Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Tuesday September 15, 2015
1830 HOURS

LOCATION:
AquaTerra Restaurant
1 Johnson Street

PRESENTING ARTICLES:
Dr. Chris Perkes & Dr. Navroop Sandhu

SPONSORED BY:
Abbvie – Ms. Penny Reid

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

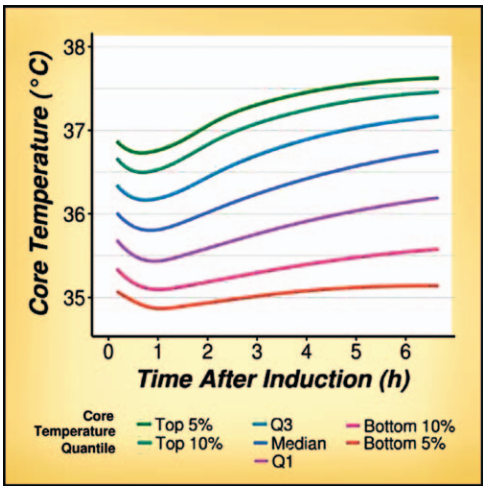
Perioperative Temperature Management

Time for a New Standard of Care?

Harriet W. Hopf, M.D.

CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

WHEN I started anesthesia residency in 1988, patients undergoing major surgery routinely arrived in the postanesthesia care unit (PACU) with a core temperature of 34.5° to 35°C. We did not fully understand how anesthesia causes hypothermia; we did not have practical, effective means of warming patients; and we did not have evidence of harm—although the shivering patients in the PACU probably had a different perspective. All this changed during my first decade in practice; by 1999, maintenance of perioperative normothermia had been incorporated into practice guidelines.[1] The most common definition of perioperative normothermia is core temperature at least 36.0°C on arrival in the PACU. This number was extrapolated from studies that compared outcomes between patients with relatively large differences in core temperature (1° to 2°C) on arrival in the PACU. Sun *et al.*[2] in this issue, using innovative analyses of a large patient dataset, demonstrate that, although most patients meet criteria for normothermia on arrival in the PACU, *intraoperative* hypothermia (35° to 36°C) is common. Moreover, longer duration of hypothermia is associated with a significant increase in transfusion requirement and a small but statistically significant increase in hospital length of stay. These results suggest the need for a more comprehensive definition of perioperative normothermia and more aggressive efforts to prevent intraoperative hypothermia.



"These results suggest the need for a more comprehensive definition of perioperative normothermia and more aggressive efforts to prevent intraoperative hypothermia."

In the 1980s and 1990s, Daniel Sessler and colleagues systematically defined the physiology of anesthesia-induced hypothermia. Perioperative hypothermia was demonstrated to have detrimental effects on patient comfort and recovery time, coagulation, and drug metabolism. Scott Augustine developed the forced air warmer (Bair Hugger, 3M, St. Paul, MN) and it became commercially available in 1988. The ability to warm patients effectively led to randomized controlled trials that demonstrated reduced surgical site infections, blood loss and transfusion, and cardiac complications in patients with a normal core temperature compared with patients with a core temperature 1° to 2°C lower on arrival in the PACU.

To understand the results of those clinical trials and the implications of the current large database study, it is important to understand the underlying physiology. Holdcroft *et al.*[3] demonstrated that central hypothermia does not require a change in total body heat content when there is redistribution of heat from the core to the periphery. Glosten *et al.*[4] demonstrated that, even with active warming, redistribution (and not heat loss) leads to an early decrease in core temperature under general and regional anesthesia. In awake patients, cold exposure leads to vasoconstriction and redistribution of heat to the core; anesthetic agents cause vasodilation and redistribution of heat to the periphery. Forced-air warming and

Image: Core temperature trajectories in 58,814 patients undergoing noncardiac surgery. From Sun et al.,*[2] figure 3 (this issue).*

Corresponding article on page 276.

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other active warming methods transfer heat to the patient and, over time, return core temperatures to normal.

In the current study, Sun *et al.*[2] evaluated esophageal core temperature throughout surgery in more than 50,000 adults having surgery lasting over an hour who were actively warmed intraoperatively. The core temperature 45 min after induction was less than 36°C in 64% of patients and less than 35.5°C in 29% of patients. Hypothermia lasting more than an hour was common although 91% of patients were normothermic by the end of surgery. Accounting for variables including type and duration of surgery, preoperative hemoglobin, and comorbidities, there was a significant association between degree-hours of hypothermia and transfusion.

The study has some limitations. The database did not include all outcomes of interest, so we do not know whether these effects are pertinent for surgical site infection or cardiac complications. The study is retrospective, so the identified associations cannot be considered evidence of causality. However, clinical trials have already established causal relations.

One major potential confounder in this study is the complex relation between duration of surgery, blood loss, fluid and blood product administration, and core temperature. Patients with more blood loss might be more likely to become hypothermic, rather than *vice versa*, because of administration of cold fluid and blood products. Inclusion of these confounders in the multivariable analysis strengthens the argument for hypothermia-driving blood loss. Moreover, exclusion of massively transfused patients gave the same association between hypothermia exposure and transfusion. However, patients in the highest quartile for hypothermia exposure had longer duration of surgery (289 [238 to 355] min) compared with the lowest quartile (137 [104 to 191] min). Given that patients with a longer duration of surgery are more likely to be normothermic at the end of surgery (because of the longer exposure to active warming), there is likely a more complicated interaction between blood loss and hypothermia.

What are the implications of this study for anesthetic practice? First, it is time to reevaluate our definition of normothermia. A first step would be to assess not only core temperature on arrival in the PACU but also the lowest core temperature and the duration of hypothermia intraoperatively. Electronic medical records could easily calculate such a variable. We also need more reliable measures of core temperature. Esophageal temperature is considered the definitive standard, but esophageal measurements are available only for anesthetized patients, the probe must be inserted to adequate depth to be accurate, and the esophagus is not always accessible.

Although better metrics for hypothermia are important, a critical implication of this study is that current standards and practice routinely lead to intraoperative hypothermia, which is associated with a higher transfusion requirement. These results should be an impetus for changes in practice that lead to lower rates of intraoperative hypothermia. The practice at most centers is to apply the warming device after induction of anesthesia and application of surgical drapes. As demonstrated in the current study, this predictably leads to hypothermia in the first hour in the majority of patients. Application of an active warming device preoperatively (*i.e.*, in the preoperative holding area) reduces the decrease in core temperature in the first hour after induction.[4,5] We implemented routine prewarming for most patients in our hospitals several years ago. Our experience suggests that routine prewarming is both feasible and effective.

The study by Sun *et al.*[2] starts a new conversation on perioperative temperature management. Future studies should evaluate the effectiveness of interventions to reduce the degree and duration of intraoperative hypothermia and the effect of these interventions on the broad range of outcomes known to be temperature sensitive. These studies will require development of better methods of assessing core temperature throughout the perioperative period.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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Intraoperative Core Temperature Patterns, Transfusion Requirement, and Hospital Duration in Patients Warmed with Forced Air

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This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Core temperature patterns in patients warmed with forced air remain poorly characterized. Also unknown is the extent to which transient and mild intraoperative hypothermia contributes to adverse outcomes in broad populations.

Methods: We evaluated esophageal (core) temperatures in 58,814 adults having surgery lasting >60 min who were warmed with forced air. Independent associations between hypothermic exposure and transfusion requirement and duration of hospitalization were evaluated.

Results: In every percentile subgroup, core temperature decreased during the first hour and subsequently increased. The mean lowest core temperature during the first hour was 35.7 ± 0.6°C. Sixty-four percent of the patients reached a core temperature threshold of <36°C 45 min after induction; 29% reached a core temperature threshold of <35.5°C. Nearly half the patients had continuous core temperatures <36°C for more than an hour, and 20% of the patients were <35.5°C for more than an hour. Twenty percent of patients had continuous core temperatures <36°C for more than 2 h, and 8% of the patients were below 35.5°C for more than 2 h. Hypothermia was independently associated with both transfusions and duration of hospitalization, although the prolongation of hospitalization was small.

Conclusions: Even in actively warmed patients, hypothermia is routine during the first hour of anesthesia. Thereafter, average core temperatures progressively increase. Nonetheless, intraoperative hypothermia was common, and often prolonged. Hypothermia was associated with increased transfusion requirement, which is consistent with numerous randomized trials. **(Anesthesiology 2015; 122:00-00)**

INTRAOPERATIVE core hypothermia causes serious complications including coagulopathy,[1] surgical wound infections,[2] and perhaps myocardial complications.[3] It also decreases drug metabolism,[4] prolongs recovery,[5] and provokes thermal discomfort.[6] It is thus now standard-of-care to warm surgical patients. Various guidelines, including the Surgical Care Improvement Project and National Institute of Health and Clinical Excellence, suggest that patients should be normothermic, defined as a core temperature of at least 36°C at the end of surgery.

Forced air remains by far the most common warming approach. Forced air markedly reduces cutaneous heat loss[7,8];

What We Already Know about This Topic

- Intraoperative core-body temperature patterns in patients warmed with forced air remain poorly characterized

What This Article Tells Us That Is New

- In almost 59,000 adults having surgery lasting more than an hour, core temperatures decreased during the first hour of surgery, thereafter rising to an average final temperature of 36.3°C
- Hypothermia significantly increased both transfusion requirements and duration of hospitalization, but only the increase in transfusions was clinically important

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 229. Drs. Sun and Honar contributed equally.

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consequently, most warmed patients are normothermic by the end of surgery.[2] But, core-to-peripheral redistribution of body heat precipitously reduces core temperature in the hour after induction of anesthesia,[9,10] even in actively warmed patients.[2,11] Most patients thus at least initially experience some intraoperative hypothermia. Intraoperative core temperature patterns in patients warmed with forced air remain poorly characterized.

While randomized trials are considered the highest level of clinical evidence, they unsurprisingly target at-risk patients. For example, infection trials targeted colorectal surgery patients[2,12] and the largest coagulation studies were conducted in patients having hip arthroplasties.[13,14] Trials thus often lack generalizability. The extent to which hypothermia trial results apply to broad surgical populations thus remains unknown.

A second limitation of published hypothermia trials is that most compared forced-air warming to routine care which, at the time, was usually just passive insulation. Consequently, temperature differences between the groups were usually 1.5°–2.0°C at the end of surgery—far more than is now typical. Whether smaller amounts of hypothermia also worsen important outcomes remains unknown.

A third issue is that final intraoperative core temperature poorly characterizes the U-shaped hypothermic exposure that usually results from current thermal management. Time-weighted averages, which incorporate temperatures from throughout surgery, would better characterize current temperature patterns.

And finally, we need to consider that most hypothermia trials date from the 1990s. Fortunately, the intervening decades have seen substantial practice improvement. For example, blood conservation is now routine; minimally invasive surgery causes less blood loss; and transfusion thresholds are generally lower. As another example, the only major study evaluating the effect of hypothermia on hospital length-of-stay dates to 1996,[2] a period when colectomy patients typically stayed in the hospital 2 weeks. Whether these and similar results still apply remains unknown.

Each of these limitations of existing results can, to an extent, be addressed through analysis of large current data sets. The Cleveland Clinic Perioperative Health Documentation System includes intraoperative core temperature and accurately characterizes transfusion requirement and hospital length-of-stay. Initially, we therefore evaluated core temperature in a large cohort of actively warmed noncardiac surgical patients. Thereafter, we used these registry data to test the hypothesis that hypothermic exposure in degree·hours below a threshold of 37°C is associated with increased intraoperative red blood cell transfusion requirement and duration of hospitalization.

