The Catecholamine, Cortisol, and Hemodynamic Responses to Mild Perioperative Hypothermia

A Randomized Clinical Trial

Steven M. Frank, M.D.,* Michael S. Higgins, M.D.,† Michael J. Breslow, M.D.,‡ Lee A. Fleisher, M.D.,*
Randolph B. Gorman, M.D.,† James V. Sitzmann, M.D.,§ Hershel Raff, Ph.D.,‖ Charles Beattie, M.D.#

Background: Unintended hypothermia occurs frequently during surgery and may have adverse effects on the cardiovascular system. Although the mechanisms responsible for the cardiovascular manifestations of hypothermia are unclear, it is possible that they are sympathetically mediated. In this prospective study, relationships between body temperature, the neuroendocrine response, and hemodynamic changes in the perioperative period were examined.

Methods: Seventy-four elderly patients, undergoing abdominal, thoracic, or lower extremity vascular surgical procedures, were randomly assigned to either "routine care" (n = 37) or "forced-air warming" (n = 37) groups. Throughout the intraoperative and early postoperative periods, the routine care group received standard thermal care, and the forced-air warming group received forced-air skin-surface warming. Core temperature, forearm minus fingertip skin-surface temperature gradient, and plasma concentrations of epinephrine, norepinephrine, and cortisol were measured throughout the perioperative period, and the two groups were compared. In addition, heart rate and arterial blood pressure were compared between groups.

Results: The routine care and forced-air warming groups did not differ with regard to age, sex, type of surgical procedures, anesthetic techniques, or postoperative analgesia. Mean core temperature was lower in the routine care group on admission to the postanesthetic care unit (routine care, 35.3 ± 0.1°C; forced-air warming, 36.7 ± 0.1°C; P = 0.0001) and remained lower during the early postoperative period. Forearm minus fingertip skin-surface temperature gradient (an index of peripheral vasoconstriction) was greater in the routine care group in the early postoperative period. The mean norepinephrine concentration (pcg/ml) was greater in the routine care group immediately after surgery (480 ± 70 *vs.* 330 ± 30, P = 0.02) and at 60 min (530 ± 50 *vs.* 340 ± 30, P = 0.002) and 180 min (500 ± 80 *vs.* 320 ± 30, P = 0.004) postoperatively. Mean epinephrine concentrations were not significantly different between groups. Mean cortisol concentrations were increased in both groups during the early postoperative period (P < 0.01), but the differences between groups were not significant. Systolic, mean, and diastolic arterial blood pressures were significantly higher in the routine care group.

Conclusions: Compared with patients in the forced-air warming group, patients receiving routine thermal care had lower core temperatures, a greater degree of peripheral vasoconstriction, higher norepinephrine concentrations, and higher arterial blood pressures in the early postoperative period. These findings suggest a possible mechanism for hypothermia-related cardiovascular morbidity in the perioperative period. (Key words: Hormones: cortisol. Hypothermia: perioperative. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine. Thermoregulation: vasoconstriction.)

* Assistant Professor, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

† Assistant Professor, Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee.

‡ Associate Professor, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

§ Associate Professor, Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

‖ Professor, Department of Medicine, St. Luke's Medical Center, The Medical College of Wisconsin, Milwaukee, Wisconsin.

Professor and Chairman, Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee.

UNINTENDED perioperative hypothermia occurs in approximately one-half of all surgical patients[1-3] and has been associated with cardiovascular complications. We previously demonstrated an increased incidence of early postoperative myocardial ischemia in vascular surgery patients with core temperatures less than 35°C[4]; however, no clear mechanism was identified to explain this finding. The metabolic demands associated with shivering have been thought to be responsible for

cardiovascular stress in the perioperative period. Twenty-five years ago, Bay et al.[5] hypothesized that patients with "cardiopulmonary disease" may not tolerate the metabolic demands of shivering. Since then, however, little or no evidence has been presented to establish a relationship between perioperative shivering and adverse outcomes. Furthermore, in our previous study, the association between hypothermia and myocardial ischemia did not appear to be related to shivering.[4] This suggests that a mechanism other than shivering is responsible for hypothermia-related cardiovascular stress.

The normal response to hypothermia includes activation of the sympathetic nervous system. Studies in healthy volunteers have demonstrated that even small changes in core temperature ($\approx 0.2°C$) are associated with thermoregulatory vasoconstriction.[6] With exposure to cold ambient temperatures or total body immersion in cold water, epinephrine[7-9] and norepinephrine[7-10] concentrations are significantly increased. Animal studies indicate that adrenal hormones play an important role in maintaining normothermia during cold exposure.[11-13] In addition, by activating glycogenolysis and providing substrate for metabolism, cortisol may play an integral role in the response to cold stress.[12,14] These cold-induced hormonal responses could adversely affect the cardiovascular system if similar changes occur in surgical patients with underlying medical problems.

Accordingly, we studied the relationship between perioperative changes in body temperature and plasma levels of stress hormones. Using a prospective randomized design, body temperature, catecholamine and cortisol responses, and hemodynamic changes were compared in patients receiving routine thermal care or forced-air skin-surface warming during the intraoperative and early postoperative periods.

Materials and Methods

With approval by the Committee on Clinical Investigation and after obtaining written informed consent, 74 patients were enrolled. All three of the following inclusion criteria were required for enrollment: (1) age older than 60 yr; (2) scheduled thoracic, abdominal, or lower extremity vascular surgery; and (3) the presence of two or more risk factors for coronary artery disease, according to criteria used in previous studies.[15] Exclusion criteria were a preoperative tympanic temperature of <36°C or >38°C measured by the infrared

technique (Thermoscan, San Diego, CA), a history of Raynaud's syndrome, or a known thyroid disorder. Patients were randomly assigned to receive either "routine care" (n = 37) or "forced-air warming" (n = 37) in the perioperative period. Randomization was stratified on type of surgery.

