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Determinants of Catecholamine and Cortisol Responses to Lower Extremity Revascularization

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Background: **Surgical trauma elicits diffuse changes in hormonal secretion and autonomic nervous system activity. Despite studies demonstrating modulation of the stress response by different anesthetic/analgesic regimens, little is known regarding the determinants of catecholamine and cortisol responses to surgery.**

Methods: **Plasma catecholamines and cortisol secretion data were obtained from 60 patients undergoing lower extremity revascularization. Patients were randomized to receive either general anesthesia combined with patient-controlled intravenous morphine (GA) or epidural anesthesia combined with epidural fentanyl analgesia (RA). All aspects of intra- and postoperative clinical care were defined by written protocol. Plasma catecholamines were measured before induction, intraoperatively, and for the first 18 h postoperatively (by HPLC). Urine cortisol was measured intra- and postoperatively using RIA. Data were evaluated using univariate and multivariate analyses to evaluate demographic and perioperative variables as determinants of stress hormone secretion.**

Results: **Plasma catecholamines increased during skin closure in the GA group, and remained higher relative to the RA group in the postoperative period. Multivariate analysis indicated that age and anesthetic regimen predicted increases in catecholamines during skin closure ($P < 0.005$), although duration of surgery, blood loss, and body temperature were not correlated. Early postoperative norepinephrine concentrations were correlated with pain score and duration of surgery ($P < 0.004$), but not with anesthetic management, blood loss, or body temperature. All postoperative norepinephrine levels were highly correlated ($r = 0.7$) with norepinephrine levels during skin closure. Cortisol excretion was higher postoperatively than intraoperatively. No patient or perioperative variable predicted cortisol excretion, and cortisol excretion was not correlated with catecholamine levels at any time.**

Conclusions: **These data indicate that patient factors, such as age and inherent sympathetic responsivity, are important determinants of the catecholamine response to surgery. Modulation of the norepinephrine response by regional anesthesia/analgesia appears to be related, in part, to superior analgesia. The lack of correlation between catecholamine and cortisol secretion indicates that the stress response may consist of discrete systems responding to different stimuli. (Key words: Analgesia: postoperative. Anesthetic techniques: general; regional. Autonomic nervous system: catecholamines; stress response.)**

SURGICAL trauma elicits diffuse changes in hormonal secretion and autonomic nervous system activity.[1–5] These neuroendocrine effects of surgery produce a variety of changes in cardiovascular, metabolic, immune, and hemostatic function. Although early investigators considered these stress-induced alterations to be adaptive,[6,7] recent evidence indicates that they can precipitate clinically important complications in patients with underlying medical problems.[8–11] This realization has prompted attempts to find anesthetic and analgesic techniques that can attenuate the stress response to

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surgery. Although regional anesthetic techniques using local anesthetics are effective in blunting intraoperative hormonal changes,[3,12] recognition that plasma catecholamine, cortisol, and vasopressin concentrations remain increased for up to 5 days postoperatively[4,13] has focused attention on postoperative strategies for modulating the stress response. Several reports indicate that neuraxial opioids can result in lower plasma catecholamine and cortisol concentrations postoperatively.[8,12,14,15] Although it is assumed that this action of epidural/intrathecal opioids is caused by superior analgesia, the role of pain and other physiologic perturbations in the genesis of the stress response have not been clearly defined. To provide further insight into the determinants of perioperative hormonal changes, catecholamine concentrations and cortisol secretion were measured in patients undergoing lower extremity revascularization. These patients were randomized to receive general anesthesia combined with postoperative PCA morphine, or epidural anesthesia combined with postoperative epidural opioid analgesia.[16] Because this study controlled the relevant aspects of perioperative care and was structured to provide optimal anesthetic and analgesic therapy to both groups, it provided a unique opportunity to study determinants of the stress response.