Materials and Methods

With Cleveland Clinic Institutional Review Board (Cleveland, Ohio) approval, we extracted data on 143,157 adults having noncardiac surgery at Cleveland Clinic between April 1, 2005 and February 15, 2013. Only the most recent visit for each patient was used for analysis. We included patients in whom core temperature was measured in the esophagus. Virtually all surgical patients are warmed with forced air (Bair Hugger, 3M, St. Paul, MN); generally, active warming begins after draping. Prewarming was not used. Ambient temperature in preoperative holding areas at the Clinic is generally maintained near 23°C; operating rooms are typically maintained at 20°–21°C, but can be as low as 18°–19°C in some rooms. Only 2 of ≈50 relevant operating rooms are equipped with laminar flow.

We excluded operations in which the duration of anesthesia was less than 60 min (induction to emergence), as coded in the electronic anesthesia record. Induction was when induction doses of general anesthetics were given; emergence was less precisely defined, but generally when clinicians began preparing patients for emergence. We also excluded patients in whom there was less than 30 min of core temperature monitoring, in whom monitoring was disrupted for more than 30 min, or in whom core temperature monitoring started more than 45 min after induction of anesthesia.

Artifactual data were removed from each patient's core temperature profile according to the algorithm depicted in figure 1. After artifact removal, temperature profiles were then smoothed using a Gaussian kernel smoothing algorithm; this is similar to a "sliding window" (or moving average), except that instead of taking the simple average of measurements within the window, a weighted average is taken where the weights are drawn from a Gaussian curve according to the horizontal distance from the desired estimate. The "ksmooth" function within the "sm" library for R statistical software Version 3.0.0* was used to produce the smoothed estimates,[15] using a bandwidth parameter of 30 min to define the width of the Gaussian kernel (specifically, the standard deviation of the Gaussian kernel is 0.25 times the selected bandwidth).

Restricted cubic spline regression curves characterized the distribution of core temperature measurements over postinduction time; separate curves were estimated for the median, 1st, and 3rd quartiles; 1st and 9th deciles; and 5th and 95th percentile of the core temperatures. Curves were fit using quantile regression.[16]

The incidence of hypothermia—defined according to progressive core-temperature thresholds of <36.0°, <35.5°, and <35.0°C—was plotted as a function of postinduction time to evaluate core-to-peripheral redistribution of body heat. Pointwise 95% confidence intervals were estimated for each of these three incidence functions using normal approximation theory for proportions. Nominal confidence interval width was set to three standard errors to better enforce the 95% confidence level in the presence of multiple simultaneous estimates.

For our primary outcome analysis of red blood cell transfusion (coded as a binary outcome) and hospital length of stay,

* Bowman AW, Azzalini A: R package SM: Nonparametric smoothing methods (version 2.2–5) 2013. Available at: http://cran.r-project.org/web/packages/sm/index.html. Accessed August 1, 2014.

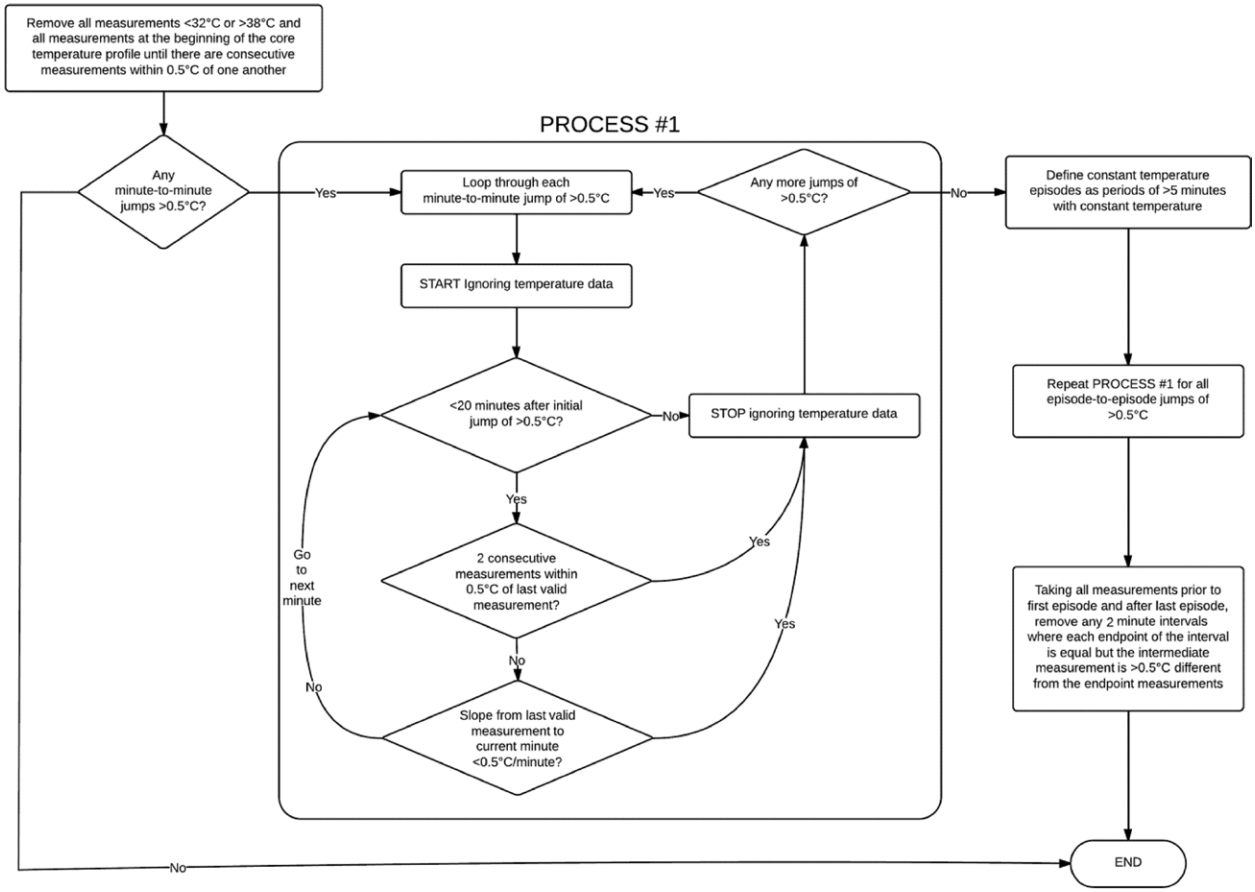

Fig. 1. Flow chart indicating the artifact removal algorithm for intraoperative core temperature measurements.

we removed from consideration patients not admitted on the same day as their surgery. Also, patients with missing baseline hemoglobin, baseline platelets, and/or body mass index were excluded. Furthermore, for the analysis of duration of hospitalization, we removed ambulatory surgery patients.

For both outcomes, we characterized the primary hypothermia exposure using an "area under the threshold" measure defined as the size of the region above the core temperature *versus* time curve but below a horizontal line at 37°C. We analyzed the independent association between area under the 37°C threshold and intraoperative erythrocyte transfusion using multivariable logistic regression. Likewise, we analyzed the independent association between area under the 37°C threshold and duration of hospitalization using multivariable linear regression. A sensitivity analysis for transfusion, in which we excluded massively transfused patients (defined as receiving four or more units), was performed. Duration of hospitalization was transformed to approximate normality using the logarithmic transformation; patients who died in the hospital were assigned a duration of hospitalization equal to the maximum observed value among patients discharged alive, which was 477 days.

For each model, we represented the adjusted relationship between area under the 37°C threshold and outcome using cubic splines. Chi-square tests were used to test whether or not there was an independent association between area under the 37°C threshold and outcome. A curve of predicted probability of transfusion *versus* area under the 37°C threshold for an "at risk" reference population (of patients > 55 yr with body mass index < 25 kg/m^2, preoperative hemoglobin < 14 g/dl, and duration of surgery > 4 h) was visualized, as was a curve of predicted geometric mean duration of hospitalization *versus* area under the 37°C threshold for all inpatients included in the analysis of duration of hospitalization. Both models adjusted for year, type, and duration of surgery, body mass index, age, preoperative platelet count, preoperative hemoglobin, estimated blood loss, and individual anesthesiologist, as well as the Elixhauser comorbidities[17] (see table 1 for a listing of these comorbidities). Principal type of surgery was characterized according to the U.S. Agency for Healthcare Research and Quality's Clinical Classifications Software for International Classification of Diseases and Injuries, version 9, Clinical Modification procedure codes. Type of surgery and anesthesiologist categories with insufficient cell sizes were aggregated into respective all-purpose "other" categories; specifically, the bottom 10% of cases were aggregated for each of the two variables. Still, type of surgery and anesthesiologist each were represented by too many individual levels to reliably model using standard regression adjustment. Thus, we created surrogate measures for each

Table 1. Baseline Characteristics for 45,866 Patients Included in the Analysis of the Association between Hypothermia and Transfusion

	Area under the 37°C Threshold - Quartile-based Groups			
	First Quartile	Second Quartile	Third Quartile	Fourth Quartile
	≤1.2°C·h	1.2–2.2°C·h	2.2–3.6°C·h	>3.6°C·h
Factor	(N = 11,474)	(N = 11,461)	(N = 11,469)	(N = 11,462)
Outpatient surgery	26	19	10	3
Estimated blood loss (cc)	48 (10, 100)	50 (20, 150)	100 (50, 250)	200 (100, 400)
Year of surgery	2009 (2007, 2011)	2009 (2008, 2011)	2009 (2007, 2011)	2009 (2007, 2011)
Preoperative hemoglobin (Units)	13.5 (12.4, 14.5)	13.7 (12.7, 14.7)	13.8 (12.7, 14.8)	13.8 (12.7, 14.8)
Preoperative platelets (Units)	255 (211, 306)	247 (205, 295)	245 (203, 290)	240 (200, 287)
Duration of surgery (min)	137 (104, 191)	168 (135, 219)	212 (174, 266)	289 (238, 355)
Body mass index (kg/m^2)	28 (24, 34)	28 (24, 33)	28 (24, 32)	27 (24, 32)
Age (years)	53 (41, 64)	56 (45, 67)	58 (47, 68)	60 (50, 69)
Elixhauser comorbidities				
Congestive heart failure	3	2	2	3
Valvular disease	2	3	3	3
Pulmonary circulation disorders	1	1	1	1
Peripheral vascular disease	2	3	4	6
Hypertension (uncomplicated)	38	40	43	45
Hypertension (complicated)	3	3	3	4
Paralysis	1	1	1	1
Other neurological disorders	5	6	6	7
Chronic pulmonary disease	12	11	11	11
Diabetes without chronic complications	13	12	13	11
Diabetes with chronic complications	2	2	2	2
Hypothyroidism	11	11	11	11
Renal failure	4	3	4	5
Liver disease	3	3	3	2
Chronic peptic ulcer disease	0	0	0	0
HIV and AIDS	0	0	0	0
Lymphoma	1	1	1	1
Metastatic cancer	5	5	5	6
Solid tumor without metastasis	10	12	17	26
Rheumatoid arthritis/collagen vascular diseases	3	3	2	3
Coagulation deficiency	1	2	2	3
Obesity	20	17	17	15
Weight loss	2	2	2	3
Fluid and electrolyte disorders	6	6	8	13
Blood loss anemia	1	1	1	2
Deficiency anemias	6	5	5	6
Alcohol abuse	1	1	1	1
Drug abuse	0	0	0	1
Psychoses	2	2	2	2
Depression	12	11	11	9

Summary statistics presented as either a percentage or median (first and third quartiles).
AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus infection.

analysis to represent potential confounding effects of each of these factors.