Treatment Protocols

All patients received their usual chronic medications (*e.g.,* antihypertensives, antianginals) before surgery. All patients were monitored with electrocardiogram, pulse oximetry, and radial intraarterial catheters for continuous display of blood pressure throughout the study.

Routine care was delivered according to the following protocol. The thermostat in the operating room was set to $\approx 21°C$. Intravenous fluids and blood were warmed (Fenwal model BW-5, Deerfield, IL). A heat-moisture exchanger (Thermovent 600, Portex, Keene, NH) was used in the respiratory circuit for those patients receiving general anesthesia. After the surgical field was prepped and draped, the patient was covered above and below the field with one layer of paper drapes. In the postoperative period, either one or two warmed cotton blankets were placed over the patient at the postanesthetic care unit (PACU) nurse's discretion.

Patients in the forced-air warming group were treated as follows. The thermostat in the operating room was set to $\approx 21°C$. Fluids and blood were warmed (Fenwal) and a heat-moisture exchanger was used (Portex) in the respiratory circuit for those patients receiving general anesthesia, as in the routine care group. Depending on the surgical site, an upper or a lower body forced-air warming blanket (Warm Touch, Mallinckrodt, St. Louis, MO) was placed over the patient and connected to a forced-air blower (Warm Touch). During the first 2 h of postoperative care, a full body forced-air warming blanket covered the patient's legs and trunk. During the intraoperative and postoperative periods, both the temperature and airflow were set to "high" or adjusted to "medium" to maintain core temperature at or near 37°C. If core temperature exceeded 37°C, the blower was turned off and the blanket left in place. After the initial 2 h postoperatively, care was similar to that used for patients in the routine care group.

Anesthetic Technique

Patients received premedication with midazolam (up to 5 mg) and/or morphine (up to 0.1 mg/kg) given

intramuscularly. Either a general or regional anesthetic regimen was used, in most cases determined by the surgical procedure. General anesthesia was chosen for patients undergoing abdominal surgical procedures. This included thiopental (4–6 mg/kg), fentanyl (3–10 μg/kg) and/or morphine (0.1–0.2 mg/kg), and pancuronium or vecuronium, all given intravenously, nitrous oxide (up to 70%), and isoflurane or enflurane (0.2–2.0%). All patients were tracheally intubated during surgery, and the trachea was extubated at the end of the surgical procedure unless standard extubation criteria were not met. These criteria include the return of consciousness, reversal of neuromuscular blockade, and ability to follow commands and ventilate spontaneously. For patients receiving general anesthesia, analgesia was provided during the initial 18–24 h postoperatively with intravenous morphine sulfate delivered by patient-controlled analgesia with a background infusion of 1 mg/h, a bolus dose of 1 mg, and a lockout interval of 6 min.

Epidural anesthesia was used for patients undergoing lower extremity vascular surgery unless there was a contraindication (anticoagulation, spinal fusion, or patient refusal), in which case general anesthesia was employed. Epidural anesthesia was delivered through a lumbar catheter using 2% lidocaine or 0.5–0.75% bupivicaine to achieve a T6–T10 sensory level. Midazolam and/or fentanyl sedation was given intravenously during the intraoperative period as needed. Postoperative analgesia was provided with a patient-controlled analgesia infusion of 0.0625% bupivicaine with 5 μg/ml fentanyl, using a background infusion of 2–4 ml/h, a bolus dose of 2 ml, and a lockout interval of 10 min.

Patients having thoracic surgical procedures received general anesthesia as described above. Instead of intravenous morphine by patient-controlled analgesia infusion, an intrathecal dose of 0.5 mg morphine was given shortly before induction of anesthesia. This general/regional anesthetic technique will be referred to subsequently as "combined" anesthesia.

Postoperative pain was assessed at 30 and 90 min postoperatively and in the morning of the first postoperative day. Pain was evaluated using a ten-point oral analog scale, with 0 = no pain and 10 = severe pain.

Temperature Monitoring

On arrival in the operating room, body temperature monitoring was initiated with an Iso-thermex electronic thermometer (Columbus Instruments, Columbus, OH).

Eight body sites were monitored: two core sites and six skin-surface sites. Core temperature was measured using a tympanic membrane thermocouple probe (Mon-a-Therm, Mallinckrodt) inserted until a scratching sound was reported by the patient. A second core temperature was measured in the urinary bladder using a catheter that incorporates a thermocouple probe (Mon-a-Therm). If the tympanic probe became dislodged during the study, the bladder temperature was used as the core temperature. Skin-surface temperatures were measured with thermocouple probes (Mon-a-Therm) on the anterior chest, the lateral mid-upper arm, the anterior radial side of the mid-forearm, the index fingertip (opposite the nailbed), the lateral mid-thigh, and the lateral mid-calf. The forearm minus fingertip skin-surface temperature gradient was used as a measure of vasoconstriction as previously described[16] and was measured in the arm that was not used to administer intravenous fluids. Mean skin temperature was calculated using the following formula: 0.3(chest + upper arm) + 0.2(thigh + calf).[17] Temperatures were recorded onto a hard disk at 5-min intervals until the morning of the first postoperative day (≈ 24 h). All temperature data were analyzed, and the two groups were compared at the following times: preoperatively, at the end of surgery, on admission to PACU, at 30, 60, 90, and 180 min postoperatively, and in the morning of the first postoperative day. Care was taken to prevent direct warming of the tympanic membrane, forearm, and fingertip thermocouple probes by the forced-air warming blanket. In the postoperative period, the blanket was placed over the patient's legs and trunk while the monitored arm remained exposed.