Materials and Methods

After approval by The Johns Hopkins Hospital human studies committee, 60 consecutive patients, recruited to participate in a randomized trial comparing epidural and general anesthesia for lower extremity bypass grafting, consented to perioperative measurement of plasma catecholamines and cortisol secretion. Details of the parent study have been published elsewhere.[16] Briefly, on the morning of surgery, patients received all chronic medications (*i.e.*, antianginals, antihypertensives, etc.), except oral hypoglycemic agents. Premedication consisted of midazolam and morphine, and additional sedation, including midazolam and fentanyl, was given as needed during placement of the radial arterial catheter and other invasive monitors. Clinical decisions, such as hemodynamic monitoring, anesthetic agents and dosages, heart rate and blood pressure limits, and the therapy to maintain these hemodynamic parameters within limits, were rigorously controlled throughout the perioperative period.

Patients randomized to epidural anesthesia received 10 ml/kg of lactated ringers solution before receiving 0.75% bupivacaine; the dose was titrated to achieve a sensory blockade at T8. Additional 0.75% bupivacaine was given intraoperatively if the sensory level fell below T8–T9. At the conclusion of surgery, 100 μg fentanyl diluted in 10 ml saline was given *via* the epidural catheter and a continuous epidural fentanyl infusion was begun at a rate of 50 μg/h (5 μg/ml) on arrival in the intensive care unit (ICU). The infusion rate was increased by 10 μg/h if pain scores were greater than 4 out of 10.

Patients were randomized to general anesthesia and received intravenous fentanyl in 50-μg increments (up to 10 μg/kg), and thiamylal in 50-mg increments (up to 5 mg/kg) until loss of consciousness. After ventilation *via* mask with oxygen, muscle paralysis was achieved with 1.5 mg/kg succinylcholine, the larynx and trachea were anesthetized with 160 mg lidocaine by topical administration, and oral endotracheal intubation was performed. Maintenance of anesthesia consisted of N_2O (up to 50%) in oxygen, and enflurane (up to 1%). Pancuronium or vecuronium were used for muscle relaxation, and the patients' lungs were mechanically ventilated to maintain end-tidal CO_2 between 35–45 mmHg. At the conclusion of surgery, residual relaxants were antagonized with neostigmine and glycopyrrolate, inhalation anesthetics were discontinued, and spontaneous ventilation was restored. Intravenous morphine was titrated to maintain the respiratory rate at 8–12/min and end-tidal CO_2 at less than 50 mmHg. The endotracheal tube was removed and intravenous patient-controlled morphine analgesia (initial settings: background 0.5 mg/h, bolus 1 mg/h, lockout 10 min) was begun after arrival in the ICU.

Blood was obtained from the arterial catheter at the following time points: preinduction; postinduction/preincision; 15 and 60 min postincision; at the beginning of skin closure; and 1, 6, 12, and 18 h after arrival in the ICU. Samples were drawn into tubes containing EDTA, cold centrifuged, and plasma was stored at −80° C for subsequent measurement of plasma epinephrine (EPI) and norepinephrine (NE). Catecholamines were measured using high-pressure liquid chromatography with electrochemical detection after alumina extraction. Details of this assay have been published previously[17]; sensitivity of the assay is 20 pg/ml, and intra- and interassay coefficients of variability are 3–5%.

Intraoperative and postoperative (first 24 h only) urine was collected on ice, frozen at −80° C, and subsequently analyzed for free cortisol by radioimmunoassay after extraction with dichloromethane.[18] Cor-

Table 1. Demographic Data

	Epidural (n = 28)	General (n = 29)	*P*
Age ≥ 65 yr	15 (54)	16 (55)	0.90
Sex (number male)	17 (61)	20 (69)	0.51
Hypertension	12 (43)	19 (66)	0.09
β-Adrenergic blockers	3 (11)	7 (24)	0.18
Diabetes	8 (29)	10 (34)	0.63
Cigarette use	24 (86)	25 (86)	0.96
Distal vascular graft	14 (50)	13 (45)	0.47

Percentages in parentheses.