For the analysis of transfusion, we adjusted for the type-of-surgery-specific mean area below the 37°C threshold and the type-of-surgery-specific transfusion rate, as well as the same two measures specific to each anesthesiologist. The same was done for the analysis of duration of hospitalization, although the mean duration of hospitalization for each factor level was used instead of the transfusion rate.

A nominal Type I error rate of 0.025 was used to restrict the Type I error rate to 5% for the simultaneous analysis of two outcomes. R statistical software version 2.15.2 for

64-bit Unix operating system (The R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Results

Among 143,157 patients considered for our study, 58,814 met criteria for inclusion in the descriptive analysis (fig. 2). Procedures were diverse (table 2).

Figure 3 displays the distribution of core temperature as a function of time after induction; generally, core temperature decreased during the first hour of anesthesia and subsequently increased for the duration of surgery. Median core temperature was about 35.8°C an hour after induction. Core temperature in the first quartile of patients was about 35.5°C after an hour, but was less than 35°C in more than 5% of the patients. The mean lowest core temperature during the first hour of anesthesia was 35.7 ± 0.6°C.

Figure 4 shows the incidence of hypothermia under various core-temperature thresholds. At 45 min after induction, 64.4% (95% confidence interval: 63.8%, 64.9%) of the patients reached a core temperature threshold of <36°C; 28.9% (28.0%, 29.1%) of the patients reached a core temperature threshold of <35.5°C at 51 min after induction; and 7.3% (6.9%, 7.6%) of the patients reached a core temperature threshold of <35°C at 71 min after induction. Even after 6 h of anesthesia, about 20% of patients had core temperatures < 36°C, 9% were <35.5°C, and 4% were <35°C.

Figure 5 shows the incidence of hypothermic episodes of varying duration (>15 min, >30 min, >60 min, *etc.*) as a function of progressive core temperature thresholds. Nearly half the patients had continuous core temperatures < 36°C for more than an hour, and 20% of the patients were below 35.5°C for more than an hour (teal line in figure, third from top). Twenty percent of patients had continuous core temperatures <36°C for more than 2 h, and 8% of the patients were below 35.5°C for more than 2 h (pink line in figure, fourth from top).

Mean core temperature over the duration of anesthesia in the entire population was 36.0 ± 0.6°C; final intraoperative core temperature averaged 36.3 ± 0.5°C (882 patients had missing end-of-case temperatures). While hypothermic incidences tended to vary across procedure categories, end-of-case temperatures were consistently above 36°C (table 3).

After removing patients not admitted on the day of surgery and patients with missing data on covariates, 45,866 remaining patients were analyzed for association between the area under the threshold hypothermic exposure and transfusion.

The overall distribution of area under the 37°C threshold was log-normal in nature (see histograms in figs. 6 and 7), with a median (Q1, Q3) of 2.2 (1.2, 3.6) degree·hours. Most patients had at least 1 degree·hour below the 37°C threshold. Patient characteristics and surgical procedures for these patients are presented according to quartiles of this area below the threshold metric in table 1.

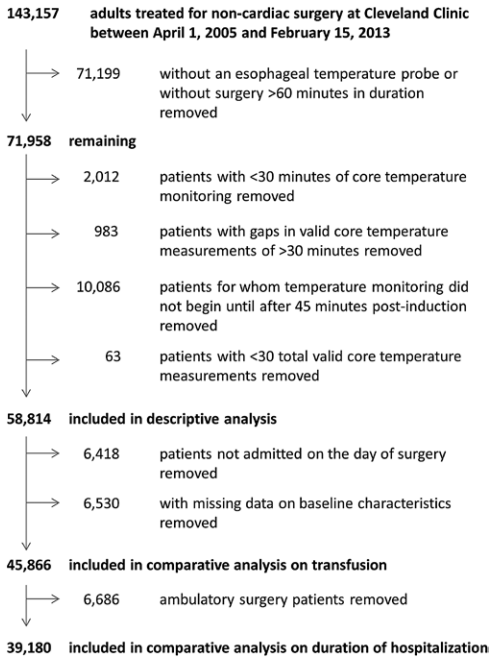

Fig. 2. Study flow diagram.

Overall, 2,251/45,866 patients (4.6%) were transfused. On the basis of our multivariable logistic regression model (which had a C-statistic of 0.98), we found a significant association between area under 37°C and transfusion ($P = 0.018$, significant after the Bonferroni correction). Odds ratios relative to a reference value of 1 degree·hour are presented in table 4. Generally speaking, transfusion was increasingly likely as area under the 37°C threshold increased to more than 4 degree·hours, with an odds ratio (pointwise 95% confidence

Table 2. Top 20 Procedures among 58,814 Patients Meeting Study Inclusion Criteria

Hysterectomy; abdominal and vaginal	6.1%
Other OR lower GI therapeutic procedures	5.6%
Colorectal resection	5.5%
Nephrectomy; partial or complete	4.7%
Laminectomy; excision intervertebral disc	4.5%
Open prostatectomy	4.3%
Spinal fusion	4.1%
Thyroidectomy; partial or complete	3.5%
Other OR gastrointestinal therapeutic procedures	3.4%
Other therapeutic endocrine procedures	3.3%
Incision and excision of CNS	2.5%
Cholecystectomy and common duct exploration	2.5%
Other hernia repair	2.5%
Other OR therapeutic nervous system procedures	2.3%
Other OR therapeutic procedures of urinary tract	2.2%
Other OR therapeutic procedures; female organs	2.1%
Other OR therapeutic procedures on skin and breast	2.0%
Other OR upper GI therapeutic procedures	2.0%
Hip replacement; total and partial	1.7%
Arthroplasty knee	1.6%
Other	33.7%

CNS = central nervous system; GI = gastrointestinal; OR = operating room.

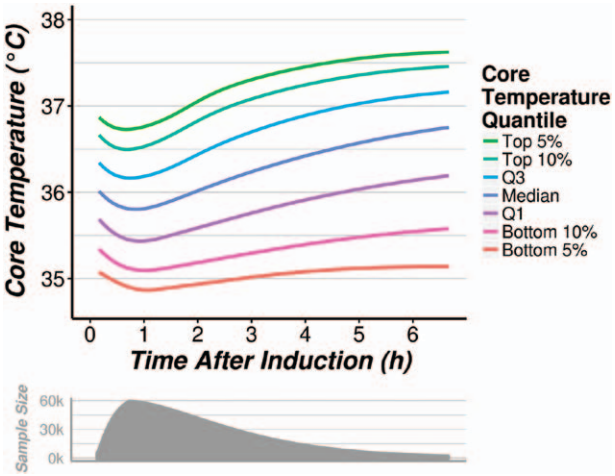

Fig. 3. Distribution of core temperature as a function of time after induction among 58,814 patients.

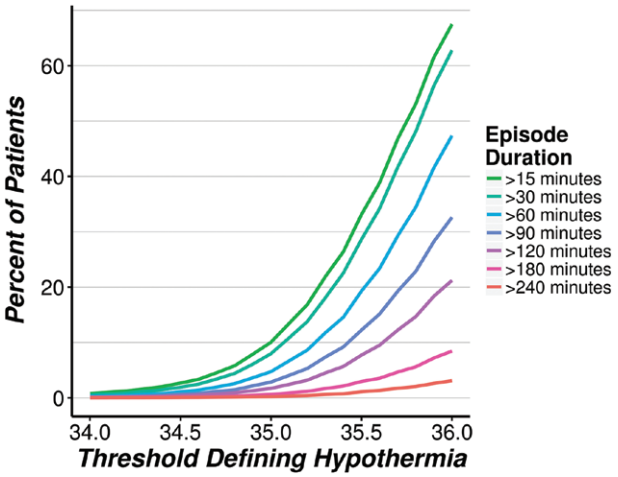

Fig. 5. Incidence of (any) hypothermic episodes during the case, according to progressive core temperature thresholds defining hypothermia.

interval) estimate of 1.48 (1.03, 2.13) for transfusion comparing patients with 8 degree·hours to patients with 1 degree·hour. Predicted probabilities of transfusion for an "at risk" reference population of patients > 55 yr with body mass index < 25 kg/m^2, preoperative hemoglobin < 14 g/dl, and duration of surgery > 4 h are given in figure 6. Results of our sensitivity analysis excluding massively transfused patients (n = 429; 0.9%) were similar to that of the primary analysis.

For the analysis of association between area-under-the-threshold and duration of hospitalization, we further removed 6,686 ambulatory surgery patients (fig. 2). Median [first quartile, third quartile] duration of hospitalization was 3 [1, 4] days. On the basis of our multivariable linear regression model (R^2 = 0.40), we found a significant association between area under the 37°C threshold and geometric mean duration of hospitalization (P < 0.001), although the strength of the association was of questionable clinical importance: the ratio of geometric mean estimates for various values of area under the 37°C threshold (compared to a reference value of 1 degree·hour; see table 4) are all modest, and a plot of predicted mean duration of hospitalization *versus* area under the 37°C threshold (fig. 7) reveals estimates only ranging from 2.4 days to approximately 2.7 days.

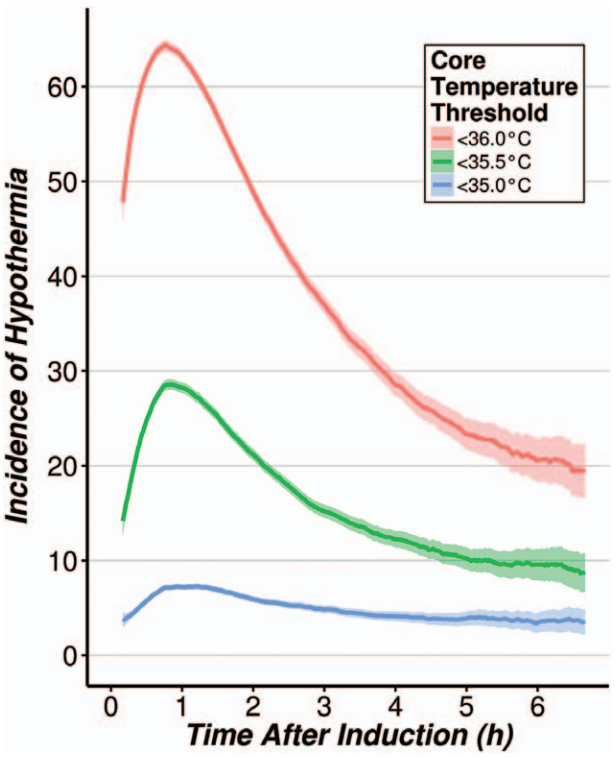

Fig. 4. Incidence of hypothermia as a function of time after induction, under progressive core temperature thresholds defining hypothermia.