Catecholamine and Cortisol Measurements

Plasma epinephrine, norepinephrine, and cortisol concentrations were measured five times during the perioperative period: preoperatively (≈ 10–20 min after insertion of the arterial catheter, before induction of anesthesia), on admission to the PACU, at 60 and 180 min postoperatively, and in the morning of the first postoperative day. These times were selected because thermoregulatory activity is most significant during rewarming in the early postoperative period. Arterial blood samples were drawn into tubes containing EDTA, cold-centrifuged, and the plasma was stored at −80°C. Catecholamines were measured using high-pressure liquid chromatography with electrochemical detection after alumina extraction as previously described.[18] The sensitivity of this assay is 20 pcg/ml,

FRANK *ET AL.*

and the intra- and interassay coefficients of variability are 3–5%. Cortisol concentrations were determined by radioimmunoassay.[18]

Hemodynamic Measurement and Management

Blood pressures were obtained by intraarterial measurements from a 20-G, 3.3-cm radial artery catheter connected by 23 cm of arterial pressure tubing to a disposable transducer (Cobe, Lakewood, CO). A bedside monitor (Marquette series 7010, Milwaukee, WI) with a frequency band width of 0–40 Hz displayed a pressure waveform and digital readout continuously. All visible air bubbles were purged from the system, and the zero reference was confirmed with electronic calibration preoperatively and on admission to the PACU. The transducer was set at the level of the right atrium (mid-axillary line). Heart rate and systolic and diastolic arterial blood pressure were recorded in all patients during the postoperative period. Mean arterial blood pressure measured intraarterially was available for 49 of the 74 patients. Heart rate and blood pressure were measured by one of the coinvestigators during the preoperative visit. Preoperative blood pressure was measured in both arms using the Korotkoff technique, and measurements from the arm with the highest systolic blood pressure[19] were used in the analysis comparing the two groups over time. Preoperative mean blood pressure was determined by the formula (diastolic + 1/3(systolic − diastolic)).

Appropriate upper and lower limits for systolic blood pressure were determined before surgery based on three preoperative blood pressure measurements, as we described previously.[20] The number of hours the blood pressure exceeded the upper limit in the postoperative period was determined by reviewing the hemodynamic flow sheet. Drug therapy for hypertension was determined by protocol[20] to maintain arterial blood pressure within predetermined limits. The requirement for antihypertensive therapy in the first 24 h postoperatively was recorded. The hemodynamic treatment protocols were carried out by the house staff in the surgical intensive care unit.

Data Analysis

Chi-square and unpaired Student's *t* tests were used to compare the two groups demographically. Analysis of variance for repeated measures was used to compare differences between and within the two groups for the variables measured over time. Multivariate analyses were used to determine the effect of randomized treatment group on outcomes, independent of anesthetic technique and requirement for postoperative mechanical ventilation. Multivariate models were used to determine independent predictors of postoperative norepinephrine, epinephrine, and cortisol concentrations on admission to the PACU and at 60 and 180 min postoperatively. Variables entered into the multivariate analyses included the design variable of the study (randomized group) and those variables determined by univariate testing to have a *P* value less than 0.20 at any of the three times. Pain scores were included in the multivariate models because pain can significantly influence the stress response.[18] Clinical variables that were tested include randomized treatment group, anesthetic technique, age, requirement for postoperative mechanical ventilation, sex, diabetes mellitus, postoperative shivering, and postoperative pain score. Shivering (presence or absence determined by PACU nurses) and pain score (0–10) were entered into the analysis in accordance with the time the blood sample was obtained for catecholamine or cortisol analysis. Regression was determined using the backward elimination method.[21] All data are given as mean ± SEM with significance defined as *P* < 0.05.

Results

There were no significant differences between the two groups with regard to patient age, sex, height, weight, history of diabetes, hypertension, or preoperative β-adrenergic blocker therapy (table 1). A comparable percentage of patients in each group underwent abdominal, thoracic, and lower extremity vascular surgical procedures, and a similar percentage of patients received general, regional, and combined anesthetic techniques. The percentage of patients requiring postoperative mechanical ventilation was similar in both groups. The mean duration of ventilatory support was 16 ± 6 h for patients who required mechanical ventilation. The proportion of patients receiving epidural or intravenous patient-controlled analgesia in the postoperative period was similar in both groups. The analgesia protocols provided comparable degrees of pain relief in both groups, as indicated by pain scores. Antihypertensive medication was required for 30% of patients in the routine care group and 19% of patients in the forced-air warming group (*P* = 0.28).

Preoperative core temperature measured at the tympanic membrane was similar in the two groups (fig.

Table 1. Clinical Characteristics of the Study Patients

	Routine Care (n = 37)	Forced-air Warming (n = 37)	P
Age (yr)	70 ± 1	71 ± 1	0.64
Male sex	18 (49)	24 (65)	0.16
Height (cm)	167 ± 2	170 ± 2	0.28
Weight (kg)	73 ± 3	74 ± 3	0.82
Diabetes	8 (22)	8 (22)	1.00
History of hypertension	22 (59)	20 (54)	0.64
Preoperative β blocker	8 (22)	11 (30)	0.42
Surgical procedure			
Vascular	12 (32)	11 (30)	
Abdominal	21 (57)	19 (51)	0.62
Thoracic	4 (11)	7 (19)	
Anesthetic			
General	25 (68)	24 (65)	
Regional	8 (22)	6 (16)	0.57
Combined	4 (11)	7 (19)	
Requirement for postoperative mechanical ventilation	8 (22)	6 (16)	0.55
Postoperative epidural analgesia	10 (27)	9 (24)	0.79
Postoperative intravenous patient-controlled analgesia	29 (78)	29 (78)	1.00
Postoperative morphine requirement (mg/24 h)	32 ± 5	23 ± 5	0.19
Pain scores (0–10)			
30 min postoperatively	6 ± 1	4 ± 1	0.18
90 min postoperatively	6 ± 1	5 ± 1	0.44
Postoperative day 1	4 ± 0	3 ± 0	0.13
Time above systolic blood pressure limit (h)	4.6 ± 0.9	3.3 ± 0.9	0.32
Requirement for antihypertensive therapy	11 (30)	7 (19)	0.28

Values in parentheses indicate percentage.