β-Adrenergic blockers = patients taking β-adrenergic receptor antagonists.

tisol excretion data were normalized for duration of collection, and are expressed in μg/h.

Data collected and evaluated for possible relationships to hormonal responses to surgery included demographic information (age, sex, history of hypertension, diabetes, smoking and preoperative treatment with β-adrenergic antagonists, type and duration of surgery, intraoperative blood loss, body temperature on arrival in the ICU, postoperative pain scores, and major perioperative complications [myocardial infarction/death, leg ischemia]). Diagnosis of myocardial infarction by a cardiologist masked to the anesthetic regimen was based on serial electrocardiograms and creatine phosphokinase MB isoenzyme measurements during the early postoperative (ICU) period. Pain scores were recorded on a linear analog scale (1–10) by a physician 1 h after arrival in the ICU, and by ICU nurses at 6, 12, and 18 h postoperatively.

Data Analysis

Chi-square analysis was used to compare demographic data between the two management groups. Possible effects of anesthetic/analgesic management on catecholamine and cortisol responses to surgery were evaluated using two-way ANOVA procedures (between-within format). Newman-Keuls tests were used for pairwise comparisons. To evaluate the contribution of patient factors and perioperative events to perioperative increases in catecholamine and cortisol secretion, associations between hypothesized determinants and hormone levels were examined by least-squares linear regression analysis (continuous data) and by *t* tests (nominal data). Catecholamine data were analyzed using actual values and changes from preinduction levels. After univariate analysis, these same data were analyzed by multiple linear regression. All multivariate analyses were done with backward elimination, with $P \leq 0.12$ as criteria for retaining variables in the equation. Least-squares linear regression was used to evaluate relationships between simultaneously measured epinephrine and norepinephrine concentrations, norepinephrine plasma concentrations at skin closure and subsequent norepinephrine plasma concentrations, and intraoperative (and postoperative) cortisol secretion and averaged intraoperative (and postoperative) catecholamine concentrations. Intraoperative norepinephrine and epinephrine values were determined by averaging the

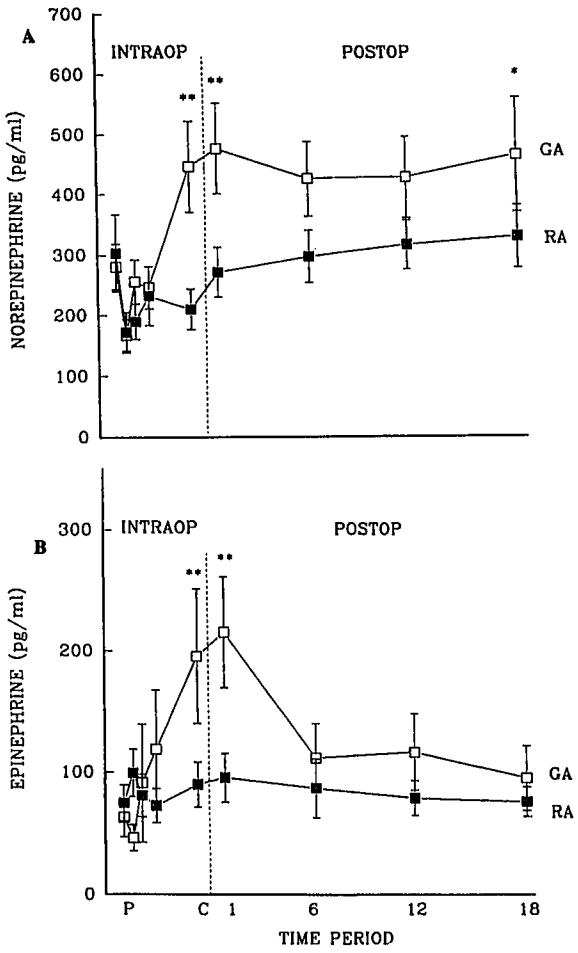

Fig. 1. Plasma norepinephrine (*A*) and epinephrine (*B*) concentrations before induction of anesthesia (P), at skin closure (C), and 1, 6, 12 and 18 h after lower extremity revascularization. Data from patients receiving general anesthesia and parenteral morphine analgesia (GA) are contrasted with data from patients receiving epidural bupivacaine anesthesia and epidural fentanyl analgesia (RA). **$P < 0.01$; *$P < 0.05$ compared with RA group. Data are mean ± SEM.