Discussion

Core temperature represents temperature of highly perfused tissues, mostly the trunk and head, representing about half the body mass. It is the considered the best single temperature and is the primary determinant of thermoregulatory responses.[18] In contrast, the peripheral thermal compartment (mostly the arms and legs) is typically 2°–4°C less than core temperature.[19,20] The gradient between core and peripheral temperatures is determined by the thermal environment and thermoregulatory vasomotion. Induction of general[10] or neuraxial[9] anesthesia causes vasodilation, which promotes heat flow from core to peripheral tissues. This redistribution of body heat is the primary cause of hypothermia during the first hour of anesthesia even in actively warmed patients.[2,11]

The magnitude of redistribution hypothermia is defined by the reduction in core temperature during the initial hour of anesthesia. We were unable to precisely determine the amount of redistribution since accurate preoperative temperatures were unavailable—although virtually all patients are normothermic before induction of anesthesia. Typically, core temperatures are about 36.5°C for first-start cases (near the circadian nadir), rising to 37.5°C in the late afternoon and

Table 3. Distribution of Primary Procedure in the Sample, Along with Incidence of Hypothermia under Varying Core Temperature Thresholds and End-of-case Temperatures

Procedure Category	N (%) of All Patients	N (%) with Hypothermia			Median (Q1, Q3) End-of-case Temperature
		<36.0°C	<35.5°C	<35.0°C	
Operations on the digestive system	16,525 (28.1%)	4,468 (27.0%)	1,078 (6.5%)	148 (0.9%)	36.3 (36.0, 36.6)
Operations on the musculoskeletal system	8,272 (14.1%)	2,407 (29.1%)	764 (9.2%)	173 (2.1%)	36.2 (36.0, 36.6)
Operations on the female genital organs	6,637 (11.3%)	2,153 (32.4%)	531 (8.0%)	73 (1.1%)	36.2 (36.0, 36.5)
Operations on the nervous system	6,466 (11.0%)	2,146 (33.2%)	590 (9.1%)	129 (2.0%)	36.2 (36.0, 36.6)
Operations on the urinary system	6,162 (10.5%)	23,73 (38.5%)	716 (11.6%)	111 (1.8%)	36.2 (36.0, 36.5)
Operations on the endocrine system	3,692 (6.3%)	607 (16.4%)	123 (3.3%)	16 (0.4%)	36.4 (36.1, 36.8)
Operations on the male genital organs	3,253 (5.5%)	984 (30.2%)	256 (7.9%)	41 (1.3%)	36.2 (36.0, 36.5)
Operations on the integumentary system	3,236 (5.5%)	1,025 (31.7%)	262 (8.1%)	56 (1.7%)	36.2 (36.0, 36.6)
Operations on the cardiovascular system	2,789 (4.7%)	933 (33.5%)	274 (9.8%)	60 (2.2%)	36.1 (35.8, 36.4)
Operations on the hemic and lymphatic system	891 (1.5%)	225 (25.3%)	66 (7.4%)	10 (1.1%)	36.3 (36.0, 36.6)
Operations on the nose; mouth; and pharynx	389 (0.7%)	83 (21.3%)	25 (6.4%)	6 (1.5%)	36.4 (36.1, 36.8)
Miscellaneous diagnostic and therapeutic procedures	237 (0.4%)	64 (27.0%)	18 (7.6%)	1 (0.4%)	36.3 (36.0, 36.6)
Operations on the ear	109 (0.2%)	10 (9.2%)	1 (0.9%)	0 (0.0%)	36.4 (36.1, 36.7)
Obstetrical procedures	63 (0.1%)	15 (23.8%)	4 (6.3%)	0 (0.0%)	36.3 (36.0, 36.7)
Operations on the eye	48 (0.1%)	4 (8.3%)	1 (2.1%)	0 (0.0%)	36.4 (36.2, 36.8)
Operations on the respiratory system	45 (0.1%)	15 (33.3%)	8 (17.8%)	5 (11.1%)	36.3 (36.0, 36.6)

early evening.[21] Furthermore, esophageal temperature monitoring did not necessarily start immediately after induction. Nonetheless, mean core temperatures decreased during the initial hour of anesthesia, reaching a nadir of 35.7 ± 0.6°C. It is thus likely that the magnitude of redistribution hypothermia was about 1°C, which is similar to previously reports, as was absolute core temperature after an hour of anesthesia.[22–25]

Intraoperative forced air did not prevent redistribution hypothermia, which is consistent with previous reports[2,11] and the fact that it results from a large internal flow of heat from core to peripheral tissues. In contrast, it is well established that prewarming reduces redistribution hypothermia[22,26,27] by warming peripheral tissues to nearly core temperature.[28] Without a thermal gradient, the second Law of Thermodynamics specifies that there can be no flow of heat—and thus no redistribution hypothermia.

As expected, redistribution reduced core temperature during the initial hour of anesthesia. Previous work shows that unwarmed surgical patients continue to become hypothermic until they become cold enough to trigger thermoregulatory vasoconstriction, typically at about 34.5°C,[29–31] which prevents further hypothermia by constraining metabolic heat to the core thermal compartment.[20] For example, final intraoperative core temperatures are typically about 34.5°C in unwarmed patients having open abdominal surgery.[2] The pattern in our actively warmed patients differed: after the initial hour of anesthesia, core temperature progressively increased throughout surgery. Consequently, 91% of the patients had core temperatures ≥ 36°C at the end of anesthesia.

Because core temperatures progressively increased after the initial hour of anesthesia (when redistribution was complete), patients having longer operations were more likely to be normothermic at the end of surgery. Although counterintuitive, it is thus more difficult to end with normothermia in shorter than longer cases. Prewarming is thus most important for short cases, and essential if normothermia is to be maintained throughout surgery. While prewarming has a relatively small effect on core temperature, prewarming would presumably have prevented hypothermia in at least some of the patients who experienced prolonged periods of intraoperative hypothermia.

Normal body temperature averages 37°C. Nonetheless, an intraoperative core temperature of 36°C is widely considered "normothermic" and existing guidelines suggest a final core temperature > 36°C. Published trials in regards to perioperative hypothermia and adverse outcomes were based on final intraoperative temperatures in patients assigned to either active warming or passive insulation, which in most trials resulted in a core temperature difference of 1°–2°C at the end of surgery. And while some hypothermia-induced complications probably are based on final temperature (*i.e.,* thermal comfort, shivering, adrenergic stress), others such as blood loss are based on instantaneous tissue temperature and thus presumably accrue throughout surgery.

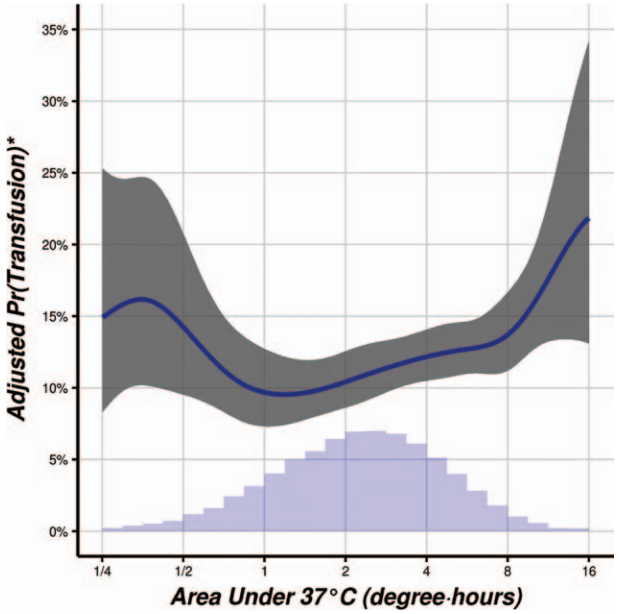

Fig. 6. Adjusted probability of transfusion estimates *versus* integrated area above the core temperature *versus* time curve and below a threshold of 37°C, Estimates adjusted to an "at-risk" reference population defined by age > 55 yr, body mass index < 25 kg/m^2, preoperative hemoglobin < 14 g/dl, and duration of surgery > 4 h. *Shaded regions* represent pointwise, Bonferroni-adjusted (for simultaneous analysis on two outcomes) 95% confidence intervals. The regression model was based on 45,866 patients who were admitted on the day of surgery and who had esophageal temperature monitoring. *Adjusted for year, type, and duration of surgery, body mass index, age, preoperative platelet count, preoperative hemoglobin, estimated blood loss, and individual anesthesiologist, as well as the Elixhauser comorbidities[16] (see table 2 for a listing of these comorbidities). Pr = probability.

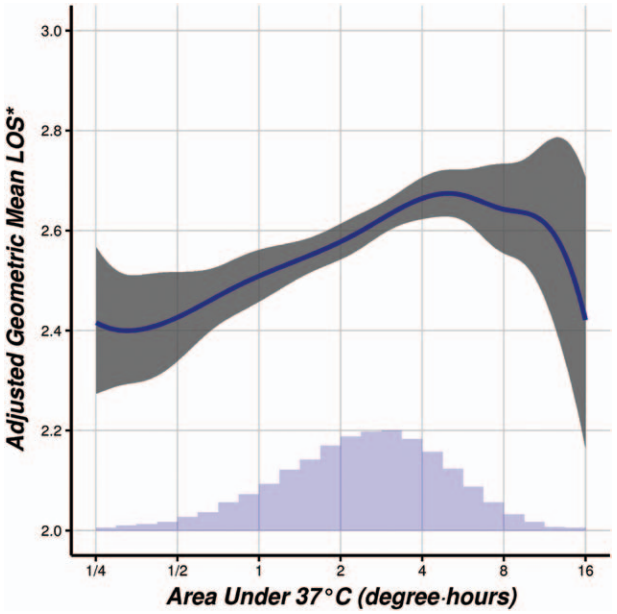

Fig. 7. Adjusted estimates of geometric mean duration of hospitalization in days *versus* integrated area above the core temperature *versus* time curve and below a threshold of 37°C, for 39,180 hospital in-patients who were admitted on the day of surgery and who had intraoperative esophageal temperature monitoring. *Shaded regions* represent pointwise, Bonferroni-adjusted (for simultaneous analysis on two outcomes) 95% confidence intervals. *Adjusted for year, type, and duration of surgery, body mass index, age, preoperative platelet count, preoperative hemoglobin, estimated blood loss, and individual anesthesiologist, as well as the Elixhauser comorbidities[16] (see table 2 for a listing of these comorbidities). LOS = length of stay.

It is difficult or impossible to determine from available hypothermia trials exactly which temperature ranges as well as which duration of time in a certain temperature range are most associated with adverse outcomes. It thus seems important to consider intraoperative temperature patterns rather than just final intraoperative temperature. Our analysis extends previous work in considering the magnitude of intraoperative hypothermia, defined in terms of integrated °C·hours within various temperature ranges, which allows us to identify time and depth of hypothermia associated with clinically important worsened outcomes.

Hypothermia trials generally have good internal validity. They were also largely restricted to specific at-risk patient populations. For example, most wound infection studies were performed in patients having colon-rectal surgery, and most blood loss and transfusion studies included only orthopedic or cardiac surgical patients. How generalizable this data might be remains unclear. We therefore included all noncardiac surgical patients into our analysis.

An important distinction is that essentially all patients at the Cleveland Clinic are actively warmed whereas the "control" groups in most hypothermia outcome trials were only provided with passive insulation. But even with forced-air warming, intraoperative core temperatures are often less than 36°C. For example, 20% of our warmed patients had a core temperature less than 35.5°C for at least an hour (*i.e.,* 0.5°C·hour for a 36°C threshold); 5% of our actively warmed patients were a °C·hour below 35°C. Whether these lesser amounts of hypothermia affect outcome remains unknown.