1). On admission to the PACU, core temperature was significantly lower in the routine care group (35.3 ± 0.1°C) than in the forced-air warming group (36.7 ± 0.1°C; P = 0.0001). Core temperature remained lower in the routine care group throughout the first 180 min postoperatively but was similar between groups in the morning of the first operative day. Mean skin temperature was significantly lower in the routine care group on PACU admission, remained lower for the first 180 min postoperatively (P = 0.0001), but was similar in the morning of the first postoperative day. Forearm minus fingertip skin-surface temperature gradient was significantly greater in the routine care group on admission to the PACU, remained higher for the first 180 min postoperatively (P = 0.0001), but was similar between groups in the morning of the first postoperative day. Significant vasoconstriction, defined by a mean forearm fingertip gradient greater than 4°C, was present in the routine care group but not in the forced-air warming group during the early postoperative period. Five patients did not maintain adequate tympanic tem-

perature probe placement for the duration of the study and bladder temperature was substituted.

Mean norepinephrine, epinephrine, and cortisol concentrations were similar in the two groups preoperatively and on postoperative day 1 (fig. 2). The norepinephrine response was significantly greater in the routine care group than in the forced-air warming group (P = 0.008). Mean norepinephrine concentrations were greater in the routine care group on admission to the PACU (P = 0.02) and at 60 (P = 0.003) and 180 min (P = 0.004) postoperatively. Within the routine care group, norepinephrine concentrations were significantly greater than the preoperative baseline level on admission to the PACU, at 60 and 180 min postoperatively, and in the morning of postoperative day 1 (P < 0.05).

The epinephrine response was not significantly different between groups (P = 0.23). Within the routine care group, however, mean epinephrine concentration was greater than the preoperative baseline level on admission to the PACU and at 60 and 180 min postop-
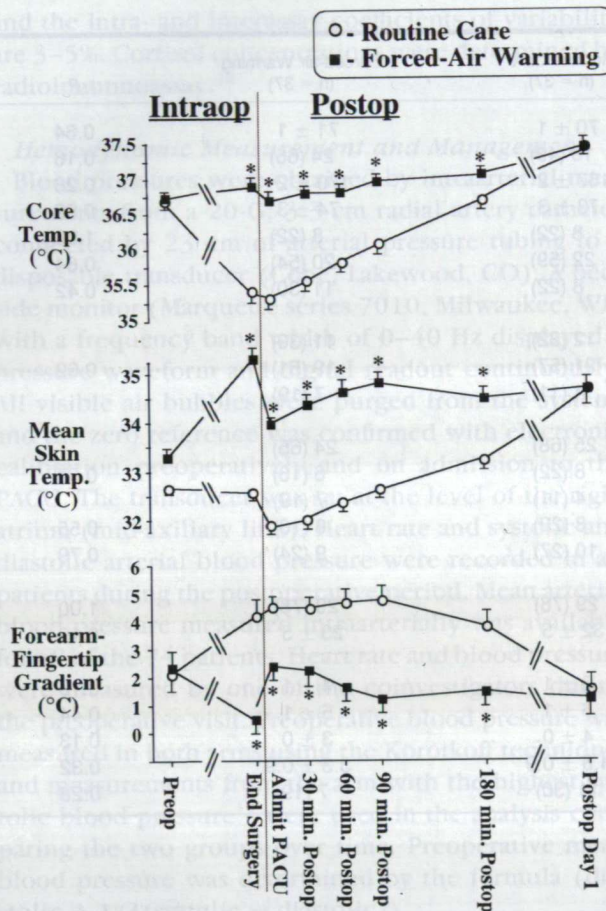
Fig. 1. Body temperature data are shown over the intraoperative and postoperative periods for the routine care and forced-air warming groups. Core temperature, measured at the tympanic membrane, was significantly lower at the end of the surgical procedure in the routine care group and remained lower for 180 min postoperatively. Mean skin temperature was lower in the routine care group. This difference was greatest at the end of surgery, but the groups remained significantly different at 180 min postoperatively. Forearm minus fingertip skin-surface temperature gradient was significantly greater in the routine care group at the end of surgery and remained greater at 180 min postoperatively, indicating a greater degree of vasoconstriction. *P < 0.01 *versus* routine care.

eratively (*P* < 0.05). There were no significant changes in mean epinephrine concentrations from the preoperative baseline within the forced-air warming group (*P* = 0.14).

Cortisol concentrations in both groups were significantly increased in the early postoperative period relative to the preoperative baseline (*P* = 0.01). Differences between the groups were not statistically significant (*P* = 0.51).