three intraoperative data points; postoperative values were averages of the four postoperative data points. Results are reported as mean ± SEM; P values < 0.05 are considered significant.

Results

Three of 60 patients enrolled in the study had missing data points, leaving 57 patients for analysis. Age and sex distribution were similar in the two anesthetic groups, and there were no differences in the incidence of underlying medical conditions (table 1). The EPI and NE data for the two different anesthetic/analgesic groups are shown in figure 1. Preinduction and early intraoperative levels were similar in the two groups. Epinephrine and NE were not increased intraoperatively over preinduction levels except during skin closure, when both EPI and NE increased in the group emerging from general anesthesia. In the postoperative period, the NE concentration was greater in the GA group than in the RA group at 1 and 18 h, and EPI was significantly higher in the GA group only during the early postoperative period.

Univariate and multivariate analyses of factors affecting EPI and NE concentrations during skin closure are shown in table 2. Anesthetic regimen was independently associated with catecholamine concentration at this time; type and duration of surgery, blood loss, and temperature were not. Elderly patients (>65 yr of age) had smaller increases in norepinephrine concentrations at this time ($P = 0.005$), although absolute concentrations were not different. The influence of age on perioperative catecholamine concentrations is shown in greater detail in figure 2. Patients over 65 yr of age (mean 75 ± 1 yr) had higher preinduction plasma norepinephrine concentrations (336 ± 44 *vs.* 188 ± 43 pg/ml; $P = 0.02$), but increases in plasma norepinephrine levels at skin closure were more marked in the younger patients (mean 56 ± 1 yr). Norepinephrine concentrations at all other postoperative times were similar in the two groups.

Univariate and multivariate determinants of plasma catecholamines at the 1-h postoperative time point are shown in table 3. Pain scores and duration of surgery were predictors of plasma norepinephrine concentration; age, presence of hypothermia and/or shivering, and quantity of intraoperative blood loss were not. Type of anesthesia was predictive of norepinephrine levels at this time ($P = 0.04$) only if pain scores were removed from the analysis. Type of anesthesia was a determinant of 1-h postoperative epinephrine levels. There was a strong correlation between plasma norepinephrine concentrations during skin closure and subsequent norepinephrine measurements. Figure 3 shows the relationship between skin closure and 1-h postoperative norepinephrine concentrations. Inclusion of skin closure norepinephrine concentrations in multivariate analyses of postoperative norepinephrine levels showed this measure to be an independent predictor ($P = 0.0002$) of norepinephrine levels 1, 6, 12, and 18 h postoperatively. Exclusion of patients with major perioperative complications from the above analyses had no effect on observed relationships. Plasma epinephrine and norepinephrine concentrations were correlated ($P < 0.001$) at all time points, particularly when each was elevated.

Cortisol excretion data are shown in figure 4. Cortisol excretion was higher in both groups postoperatively than intraoperatively ($P < 0.05$); there was no significant difference in cortisol excretion in the two anesthetic groups. Univariate and multivariate analysis showed no relationship between intra- or postoperative cortisol secretion and age, duration of surgery, blood

Table 2. Univariate and Multivariate Predictors of Catecholamine Levels at Skin Closure

	Norepinephrine		Epinephrine	
	Univariate *P*	Multivariate *P*	Univariate *P*	Multivariate *P*
Duration of surgery	0.60	0.90	0.62	0.91
Body temperature ≤ 35° C	0.64	0.42	0.59	0.42
Blood loss	0.89	0.40	0.57	0.35
Age ≥ 65 yr	0.36	0.23	0.37	0.29
Anesthetic technique	0.008	0.007	0.08	0.06
Distal vascular graft	0.21	0.13	0.11	0.08

loss, or pain scores. Furthermore, no correlation could be demonstrated between the cortisol and catecholamine response to surgery, either intraoperatively or postoperatively (fig. 5). This was also true when the GA group was examined alone.