Transfusion requirements progressively increased from 1 to 8°C·hour below 37°C. That hypothermia impairs platelet function[32] and the enzymes of the coagulation cascade[33] is well established, as is the relationship between hypothermia and blood loss.[1] Furthermore, numerous randomized trials, summarized in a meta-analysis,[1] show that hypothermia increases transfusion requirements. Specifically, core temperatures around 35.5°C at the end of surgery significantly increased the relative risk for transfusion by approximately 22% (CI 3–37%). Our registry analysis extends previous work by including a broad noncardiac surgery population rather than generally being restricted to procedures known for blood loss.

The other outcome we evaluated was hospital length-of-stay which was significantly prolonged, but not by a clinically meaningful amount (*i.e.,* from ≈2.4 to ≈2.7 days in the range from 0.5 to 4°C·hour below 37°C. In contrast, the single major trial evaluating the duration of hospitalization

Table 4. Association between Intraoperative Hypothermia and Outcomes Transfusion Requirement and Duration of Hospitalization

Area under 37°C (degree·hours)	Adjusted* Odds Ratio (Pointwise 95% CI) for Intraoperative Erythrocyte Transfusion (N = 45,866)	Adjusted* Ratio of Geometric Mean Duration of Hospitalization (Pointwise 95% CI) (N = 39,180)
0.25	1.34 (1.04, 1.73)	0.96 (0.90, 1.03)
0.50	1.10 (0.98, 1.24)	0.97 (0.93, 1.01)
1.00	(Reference)	(Reference)
2.00	1.00 (0.89, 1.13)	1.03 (1.00, 1.05)
4.00	1.12 (0.91, 1.39)	1.06 (1.03, 1.09)
8.00	1.41 (1.08, 1.84)	1.05 (1.01, 1.10)
16.00	2.02 (1.30, 3.14)	0.96 (0.86, 1.08)

*Estimates adjusted for year, type, and duration of surgery, body mass index, age, preoperative platelet count, preoperative hemoglobin, estimated blood loss, and individual anesthesiologist, as well as the Elixhauser comorbidities, which are listed in table 1.

CI = confidence interval.

observed a 20% prolongation in patients who were 2°C hypothermic at the end of surgery.[2] Although integrated core temperature was not determined in that study,[2] the difference between the groups was probably well over 4°C·hour. Sparse available data thus suggest that moderate degrees of hypothermia have little effect on the duration of hospitalization, but that substantial amounts may produce clinically important prolongations.

Active warming is not yet a worldwide standard-of-care. It is thus likely that a substantial fraction of the roughly 240 million patients having noncardiac surgery each year reach core temperatures that increase transfusion requirements and prolong hospitalization. This cost to the healthcare system surely exceeds the now-modest price of active warming.

Our analysis was restricted to two major hypothermic complications: transfusion requirement and hospital length-of-stay. Other major outcomes demonstrated in randomized trials include surgical wound infection and morbid myocardial outcomes. They were not included here simply because neither is reliably included in our registry.

There is a temperature gradient within the esophagus. Probes inserted insufficiently far may thus be cooled by respiratory gases in the adjacent trachea. While our routine practice is to insert the probes about 40 cm which is enough,[34] we cannot determine how often probes were only proximally inserted. Similarly, we have no way of determining the extent to which temperatures monitored at less reliable sites might have been inadvertently coded as esophageal temperatures in our electronic record. Either factor would result in artifactually low temperatures. However, we show that low esophageal temperatures are significantly associated with transfusion requirement and the duration of hospitalization. If artifact contributed substantially to low apparent temperatures, there is no reason to believe that they would be associated with hypothermic complications. That they were thus suggests that recorded low temperatures indeed represented patient hypothermia.

Our analysis is restricted to a single center. Results will differ in other centers to the extent that they use different preoperative and intraoperative ambient temperatures, more laminar flow, have shorter or longer cases, or a different case-type mix. Results will also differ to the extent that other centers use more or less effective active warming. We restricted analysis to patients in whom temperature monitoring was coded as esophageal in our electronic anesthesia record. While our routine is to start forced-air warming after draping, it is possible that warming was delayed in some patients.

As with any retrospective analysis, we present associations, which should not be considered evidence of causality. But in this case, causality has already been demonstrated in randomized trials. Our results are more-or-less consistent with randomized results and extend previous work by addressing important issues specifically suited to a registry analysis: (1) generalizability, (2) the smaller magnitude of hypothermia that is now common in actively warmed patients, (3) the distinction between final core temperature and transient intraoperative hypothermia, and (4) practice changes in the decades since most randomized trials were conducted.

In summary, core temperature decreased during the first hour and subsequently increased in every percentile subgroup. More than half the patients had core temperatures below 36°C within the first hour of anesthesia, and nearly a third had core temperatures below 35.5°C during this period. Even in actively warmed patients, redistribution thus contributes to hypothermia in the first hour of anesthesia. Thereafter, core temperature progressively increased. Nonetheless, intraoperative hypothermia was common, and often prolonged. For example, nearly half the patients had continuous core temperatures < 36°C for more than an hour, and 20% of the patients were <35.5°C for more than an hour. Mean core temperature over the duration of anesthesia, 36.0 ± 0.6°C, was thus lower than final intraoperative core temperature which averaged 36.3 ± 0.5°C. Our outcome analysis differs from previous reports in considering hypothermic exposure throughout surgery, not just to final intraoperative temperature and that it includes a large variety of surgical procedures. While hypothermia significantly increased both transfusion requirements and duration of hospitalization, only the increase in transfusions was clinically important. Additional randomized trials are needed to evaluate outcomes of very mild hypothermia (*i.e.*, between 35° and 36°C) and whether maintaining even higher temperatures (*i.e.*, between 36° and 37.5°C) are helpful.

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Competing Interests

Drs. Kurz and Sessler serve on advisory boards for 3M (St. Paul, Minnesota); all fees are donated to charity. All other authors have no competing interests.

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Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery

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ABSTRACT

Background: During spinal anesthesia for cesarean delivery, phenylephrine can cause reflexive decreases in maternal heart rate and cardiac output. Norepinephrine has weak β-adrenergic receptor agonist activity in addition to potent α-adrenergic receptor activity and therefore may be suitable for maintaining blood pressure with less negative effects on heart rate and cardiac output compared with phenylephrine.

Methods: In a randomized, double-blinded study, 104 healthy patients having cesarean delivery under spinal anesthesia were randomized to have systolic blood pressure maintained with a computer-controlled infusion of norepinephrine 5 μg/ml or phenylephrine 100 μg/ml. The primary outcome compared was cardiac output. Blood pressure heart rate and neonatal outcome were also compared.

Results: Normalized cardiac output 5 min after induction was greater in the norepinephrine group *versus* the phenylephrine group (median 102.7% [interquartile range, 94.3 to 116.7%] *versus* 93.8% [85.0 to 103.1%], $P = 0.004$, median difference 9.8%, 95% CI of difference between medians 2.8 to 16.1%). From induction until uterine incision, for norepinephrine *versus* phenylephrine, systolic blood pressure and stroke volume were similar, heart rate and cardiac output were greater, systemic vascular resistance was lower, and the incidence of bradycardia was smaller. Neonatal outcome was similar between groups.

Conclusions: When given by computer-controlled infusion during spinal anesthesia for cesarean delivery, norepinephrine was effective for maintaining blood pressure and was associated with greater heart rate and cardiac output compared with phenylephrine. Further work would be of interest to confirm the safety and efficacy of norepinephrine as a vasopressor in obstetric patients. **(ANESTHESIOLOGY 2015; 122:736-45)**

PHENYLEPHRINE is commonly used to maintain blood pressure during spinal anesthesia for cesarean delivery.[1,2] However, because phenylephrine is a potent α-adrenergic receptor agonist without β-adrenergic receptor activity at usual clinical doses, its use is often associated with a dose-related reflexive slowing of maternal heart rate (HR) and a corresponding decrease in cardiac output (CO).[3–5] Although the clinical significance of these decreases in HR and CO in healthy patients with unstressed fetuses is unknown, concern has been expressed that there may be potential for harm in the presence of a compromised fetus.[3] Therefore, investigation of alternative vasopressors with less pronounced reflexive negative chronotropic effects is of interest.

Norepinephrine has pharmacologic properties that suggest it may be a useful alternative to phenylephrine. Norepinephrine is a potent α-adrenergic receptor agonist, but unlike phenylephrine, it is also a relatively weak agonist at β-adrenergic receptors. We postulated that norepinephrine might therefore

What We Already Know about This Topic

- Although norepinephrine has theoretical advantages over phenylephrine to treat spinal anesthesia–induced hypotension in obstetric patients, it has not been assessed in this setting

What This Article Tells Us That Is New

- In a randomized study of 104 healthy patients undergoing cesarean delivery under spinal anesthesia, maternal blood pressure and Apgar scores of neonates were similar whether norepinephrine or phenylephrine was administered
- Maternal cardiac output and heart rate were greater in women treated with norepinephrine compared with that in women treated with phenylephrine, but further work is needed to assess safety and efficacy of norepinephrine in this setting

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be an effective vasopressor for maintaining blood pressure during spinal anesthesia with less tendency to decrease HR and CO compared with phenylephrine. Although treatment of hypotension during spinal anesthesia is listed by the manufacturer as an indication for the use of norepinephrine, there is limited information available for its use for this purpose in the literature and few reports of its use in obstetric patients.[6]

The aim of this randomized, double-blinded study was to compare computer-controlled infusions of phenylephrine and norepinephrine titrated to maintain blood pressure in parturients having spinal anesthesia for elective cesarean delivery. We hypothesized that an infusion of norepinephrine would be effective for maintaining blood pressure but with greater HR and CO compared with phenylephrine. Secondary outcomes assessed included neonatal outcome and assessment of umbilical cord blood metabolic markers.

Materials and Methods

Approval was obtained from the Joint Chinese University of Hong Kong, New Territories East Cluster Clinical Research Ethics Committee, Shatin, Hong Kong, China, and a Certificate for Clinical Trial/Medicinal Test was obtained from the Department of Health of the Government of the Hong Kong Special Administrative Region, Hong Kong, China, before commencing the study. The study protocol was registered in the Centre of Clinical Trials Clinical Registry of the Chinese University of Hong Kong, Shatin, Hong Kong, China (reference no. CUHK_CCT00315) and in the Chinese Clinical Trial Registry (registration no. ChiCTR-TRC-12002135) with the title *Randomized Evaluative Study of Phenylephrine Or Norepinephrine for maintenance of blood pressure during spinal anesthesia for cesarean Delivery: The RESPOND study*. All patients gave written informed consent to participate.

We enrolled 104 patients who matched the following inclusion criteria: American Society of Anesthesiologists physical status 1 to 2, singleton, term pregnancy, and scheduled for elective cesarean delivery under routine spinal anesthesia. Exclusion criteria were as follows: onset of labor, known fetal abnormality, hypertension, cardiovascular or cerebrovascular disease, renal impairment, allergy to any study medication, weight less than 50 kg or more than 100 kg, height less than 140 cm or more than 180 cm, age less than 18 yr, patients taking monoamine oxidase inhibitors or tricyclic antidepressants, and presence of mesenteric or peripheral vascular thrombosis.

Patients were fasted overnight and were given routine antacid prophylaxis. On arrival in the operating room, they were positioned on the operating table in the supine position with left lateral tilt and routine monitors were attached (Infinity C500; Dräger Medical AG & Co. KG, Germany). After a brief settling period, baseline hemodynamic measurements were made. HR was recorded using pulse oximetry and electrocardiography, and blood pressure was recorded using an automated noninvasive device that was cycled every 1 to 2 min until three consecutive measurements of systolic blood pressure were recorded with a difference of not more than 10%. The mean values of blood pressure and HR at these times were calculated and defined as baseline values. We then measured baseline CO noninvasively using suprasternal Doppler (USCOM 1A Cardiac Output Monitor; USCOM Ltd., Australia) as we have previously described.[7] Values for stroke volume (SV) and systemic vascular resistance (SVR) were also derived by the apparatus. All measurements were made by the same experienced operator (S.W.Y.L.) who was blinded to group assignment and were repeated three times with the mean of the three measurements recorded as the baseline value.

