      | 109.0 (87.0-135.5) | 97.0 (75.0-122.0) | <.001 |
| Crossclamp time               | 79.0 (61.0-103.0) | 73.0 (54.0-95.0) | <.001 |

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.

242 JTCVS Open • September 2021