Discussion

Results of the current study indicate that pain and duration of surgery are determinants of the early catecholamine response to surgery, and other perioperative events, such as hypothermia and blood loss, are less important. There is considerable interindividual variability in the sympathetic response to surgery, with older individuals having higher basal catecholamines and somewhat delayed postoperative increases. Moreover, this inherent variability in sympathetic responsivity appears to be an important determinant of postoperative increases in catecholamine levels. Although epidural anesthesia with bupivacaine directly attenuates intraoperative catecholamine increases, modulation of the early postoperative norepinephrine response by epidural administration of fentanyl appears to be caused, in part, by superior analgesic efficacy. Determinants of perioperative catecholamine secretion do not predict the cortisol response, indicating that these two systems function independently after surgery.

Restricting the patient population to a single surgical procedure, and standardizing perioperative management, were important elements of the study design. This reduced the number of confounding variables and improved the likelihood of identifying factors that predict perioperative hormone changes. Available data indicate that the magnitude and duration of the stress response are proportional to the extent of tissue trauma.[13] Furthermore, afferent stimuli responsible for perioperative increases in cortisol secretion appear to vary depending on the surgical site.[19] Even minor variations in the type of vascular bypass procedure performed may be important; patients undergoing distal bypass procedures tended to have higher plasma catecholamines during emergence. Thus, caution should be exercised in extrapolating the results of the current study to patients having other procedures, particularly intraabdominal or intrathoracic operations.

Plasma norepinephrine concentrations were low in both groups intraoperatively until skin closure, at which time both epinephrine and norepinephrine concentrations increased to approximately twice baseline levels in the general anesthesia group. Multivariate analysis of the determinants of skin closure catecholamine levels confirmed the importance of anesthetic management in this response. Other intraoperative variables, including duration of surgery, blood loss, and development of hypothermia, did not predict plasma catecholamines at this time. Similarly, patient variables, such as preexisting medical conditions, chronic medications, and gender, were also not contributory. It is likely that increases in catecholamines in the general anesthesia group at this time are caused by decreasing anesthetic depth, possibly as a result of perceptions of surgical pain, airway reflex stimulation,