A large-bore intravenous cannula was then inserted into a forearm vein under local anesthesia, but no prehydration was given. Patients were positioned in the right lateral position, and spinal anesthesia was administered using full aseptic precautions. After skin infiltration with lidocaine 1% (w/v), a 25-gauge pencil-point spinal needle was inserted through an introducer needle at what was estimated to be the L3 to L4 or L4 to L5 vertebral interspace. After confirmation of free flow of cerebrospinal fluid, 2.2 ml of hyperbaric bupivacaine 0.5% (w/v) and 15 μg fentanyl were injected intrathecally, and the patient was returned to the tilted supine position. At the start of intrathecal injection, rapid intravenous cohydration of lactated Ringer's solution was commenced. Infusion bags were suspended approximately 1.5 m above the mid-point of the top surface of the operating table, and the fluid was administered through a wide-bore administration set with the clamp fully opened. Cohydration was continued to a maximum of 2 l after which the flow was reduced to a slow maintenance rate.

Infusion of the study drug was started at the same time as cohydration. An investigator (F.F.N.) who was not involved in subsequent patient care or assessment opened the topmost of 104 opaque sequentially numbered envelopes that had been prepared by a member of the secretarial staff. Each envelope contained a randomization code corresponding to one of the study drugs. The codes had been prepared using an on-line random number generator* that had been set to use a closed-sequence algorithm to ensure equal numbers in each group. According to the randomization code, a solution of either norepinephrine 5 μg/ml (norepinephrine group) or phenylephrine 100 μg/ml (phenylephrine group) was selected. The concentration of phenylephrine was our standard preparation, and the concentration of norepinephrine was chosen as that estimated to be approximately equipotent based on the results of previous comparative studies on human saphenous vein,[8] adjusted to a round number for ease of preparation. The drugs were prepared by careful dilution in 5% dextrose solution in 50-ml syringes that were labelled "study drug" and were administered through fine-bore tubing connected to a three-way stopcock that was attached directly to the intravenous catheter. The randomization code was not revealed until after recruitment of the final patient in the study.

* Available at: http://www.psychicscience.org/random.aspx. Accessed January 9, 2012.

From the start of intrathecal injection until delivery, the vasopressor infusion was regulated using a computer-controlled closed-loop feedback system that we have previously described.[7,9,10] The infusion was initially commenced at a fixed rate of 30 ml/h. After the completion of the first blood pressure measurement after spinal injection, the infusion was regulated to maintain systolic blood pressure according to the following algorithm:

$$\text{Infusion rate}\,(\text{ml/h}) = (10 - \text{error}\%) \times 3 \quad (1)$$

where error% = (measured systolic blood pressure − baseline systolic blood pressure)/baseline systolic blood pressure × 100). The infusion rate was constrained to be within the limits 0 to 60 ml/h (0 to 5 μg/min of norepinephrine or 0 to 100 μg/min of phenylephrine). The computer program sampled hemodynamic parameters at 1-s intervals and defaulted to an infusion rate of 0 ml/h during any periods when HR was less than 50 beats/min. The total volume of vasopressor solution given up to the time of uterine incision was recorded.

The noninvasive blood pressure monitor was started 1 min after intrathecal injection, and the automatic cycling time was set to 1 min until delivery. The actual times of starting and completing measurements were determined by the internal algorithm of the monitor which is preset by the manufacturer. HR was recorded at the time of completion of each blood pressure measurement. CO was measured at 5-min intervals until delivery according to a stopwatch that was started at the time of intrathecal injection. The incidences of hypotension (defined as systolic blood pressure <80% of baseline), hypertension (defined as systolic blood pressure >120% of baseline), and bradycardia (defined as HR <60 beats/min) were recorded. Episodes of bradycardia were managed expectantly without administration of anticholinergic drugs.

The highest level of sensory anesthesia assessed using ice was recorded 5 min after intrathecal injection for the purpose of comparison. Further assessments were made as clinically indicated but were not recorded for analysis. Surgery was allowed to commence when the attending anesthesiologist considered the block was adequate. Supplemental oxygen was not given unless the pulse oximeter reading decreased below 95%.

After delivery, Apgar scores were assessed by a midwife 1 and 5 min after delivery. Samples of umbilical arterial (UA) and umbilical venous (UV) blood were collected from a double-clamped segment of umbilical cord. Immediate measurement was made of blood gases using a Rapid Point 400 analyzer (Bayer Diagnostics Mfg [Sudbury] Ltd., United Kingdom), oxygen content with correction for 70% fetal hemoglobin using an IL 682 Co-Oximeter (Instrumentation Laboratory, USA) and plasma concentrations of lactate and glucose using the Vitros DT60 II Chemistry System (Ortho-Clinical Diagnostics, USA). In addition, blood samples were placed in ice for measurement of plasma concentrations of epinephrine and norepinephrine using methods described in the appendix.

Statistical Analysis

The primary outcome measurement compared was defined as CO. Sample size calculation was based on data from our previous published[7] and unpublished data (personal database of hemodynamic data from obstetric patients, Warwick D. Ngan Kee M.B.Ch.B., M.D., F.A.N.Z.C.A., F.H.K.A.M., Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China). We calculated that a sample size of 47 patients per group would have greater than 90% power to detect a 20% difference in CO between groups 5 min after spinal injection with an α error probability of 0.05 assuming an anticipated mean value in the phenylephrine group of 6.2 l/min and SD of 1.8 l/min. To account for potential dropouts, the sample size was increased by 5% giving a final sample size of 52 patients per group.

Univariate intergroup data were tested for normality using the Kolmogorov–Smirnov test and compared using Student *t* test or the Mann–Whitney U test as appropriate. Nominal data were compared using the chi-square test or Fisher exact test. Serial hemodynamic data were compared between groups using a summary measures technique.[11,12] For systolic blood pressure and HR, because the noninvasive blood pressure monitor took variable times to complete measurements and cycle, data were grouped according to the chronological recording order with the apparatus set to a 1-min cycle time. For CO, SV, and SVR, data measured at 5-min real-time intervals were analyzed for the first 20 min which was greatest time point for which data were available for all patients; these values were normalized to percentage of baseline values using the formula:

$$\text{Normalized value} = \frac{\text{Measured value}}{\text{Baseline value}} \times 100\% \quad (2)$$

The area under the curve for values plotted against time were calculated using the trapezium rule.[11,12] For systolic blood pressure and HR, because the number of data points recorded varied among patients, values for area under the curve for each patient were divided by the number of data points recorded to give standardized values.[12] Values for area under the curve and standardized area under the curve were then compared between groups using the Mann–Whitney U test.

Analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, USA), IBM SPSS Statistics version 20 (IBM SPSS Inc., USA), and Confidence Interval Analysis 2.2.0 (Trevor Bryant, University of Southampton, United Kingdom). Values of *P* less than 0.05 were considered statistically significant.

Results

Patient recruitment and flow are shown in figure 1. One hundred four patients entered the study, and after exclusions, data were analyzed from 49 patients in the norepinephrine group and 52 patients in the phenylephrine group. Data from all patients were analyzed according to

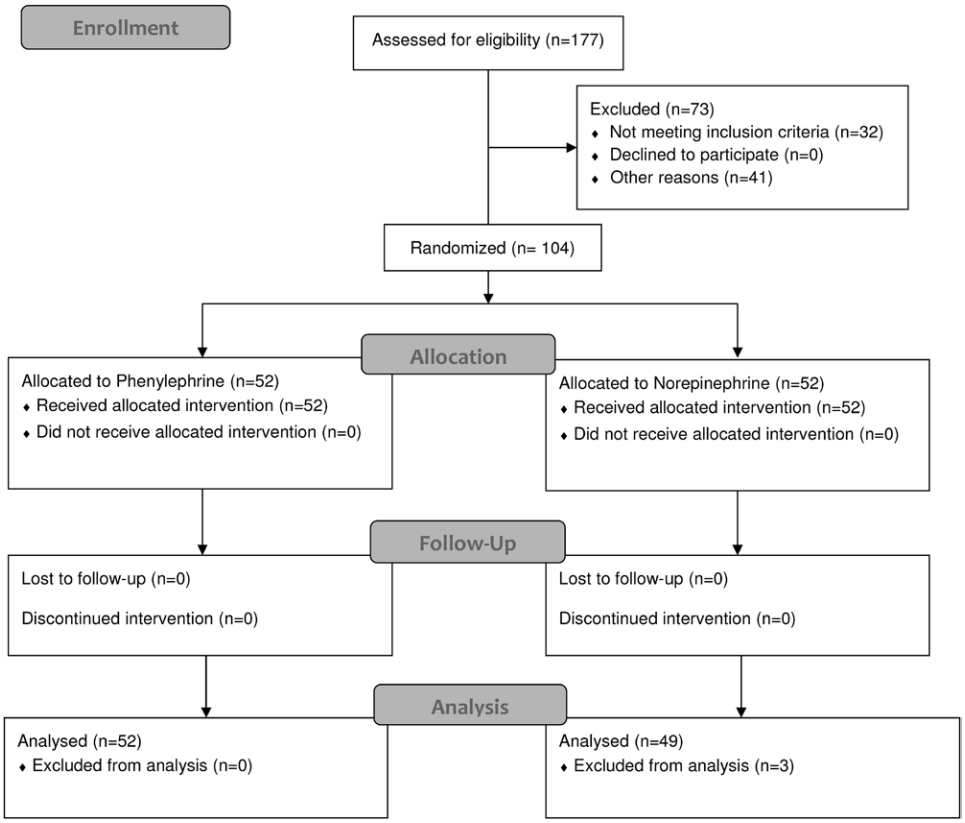

Fig. 1. CONSORT diagram showing patient recruitment and flow.

their assigned groups. Patient characteristics are shown in table 1. One patient in the norepinephrine group required supplemental oxygen. Because the noninvasive blood pressure apparatus took a varying time for each measurement and surgical time varied among patients, a variable number of measurements of blood pressure and HR were recorded for each patient (norepinephrine group: median 14 [range, 10 to 34] and phenylephrine group: median 13 [range, 9 to 26]). For measurements of CO, which were timed according to a stopwatch, a minimum of four recordings after induction of anesthesia were obtained from all patients. Because of equipment failure, umbilical cord blood gases could not be measured for one patient in the norepinephrine group and oxygen content could not be measured for three patients in the phenylephrine group and three patients in the norepinephrine group. In the norepinephrine group, insufficient blood was obtained for the following measurements: UA epinephrine (two patients), UV epinephrine (one patient), UA norepinephrine (two patients), and UV norepinephrine (one patient). In the phenylephrine group, insufficient umbilical cord blood was obtained for the following measurements: UA epinephrine (five patients), UV epinephrine (one patient), UA norepinephrine (four patients), and UV norepinephrine (one patient).