Heart rate and blood pressure were comparable between groups in the preoperative period (fig. 3). Heart rate was significantly lower in the routine care group (*P* = 0.05) in the early postoperative period, but the difference between groups was less than 10 beats/min at any given time. Arterial blood pressure was higher
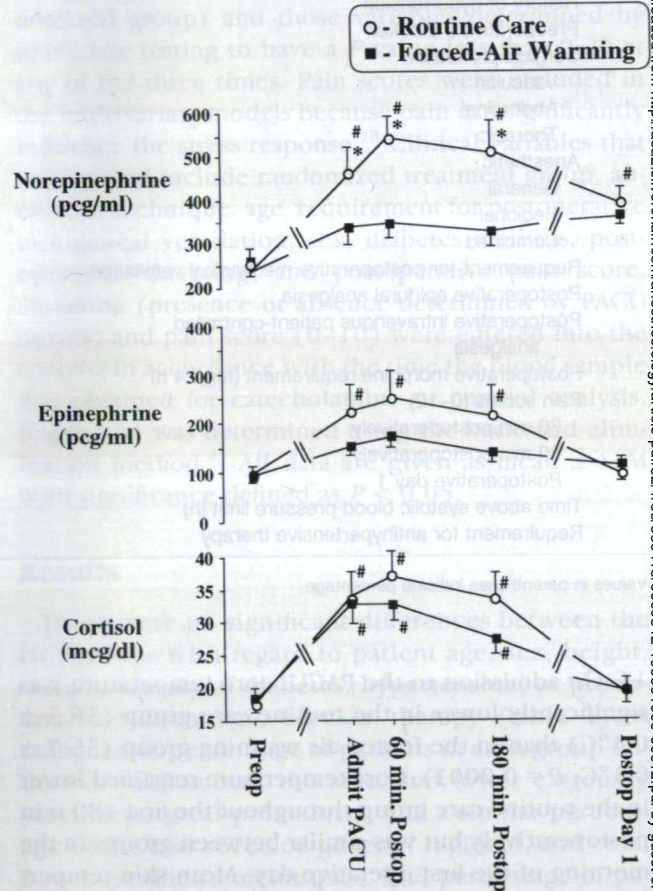

Fig. 2. Plasma norepinephrine, epinephrine, and cortisol levels were measured in arterial blood, and the routine care and forced-air warming groups were compared. Norepinephrine levels were significantly greater than the preoperative baseline in the routine care group on admission to the postanesthesia care unit (PACU), at 60 and 180 min postoperatively, and in the morning of postoperative day 1. Between-group comparison showed norepinephrine levels to be significantly greater in the routine care group on admission to the PACU and at 60 and 180 min postoperatively. Epinephrine levels were significantly elevated above the preoperative baseline in the routine care group on admission to the PACU and at 60 and 180 min postoperatively. Comparison between groups showed no significant differences. Postoperative cortisol levels were increased above the preoperative baseline in both groups. The differences in cortisol levels between groups were not significant. *P < 0.01 *versus* forced-air warming. #P < 0.05 *versus* preoperative.
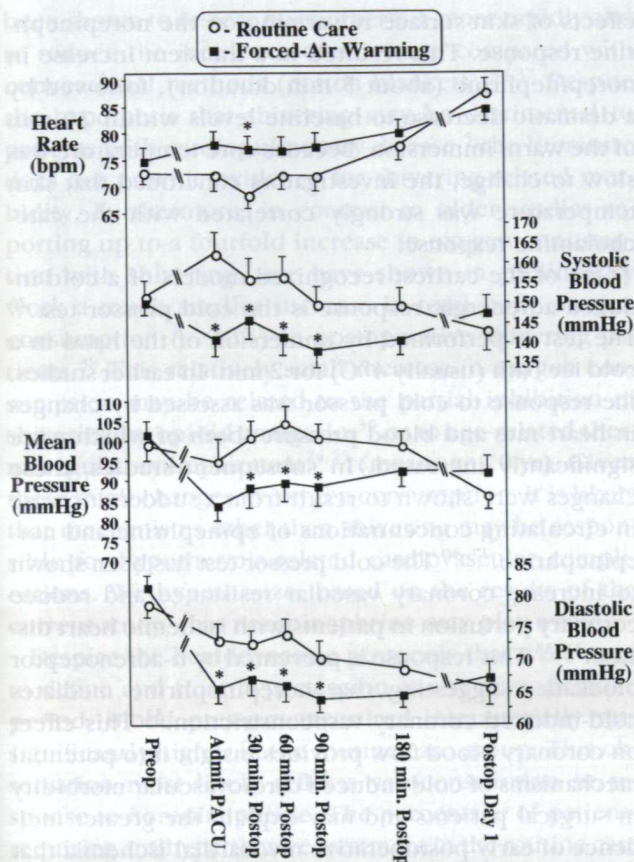
Fig. 3. Hemodynamic parameters were compared in the routine care and the forced-air warming groups during the perioperative periods. The difference in the heart rate response between the two groups was statistically significant ($P = 0.05$), but the difference at any given time was small (<10 beats/min). Systolic blood pressure was significantly higher in the routine care group on admission to the postanesthesia care unit (PACU) and at 30, 60, and 90 min postoperatively. Mean blood pressure was significantly higher in the routine care group at 30, 60, and 90 min postoperatively. Diastolic blood pressure was significantly higher in the routine care group on admission to the PACU and at 30, 60, and 90 min postoperatively. *$P < 0.01$ *versus* routine care.

in the routine care group during the early postoperative period. Differences were significant for systolic ($P = 0.003$), mean ($P = 0.005$), and diastolic ($P = 0.02$) measurements.

A significant relationship was noted between the norepinephrine response and hemodynamic changes. Patients were divided into two groups according to the norepinephrine response in the early postoperative period: those who had >50% (n = 52) and those with <50% (n = 22) increase in norepinephrine above the preoperative baseline at any measurement point in the

first 180 min postoperatively. The >50% group had significantly higher arterial blood pressures upon admission to the PACU and at 30 and 60 min postoperatively. This increased blood pressure was noted for systolic ($P = 0.003$), mean ($P = 0.004$), and diastolic ($P = 0.02$) blood pressures. Heart rate was not significantly different in these two groups. When 100% and 150% increases in norepinephrine were used to define the response, similar differences were noted in arterial blood pressure, but these differences were less dramatic.

Multivariate analyses were performed to determine independent predictors of the catecholamine and cortisol responses at each of three different times: PACU admission and at 60 and 180 min postoperatively. Randomization was a significant independent predictor of the norepinephrine response by multivariate testing at these three times. For the epinephrine response, there were no significant independent predictors. The randomized group to which the patient was assigned was not correlated with epinephrine level at any of the three times. The only significant independent predictor of the cortisol response was anesthetic technique. General anesthesia was associated with higher cortisol concentrations at all three times.

Discussion

In this randomized clinical trial, a decrease in core temperature of $\approx 1.5 °C$ was associated with higher norepinephrine concentrations in the early postoperative period. In contrast, thermal maintenance had little effect on the epinephrine or cortisol responses. This degree of hypothermia was accompanied by vasoconstriction and higher arterial blood pressures, both of which indicate a clinically significant effect of norepinephrine on the peripheral vasculature. Higher norepinephrine concentrations in the colder patients may represent a component of the thermoregulatory response. Although prior studies have established a relationship between "cold stress" and catecholamines,[7,10] the adrenergic response to mild perioperative hypothermia has not been previously studied in a prospective randomized fashion.

Prior studies have been unable to establish a relationship between hypothermia and the catecholamine response in the perioperative period. Previous investigators, however, did not use a randomized design to assess the effects of temperature. Halter *et al.*[22] studied eight patients undergoing abdominal surgery. All pa-

tients had increased epinephrine and norepinephrine concentrations in the first 2 h of the postoperative period, which they attributed to afferent pain stimuli. In this small series, without randomization or standardized postoperative analgesia, it is not surprising that no effect of temperature on the catecholamine response was observed.

We studied the stress response in patients undergoing peripheral vascular surgery who were randomized to receive epidural or general anesthesia.[18] In contrast to the present study, we did not find body temperature to be related to the catecholamine response. As previously mentioned, without a randomized design with respect to temperature management, it is difficult to draw conclusions regarding the effects of temperature. Age may have been a confounding variable. The elderly had higher preoperative norepinephrine concentrations and less change from baseline in the postoperative period. Elderly patients are also more likely to develop hypothermia.[23-25] Another possible explanation for the disparity between the results of our previous and current studies may be that skin-surface temperatures were higher in the active warming group in the current study than in the "normothermic" patients in the prior study, when no active warming measures were employed. By using aggressive skin-surface warming in the current study, both the skin and the core were maintained at higher temperatures.

Increased catecholamine secretion during exposure to cold ambient temperatures has been demonstrated in healthy young volunteers. Both epinephrine and norepinephrine urinary excretion have been shown to be increased with ambient temperatures between 6.5°C and 15°C.[7-9] As might be expected in young individuals with an active thermoregulatory response, core temperature was not significantly altered (<0.5°C decrease) during cold exposure in these studies. However, mean skin temperature was decreased by 4°C during 15°C cold exposure.[8] These results suggest that skin-surface cooling was responsible for initiating the adrenergic response.

Johnson *et al.*[10] studied young healthy volunteers who were immersed in a cold-water bath (10°C) for 1 h. Epinephrine was not measured, but norepinephrine increased twofold in the first 2 min of exposure and increased three- to fourfold after 45 min. Although core temperature eventually decreased to 34.5°C, the rapid norepinephrine response preceded changes in core temperature. At the end of the 1-h period, the volunteers were immersed in a 40°C water bath to assess the

effects of skin-surface rewarming on the norepinephrine response. This resulted in a transient increase in norepinephrine (about 5 min duration), followed by a dramatic decrease to baseline levels within 20 min of the warm immersion. Because core temperature was slow to change, the investigators concluded that skin temperature was strongly correlated with the catecholamine response.

One of the earliest recognized models of a cold-induced adrenergic response is the cold pressor test.[26] The test is performed by immersion of the hand in a cold ice bath (usually 4°C) for 2 min. In earlier studies, the response to cold pressor was assessed by changes in heart rate and blood pressure, both of which were significantly increased. In subsequent studies, these changes were shown to result from a sudden increase in circulating concentrations of epinephrine and norepinephrine.[27-30] The cold pressor test has been shown to increase coronary vascular resistance and reduce coronary perfusion in patients with ischemic heart disease.[31-33] This response is prevented by α-adrenoceptor blockade, suggesting that norepinephrine mediates cold-induced coronary vasoconstriction.[32] This effect on coronary blood flow provides insight into potential mechanisms of cold-induced cardiovascular morbidity in surgical patients and may explain the greater incidence of early postoperative myocardial ischemia that we previously described in high-risk patients who develop unintended hypothermia during surgery.[4]

In the current study, the cortisol response was not affected by temperature management. In accordance with previously published results,[34] patients receiving general anesthesia had greater postoperative cortisol levels relative to those receiving combined or regional anesthetics. Although cortisol release is controlled by the hypothalamic-pituitary-adrenal system which involves corticotropin releasing hormone and adrenocorticotropic hormone,[35] the afferent pain stimuli that trigger this response are attenuated by either neuraxial narcotics or regional conduction blockade. Thus we conclude that the cortisol response is determined primarily by anesthetic technique and not by the relatively small changes in body temperature that we observed. Perhaps temperature changes of a greater magnitude would be associated with a significant cortisol response, but further studies will be necessary to identify such an effect.