Table 1. Patient Characteristics and Surgical Times

	Phenylephrine Group (n = 52)	Norepinephrine Group (n = 49)
Age (yr)	33.9 (3.9)	33.1 (4.1)
Weight (kg)	68.3 (6.9)	67.9 (9.2)
Height (cm)	158 (6.1)	157 (5.6)
Block height (dermatome)	T4 [T3–T5]	T3.5 [T3–T5]
Induction-to-delivery interval (min)	28.5 [26.2–34.2]	29.4 [26.1–34.1]
Incision-to-delivery interval (min)	9.6 [6.7–12.6]	9.1 [7.1–12.2]
Uterine incision-to-delivery interval (s)	84 [57–109]	92 [61–129]

Values are mean (SD) or median [interquartile range].

Normalized CO at 5 min (primary outcome) was greater in the norepinephrine group compared with that in the phenylephrine group (median 102.7% [interquartile range, 94.3 to 116.7%] *versus* 93.8% [85.0 to 103.1%], $P = 0.004$, median difference 9.8%, 95% CI of difference between medians 2.8 to 16.1%). Changes in systolic blood pressure and HR over time are shown in figure 2; systolic blood pressure was similar between groups ($P = 0.36$), whereas HR was greater in the norepinephrine group compared with that in the phenylephrine group ($P = 0.039$). Changes in CO, SV, and SVR over time are shown in figure 3; CO was greater ($P < 0.001$) and SVR was lower ($P < 0.001$) in the norepinephrine group compared with that in the phenylephrine group, but there was no difference in SV ($P = 0.44$).

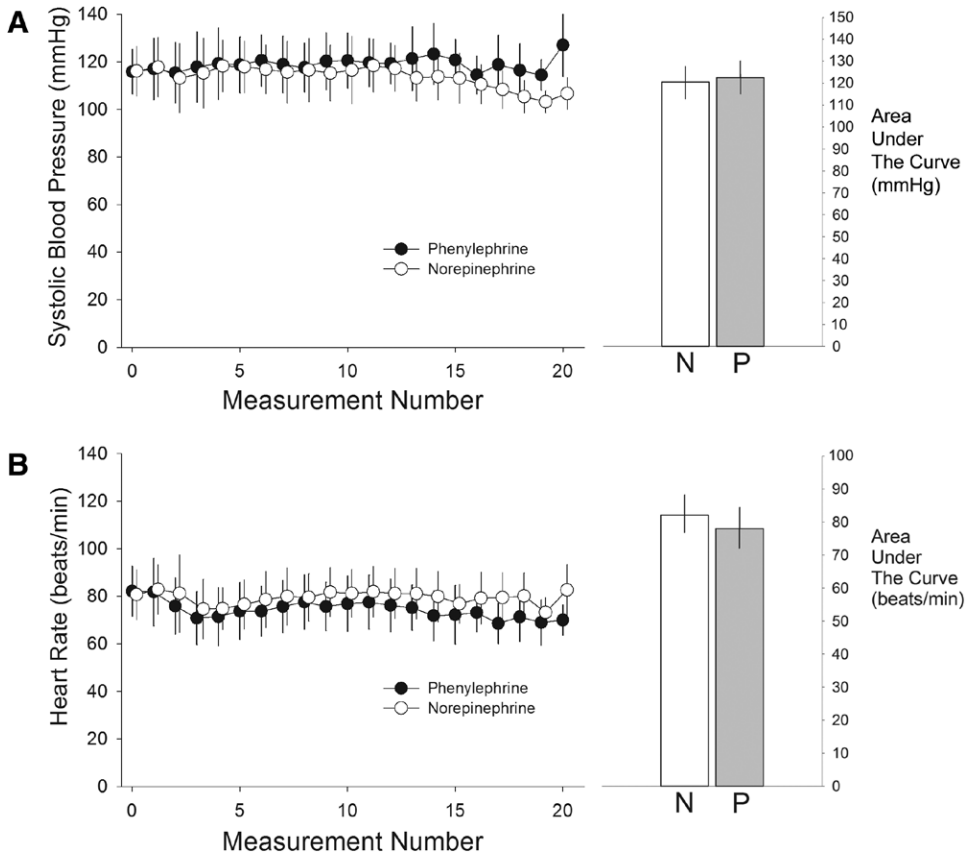

Fig. 2. Serial changes in systolic blood pressure (*A*) and heart rate (*B*). On the left side of the panels, data are serial values for the first 20 measurements shown as mean and SD. Because the noninvasive blood pressure monitor took a variable time to start and complete each blood pressure measurement, tick values on the horizontal axis represent the sequential number of each measurement made with the monitor set to an automatic 1-min cycling time rather than exact chronological time. On the right side of the panels, *bars* show the area under the curve for the two groups (N = norepinephrine and P = phenylephrine) standardized for each patient by dividing by the number of data points recorded and shown as median and interquartile range. Comparison of the calculated values for standardized area under the curve showed that systolic blood pressure was similar between groups ($P = 0.36$), but heart rate was greater over time in the norepinephrine group *versus* the phenylephrine group ($P = 0.039$).

The incidence of bradycardia, defined as an HR less than 60 beats/min, was lower in the norepinephrine group (18.4%) compared with that in the phenylephrine group (55.8%, $P < 0.001$). The rate of vasopressor administration was greater in the norepinephrine group (median 0.47 ml/min [interquartile range [0.39 to 0.58 ml/min]) compared with that in the phenylephrine group (39.1 ml/min [32.7 to 45.4 ml/min], $P = 0.002$). Three patients (6.1%) in the norepinephrine group and two patients (3.8%) in the phenylephrine group had nausea or vomiting ($P = 0.67$).

Neonatal outcome is summarized in table 2. All Apgar scores at 1 and 5 min were greater than 7, and no patient had UA pH less than 7.2. UA P_{O_2} was less than the lower limit of detection of the blood gas analyzer (10 mmHg) in two patients in the norepinephrine group and five patients in the phenylephrine group, and UV P_{O_2} was less than the lower limit of detection of the blood gas analyzer in one patient in the phenylephrine group; for analysis, these data values were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$,[13] and the data were analyzed by ranks. UV pH and UV oxygen content were higher in the norepinephrine group compared with that in the phenylephrine group. All other parameters were similar between groups.

Umbilical cord plasma concentrations of glucose, lactate, epinephrine, and norepinephrine are shown in table 3. Plasma concentrations were below the lower limit of detection (25 pg/ml) for the following: norepinephrine group: UA epinephrine (2 patients) and UV epinephrine (14 patients); phenylephrine group: UA epinephrine (2 patients) and UV epinephrine (14 patients). For analysis, data for these cases were entered as constant values equal to the lower limit of detection divided by $\sqrt{2}$,[13] and the data were analyzed by ranks. UA plasma concentrations of epinephrine and UA and UV plasma concentrations of norepinephrine were lower in the norepinephrine group compared with that in the phenylephrine group. UA and UV plasma concentrations of glucose were greater in the norepinephrine group compared with that in the phenylephrine group.

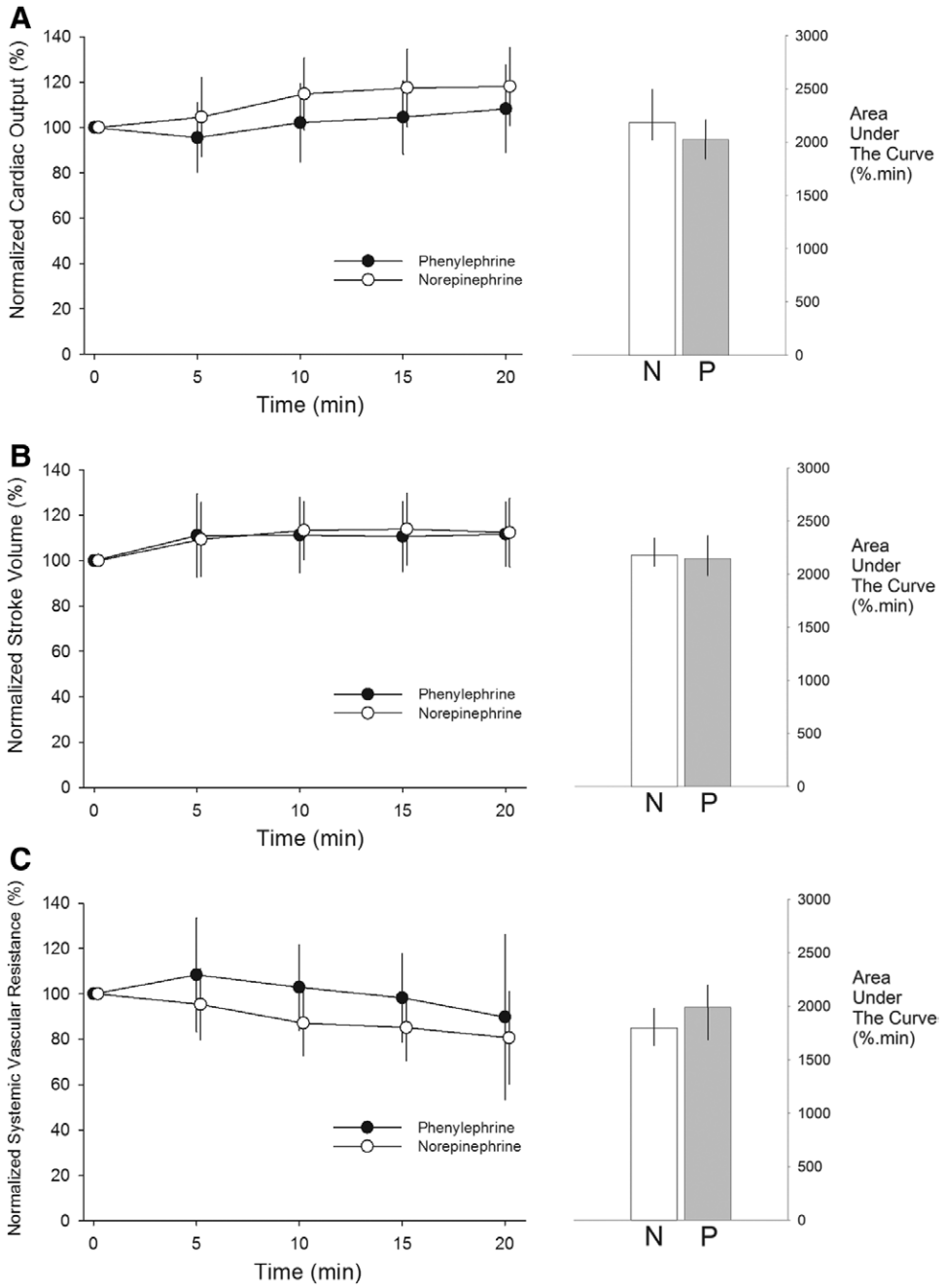

Fig. 3. Serial changes in cardiac output (*A*), stroke volume (*B*), and systemic vascular resistance (*C*). On the left side of the panels, data are serial values for the first 20 min after induction of spinal anesthesia normalized to percentage of baseline values. On the right side of the panels, *bars* show the area under the curve for the two groups (N = norepinephrine and P = phenylephrine). Comparison of the calculated values for area under the curve showed that cardiac output was greater over time ($P < 0.001$) and systemic vascular resistance was lower over time ($P < 0.001$) in the norepinephrine group compared with that in the phenylephrine group, but there was no difference in stroke volume ($P = 0.44$). Values are shown as median and interquartile range.

Discussion

The results of our study show that compared with phenylephrine, norepinephrine had similar efficacy for maintaining blood pressure during spinal anesthesia for cesarean delivery but was associated with greater HR and CO and lower SVR. These findings confirm our postulate that the use of a drug such as norepinephrine that has mild β-adrenergic receptor activity in addition to potent α-adrenergic receptor activity would exhibit similar vasopressor efficacy as phenylephrine but with a reduction in the undesirable negative chronotropic effects.