The beneficial effects of perioperative patient warming have been proposed in previous studies. Forced-air warming in the immediate postoperative period has

been shown to restore normothermia more rapidly and to reduce the incidence of shivering compared with conventional methods (cotton blankets).[36,37] Despite the hypothesis that shivering may be detrimental to patients with cardiopulmonary disease,[5] the literature does not provide evidence for shivering-related morbidity. Furthermore, in contrast to older studies reporting up to a fourfold increase in oxygen consumption with shivering,[5] we have shown in preliminary work a much smaller increase in total body oxygen consumption ($\approx 30\%$) in postoperative shivering patients.[38] This relatively small increase in oxygen consumption may be related to the partial inhibition of shivering by opioid analgesics[39] or to age-related thermoregulatory impairment[24,25] (mean age 70 yr). Given these small changes in oxygen consumption, it is likely that mechanisms other than shivering may be responsible for hypothermia-related cardiovascular complications. We hypothesize, based on the results of the current study, that norepinephrine may play a role.

Despite the hemodynamic protocols that were used to define and treat hypertension in the postoperative period, blood pressure measured intraarterially was significantly higher in the routine care group. This observation most likely reflects vasoconstriction in response to norepinephrine. The percentage of patients requiring antihypertensive treatment in the routine care group (30%) was not significantly greater than the percentage requiring treatment in the skin-surface warming group (19%). Although the difference in requirement for antihypertensive medication was not significant, these treatment protocols may have resulted in an underestimation of the increased blood pressure in the hypothermic patients.

The relationship between core temperature, vasoconstriction, and arterial blood pressure has been reported by Hynson et al.[40] In that study, systolic, diastolic, and mean blood pressures were lower in warmed volunteers than in those who developed thermoregulatory vasoconstriction during exposure to 21°C ambient temperature. Although the Hynson et al. study nicely demonstrates the effects of vasoconstriction and warming on arterial blood pressure, the effects of core hypothermia are not evident because the volunteers were anesthetized when hypothermia developed. Our results are consistent with those from this previous study but differ in that we report the hemodynamic effects of postoperative hypothermia in elderly surgical patients. In addition, our inclusion criteria resulted in over one-half the patients having a history of hyperten-

sion requiring treatment with medication. Thus, the hemodynamic effects of hypothermia may be specific for this subset of patients and may not apply to younger normotensive individuals.

In the same study, Hynson et al. present data to suggest that intraarterial measurements in vasoconstricted patients result in a falsely elevated systolic blood pressure when compared with measurements taken by the oscillometric technique.[40] Our findings indicate that, in addition to differences in systolic blood pressure, mean and diastolic blood pressures were increased in the hypothermic patients. When measured by intraarterial catheters, mean and diastolic pressures correlate with oscillometric measurements and are likely to reflect true blood pressure, even in the presence of vasoconstriction.[40]

It is possible that arterial blood samples do not reflect the true magnitude of the norepinephrine response. Compared to arterial blood, venous blood has been shown to contain higher concentrations of norepinephrine.[41] This may be explained by the release of norepinephrine at the sympathetic nerve terminals, which is taken up as the blood passes from the arterial to the venous circulation. Both arterial and venous samples are likely to underestimate the peripheral sympathetic release of norepinephrine, because the measured concentrations represent only "spillover" into the circulation. Thus, the arterial norepinephrine levels that we measured may have underestimated the true magnitude of the adrenergic response in patients who develop inadvertent hypothermia.

In conclusion, we have demonstrated in a prospective randomized study that, compared to patients who are maintained at normothermic temperatures, patients developing mild hypothermia during surgery have a greater increase in norepinephrine concentrations, more significant vasoconstriction, and an increased arterial blood pressure in the early postoperative period. In contrast, the epinephrine and cortisol concentrations were not significantly altered by thermal management in the range of temperatures that were observed. Although it is possible that the adrenergic response may play a role in the development of cold-induced cardiovascular complications, further work will be necessary to determine the relationship between stress hormones and perioperative morbidity in patients who develop hypothermia.

References

1. Hendolin H, Lansimies E: Skin and central temperatures during continuous epidural analgesia and general anaesthesia in patients subjected to open prostatectomy. Ann Clin Res 14:181–186, 1982

2. Vaughan MS, Vaughan RW, Cork RC: Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering in rewarming. Anesth Analg 60:746–751, 1981

3. Slottman GJ, Jed EH, Burchard KW: Adverse effects of hypothermia in postoperative patients. Am J Surg 149:495–501, 1985

4. Frank SM, Beattie C, Christopherson R, Norris EJ, Perler BA, Williams GM, Gottlieb SO: Unintentional hypothermia is associated with postoperative myocardial ischemia. ANESTHESIOLOGY 78:468–476, 1993

5. Bay J, Nunn JF, Prys-Roberts C: Factors influencing arterial PO2 during recovery from anaesthesia. Br J Anaesth 17:398–407, 1968

6. Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. ANESTHESIOLOGY 80:780–788, 1994

7. Arnett EL, Watts DT: Catecholamine excretion in men exposed to cold. J Appl Physiol 15:499–500, 1960

8. Lamke LO, Lennquist S, Liljedahl SO, Wedin B: The influence of cold stress on catecholamine excretion and oxygen uptake of normal persons. Scand J Clin Lab Invest 30:57–62, 1972

9. Wilkerson JE, Raven PB, Bolduan NW, Horvath SM: Adaptations in man's adrenal function in response to acute cold stress. J Appl Physiol 36:183–189, 1974

10. Johnson DG, Hayward JS, Jacobs TP, Collis ML, Eckerson JD, Williams RH: Plasma norepinephrine responses of man in cold water. J Appl Physiol 43:216–220, 1977

11. Leduc J: Catecholamine production and release in exposure and acclimation to cold. ACTA Physiol Scand 53:5–101, 1961

12. Maickel RP, Matussek N, Stern DN, Brodie BB: The sympathetic nervous system as a homeostatic mechanism: I. Absolute need for sympathetic nervous function in body temperature maintenance of cold-exposed rats. J Pharmacol Exp Ther 157:103–110, 1967

13. Pouliot M: Catecholamine excretion in adreno-demedullated rats exposed to cold after chronic guanethidine treatment. Acta Physiol Scand 68:164–168, 1966

14. Alexander G, Bell AW: The role of the adrenal gland in the metabolic response of young lambs to cold. J Develop Physiol 4:53–73, 1982

15. Hollenberg M, Mangano DT, Browner WS, London MJ, Tubau JF, Tateo IM, The Study of Perioperative Ischemia Research Group: Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. JAMA 268:205–209, 1992

16. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 73:541–545, 1990

17. Ramanathan NL: A new weighting system for mean surface temperature of the human body. J Appl Physiol 19:531–533, 1964

18. Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, Rock P, Christopherson R, Rosenfeld BA, Beattie C, The PIRAT Study Group: Determinants of catecholamine and cortisol responses to lower extremity revascularization. ANESTHESIOLOGY 79:1202–1209, 1993

19. Frank SM, Norris EJ, Christopherson R, Beattie C: Right- and left-arm blood pressure discrepancies in vascular surgery patients. ANESTHESIOLOGY 75:457–463, 1991

20. Christopherson R, Beattie C, Frank SM, Norris EJ, Meinert CL, Gottlieb SO, Yates H, Rock P, Parker SD, Perler BA, Williams GM, The PIRAT Group: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. ANESTHESIOLOGY 79:422–434, 1993

21. Draper NR, Smith H: Applied Regression Analysis. 2nd edition. New York: John Wiley and Sons, 1981, pp 167–168

22. Halter JB, Pflug AE, Porte D: Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 45:936–944, 1977

23. Frank SM, Beattie C, Christopherson R, Norris EJ, Rock P, Parker S, Kimball AW: Epidural *versus* general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. ANESTHESIOLOGY 77:252–257, 1992

24. Frank SM, Shir Y, Raja SN, Fleisher LA, Beattie C: Core hypothermia and skin surface temperature gradients: Epidural *versus* general anesthesia and the effects of age. ANESTHESIOLOGY 80:502–508, 1994

25. Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F: The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. ANESTHESIOLOGY 79:465–469, 1993

26. Hines EA, Brown GE: The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. Am Heart J 11:1–9, 1936

27. Cummings MF, Steele PM, Mahar LJM, Frewin DB, Russell WJ: The role of adrenal medullary catecholamine release in the response to a cold pressor test. Cardiovasc Res 17:189–191, 1983

28. Cuddy RP, Smulyan H, Keighley JF, Markason CR, Eich RH: Hemodynamic and catecholamine changes during a standard cold pressor test. Am Heart J 71:446–454, 1966

29. McLean JK, Sathasivam P, MacNaughton K, Graham TE: Cardiovascular and norepinephrine responses of men and women to two cold pressor tests. Can J Physiol Pharmacol 70:36–42, 1992

30. Winer N, Carter C: Effect of cold pressor stimulation of plasma norepinephrine, dopamine-beta-hydroxylase, and renin activity. Life Sci 20:887–894, 1977

31. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP: Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. Circulation 77:43–52, 1988

32. Mudge GH, Grossman W, Mills RM, Lesch M, Braunwald E: Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 295:1333–1337, 1976

33. Shea MJ, Deanfield JE, deLandsheere CM, Wilson RA, Kensett M, Selwyn AP: Asymptomatic myocardial ischemia following cold provocation. Am Heart J 114:469–476, 1987

34. Engquist A, Brandt MR, Fernandes A, Kehlet H: The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic responses to surgery. Acta Anaesthesiol Scand 21:330–335, 1977

35. Brodish A, Lymangrover JR: The hypothalamic-pituitary adrenocortical system. Int Rev Physiol 16:93–99, 1977

36. Gorman RB, Frank SM, Kelly S, Fleisher LA, Higgins M, Furman W, Beattie C, Sitzmann JV: Inadvertent hypothermia and convective

warming: Effects on early postoperative hemodynamic and metabolic demands (abstract). ANESTHESIOLOGY 79:A135, 1993

37. Lennon RL, Hosking MP, Conover MA, Perkins WJ: Evaluation of a forced-air system for warming hypothermic postoperative patients. Anesth Analg 70:424–427, 1990

38. Frank SM, Higgins MS, Fleisher LA, Gorman RB, Breslow MJ, Sitzmann JV, Beattie C: Multivariate determinates of early postoperative oxygen consumption: The effects of shivering, core temperature, and gender (abstract). ANESTHESIOLOGY 81:A1423, 1994

39. Pauca AL, Savage RT, Simpson S, Roy RC: Effect of pethidine, fentanyl, and morphine on postoperative shivering in man. Acta Anaesthesiol Scand 28:138–143, 1984

40. Hynson JM, Sessler DI, Moayeri A, McGuire J, Schroeder M: The effects of preinduction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. ANESTHESIOLOGY 79:219–228, 1993

41. Esler M, Jennings G, Korner P, Blombery P, Sacharias N, Leonard P: Measurement of total and organ-specific norepinephrine kinetics in humans. Am J Physiol 247:E21–E28, 1984