The typical hemodynamic response to spinal anesthesia in parturients is a decrease in SVR with a compensatory increase in HR and CO; thus, immediate treatment with an

Table 2. Neonatal Outcome

	Norepinephrine Group	Phenylephrine Group	*P* Value
Birth weight (kg)	3.11 [2.85–3.37]	3.19 [3.04–3.36]	0.37
Apgar score at 1 min <8	0	0	
Apgar score at 5 min <8	0	0	
Umbilical arterial blood gases			
pH	7.30 [7.28–7.33]	7.29 [7.28–7.32]	0.45
P_{CO_2} (mmHg)	50 [48–56]	52 [48–56]	0.77
P_{O_2} (mmHg)	15 [13–18]	14 [11–16]	0.20
Base excess (mmol/l)	−2.0 [−3.7 to −1.0]	−2.4 [−4.2 to −0.8]	0.87
Oxygen content (ml/dl)	6.0 [4.4–7.7]	5.2 [3.8–7.0]	0.29
Umbilical venous blood gases			
pH	7.35 [7.34–7.37]	7.34 [7.32–7.36]	0.031
P_{CO_2} (mmHg)	41 [38–43]	41 [38–45]	0.69
P_{O_2} (mmHg)	27 [23–30]	26 [23–28]	0.23
Base excess (mmol/l)	−3.2 [−4.1 to −2.0]	−3.5 [−5.6 to −2.4]	0.06
Oxygen content (ml/dl	12.7 [11.3–14.4]	11.8 [9.6–13.7]	0.047

Values are median [interquartile range] or number.

Table 3. Umbilical Cord Plasma Concentrations of Epinephrine, Norepinephrine, Glucose, and Lactate

	Phenylephrine Group	Norepinephrine Group	*P* Value
Umbilical arterial			
Epinephrine (pg/ml)	400 [227–700]	281 [78–491]	0.042
Norepinephrine (pg/ml)	2,178 [1,403–3,921]	1,756 [1,048–2,435]	0.035
Glucose (mg/dl)	46 [43–52]	53 [48–60]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.7–2.4]	0.088
Umbilical venous			
Epinephrine (pg/ml)	40 [18–73]	23 [18–63]	0.16
Norepinephrine (pg/ml)	457 [281–647]	347 [225–486]	0.031
Glucose (mg/dl)	51 [44–56]	56 [51–62]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.6–2.4]	0.33

Values are median [interquartile range].

α-adrenergic agonist is appropriate and recommended.[14] In this context, of available drugs, phenylephrine has become the agent most commonly recommended[14] although alternatives such as metaraminol are also effective.[15] Previously, we have shown that titrating phenylephrine to maintain maternal blood pressure near baseline values can reduce the incidence of maternal symptoms such as nausea and vomiting.[16] However, a drawback of the use of pure α-adrenergic drugs such as phenylephrine is that they have a dose-related tendency to decrease HR and CO, which can occur even without marked increases in blood pressure above baseline.[16] Concern has been expressed that this decrease in CO may adversely affect uteroplacental perfusion.[3] In this respect, a drug such as norepinephrine may potentially be advantageous. Norepinephrine has both direct positive chronotropic and reflexive negative chronotropic actions with the overall effect on HR considered to be approximately neutral.[17]

In our study, because SV was similar between groups, the greater CO in the norepinephrine group was primarily related to greater HR. The latter can most likely be attributed to the positive chronotropic effects of norepinephrine. However, it is possible that a positive effect on venous return may also have contributed. In nonobstetric subjects, it has been shown that pure α-adrenergic agonists can increase venous return by constricting capacitance vessels, but this may be opposed by an increase in venous resistance which can reduce venous return.[18,19] However, veins also have β-adrenergic receptors, and norepinephrine has been demonstrated to constrict capacitance vessels without an increase in venous resistance.[18,20] More work is required to determine whether venous return is greater during administration of norepinephrine compared with phenylephrine under conditions of spinal anesthesia in parturients. This may be particularly relevant for the occasional patient in whom bradycardia accompanies hypotension. In this situation, use of a drug such as norepinephrine that has positive effects on HR and venous return may be more appropriate than phenylephrine.

We found that blood pressure was maintained similarly in both groups, but in the norepinephrine group, this was associated with greater CO and lower SVR. Theoretically, this may be potentially more favorable for maintaining perfusion in the uteroplacental and other peripheral vascular beds. Interestingly, UV pH and UV oxygen content were greater in the norepinephrine group which possibly may

relate to greater placental blood flow and oxygen delivery in the norepinephrine group. However, the differences were small, umbilical cord blood gases were not the primary outcome of the study, and the use of multiple comparisons gives rise to the possibility of type I statistical error. Further work is required to confirm this observation and to determine whether norepinephrine may have any clinical advantage, for example, in patients with preeclampsia or in other conditions in which uteroplacental circulation may be compromised. Of note, we have previously observed greater umbilical cord blood P_{O_2} when ephedrine was used *versus* phenylephrine in both elective[21,22] and nonelective cesarean delivery[23] which may reflect a similar mechanism.

To our knowledge, this study is the first formal evaluation of norepinephrine as a vasopressor in obstetric patients. More commonly, norepinephrine is used in an intensive care setting, for example, in the treatment of patients with septic shock. In this context, it is noteworthy that phenylephrine is usually considered a second-line agent because of concerns that it increases blood pressure solely by vasoconstriction with a concomitant potential to decrease CO.[24–26] It has been reported that when phenylephrine is used to treat patients with septic shock, it decreases HR, decreases hepatosplanchnic perfusion, and impairs renal function compared with norepinephrine.[27,28] These findings are consistent with experimental work showing that regional and organ blood flow are better preserved with the use of norepinephrine compared with phenylephrine.[19] However, it is unknown whether these issues are relevant in the context of obstetric patients undergoing spinal anesthesia.

Umbilical arterial and UV plasma concentrations of norepinephrine and UA plasma concentration of norepinephrine were lower in the norepinephrine group than in the phenylephrine group. Because catecholamines are not thought to readily cross the placenta,[29] these findings probably reflect differences in fetal catecholamine production. Fetal catecholamine levels have been shown to be greater with increased stress during delivery and fetal asphyxia,[29,30] and an inverse correlation has been shown between umbilical blood catecholamine concentrations and P_{O_2}.[31] In our study, lower umbilical plasma catecholamine concentrations together with greater UV pH and oxygen content in the norepinephrine group suggest the possibility of decreased fetal stress in this group compared with the phenylephrine group which could be related to greater uteroplacental oxygen delivery. However, it should be noted that differences observed in our study were small, and the clinical significance of these findings in our low-risk patients is unclear.

Umbilical arterial and UV plasma glucose concentrations were greater in the norepinephrine group compared with that in the phenylephrine group. Because this was not associated with a difference in umbilical blood lactate concentration, pH, or base excess, stimulation of fetal metabolism as is thought to occur with ephedrine[22] is unlikely. It is possible that the higher umbilical blood concentrations of glucose in the norepinephrine group were the result of increased maternal glucose concentration and thus increased placental transfer that may have arisen from a stress hormone effect in parturients who received norepinephrine infusions.[32] However, we did not measure maternal plasma concentrations of glucose to confirm this suggestion.

We compared norepinephrine at a concentration of 5 μg/ml *versus* phenylephrine at a concentration of 100 μg/ml according to our estimate of a potency ratio of 20:1; this ratio has been used in previous clinical comparisons of norepinephrine and phenylephrine.[33,34] However, we found that the median infusion rate required to maintain blood pressure was greater in the norepinephrine group. This suggests that the true potency ratio for norepinephrine:phenylephrine for maintaining blood pressure under the conditions of our study is probably less than 20:1. Of note, this ratio relates to efficacy for maintaining blood pressure, which is affected by both CO and SVR. Our initial estimate of potency was based on previously reported work by Sjöberg *et al.*[8] who compared the effects of norepinephrine and phenylephrine according to the drugs' vasoconstrictor activity alone. Further work is required to determine the relative potencies of norepinephrine and phenylephrine used to maintain blood pressure in obstetric patients.

We measured CO using the technique of suprasternal Doppler. This technique has been shown to have good repeatability and also to be reliable in younger patients.[35] However, a disadvantage of the technique is that it depends on an estimate of aortic valve cross-sectional area that is determined using an algorithm based on patients' height. This introduces potential for systematic error in the derivation of absolute values although the ability to track trends is not affected.[35] We accounted for this in our analysis by normalizing all CO measurements and related derived parameters to percentage of baseline values.

Finally, we administered both vasopressor drugs by closed-loop computer-controlled infusion. In the context of a research study, this has the advantage of reducing possible bias that might arise from investigator-controlled manual infusions. Our computer-controlled system used a simple algorithm that is not dissimilar to manual-controlled algorithms.[36] Importantly, norepinephrine has the advantages of a fast onset of action and short duration which are desirable properties for a drug that is titrated by infusion. However, we acknowledge that some clinicians favor the use of intermittent boluses of vasopressors rather than infusions.[37] Further work is required to determine the efficacy of norepinephrine given by manually controlled infusion and intermittent boluses in obstetric patients.

In summary, our results showed that compared with phenylephrine, norepinephrine had similar efficacy for maintaining blood pressure during spinal anesthesia for cesarean delivery but with maintenance of greater maternal HR and CO. Neonatal outcome was similar. We suggest further work be done to determine the safety of norepinephrine in

obstetric patients, evaluate other methods of administration, determine its relative potency *versus* phenylephrine, and investigate whether its use may possibly be associated with greater uteroplacental blood flow and oxygen delivery compared with phenylephrine, particularly in conditions where uteroplacental perfusion is restricted such as preeclampsia.

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Competing Interests

The authors declare no competing interests.

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Appendix 1. Method Used to Measure Plasma Concentrations of Epinephrine and Norepinephrine

Blood samples were collected and transferred into lithium heparin tubes containing dilute sodium metabisulfite as an antioxidant and were placed in ice. Samples were immediately centrifuged at 4°C, and the plasma was separated and stored at −80°C pending batch analysis. Epinephrine and norepinephrine were measured by using high-performance liquid chromatography with electrochemical detection. The catecholamines were isolated using alumina adsorption under basic conditions and then reextracted from the alumina using dilute acid solution before their analysis on the high-performance liquid chromatography with an electrochemical detection system. The analytes were separated on a reversed-phased column (Ultrasphere IP C18; Beckman Instruments Inc., USA), using a mobile phase containing methanol–citric acid–EDTA–octane sulfonic acid–water under isocratic condition. Quantitation was then performed by monitoring the drugs by electrochemical detection using a coulometric detector (Coulochem III; Thermo Scientific Dionex, USA). The assay was linear to the lower limit of detection (25 pg/ml for both epinephrine and norepinephrine). There were good linear responses for both epinephrine and norepinephrine with correlation coefficients better than 0.9970. The lowest limit of detection was at 25 pg/ml at a signal-to-noise ratio of 3. The within-day coefficients of variation for epinephrine and norepinephrine ranged from 3.71 to 13.11% (mean, 7.81%) and 2.67 to 9.79% (mean, 6.00 %), respectively. The between-day coefficients of variation were 6.46 to 15.06% (mean, 10.80%) and 7.84 to 13.68% (mean, 10.61%), respectively.