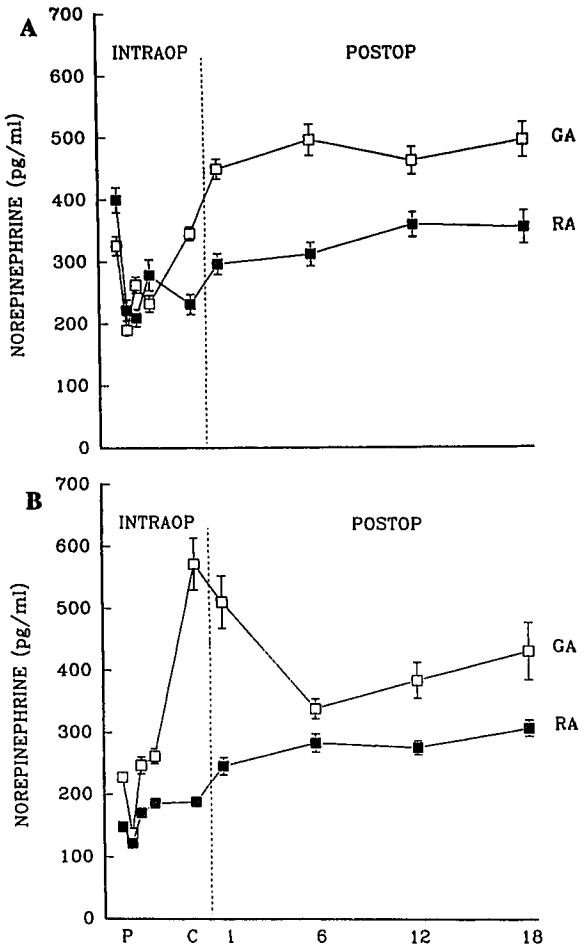

Fig. 2. Perioperative norepinephrine (NE) levels as a function of age. (*A*) Patients > 65 yr of age (mean 74.2 ± 1.1 yr) had higher preinduction NE levels. (*B*) Younger patients (mean 56.3 ± 1.2 yr) had more prominent increases in NE levels during skin closure. Patients receiving general anesthesia (GA) and regional anesthesia (RA) are shown separately. C = skin closure; P = preop. Data are mean ± SEM.

Table 3. Univariate and Multivariate Predictors of Catecholamine Levels 1 h Postoperatively

	Norepinephrine		Epinephrine	
	Univariate *P*	Multivariate *P*	Univariate *P*	Multivariate *P*
Body temperature ≤ 35° C	0.11	0.11	0.47	0.94
Emergence concentration	0.0001	0.02	0.002	0.85
Duration of surgery	0.0001	0.0002	0.17	0.72
Pain score	0.03	0.04	0.29	0.61
Age ≥ 65 yr	0.95	0.26	0.61	0.44
Distal vascular graft	0.50	0.78	0.37	0.27
Anesthetic technique	0.02	0.85	0.02	0.02

Emergence concentration = norepinephrine (and epinephrine) concentration at skin closure.

or removal of general anesthetic-inhibition of injury-induced sympathetic activation. Presumably, residual local anesthetic blockade prevents afferent neural activation of catecholamine secretion and attenuates efferent sympathetic outflow in the regional anesthesia group.

There was considerable variability in the catecholamine response to skin closure that was not explained by anesthetic management. Some of this variability appears to be age related. Older patients had higher preoperative norepinephrine levels. This observation is in agreement with studies of plasma catecholamines in nonstress situations.[20] Despite higher preoperative plasma norepinephrine concentrations, older patients had smaller increases with skin closure. Whether this is because of slower emergence from general anesthesia or reflects altered sympathetic responsivity is not clear.

Early postoperative catecholamine levels remained lower in the epidural anesthesia group. Multivariate analysis indicated that this difference was caused, in part, by superior analgesia. Duration of surgery was also a determinant of 1-h postoperative catecholamine levels. Although this relationship may reflect greater tissue trauma or a receding local anesthetic block, the actual mechanism is unknown.

Norepinephrine levels throughout the postoperative period were highly correlated with plasma norepinephrine concentrations measured during skin closure.

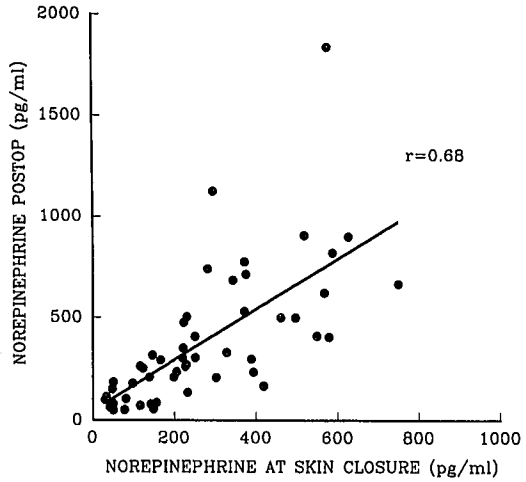

Fig. 3. Relationship between norepinephrine (NE) concentrations during skin closure (shown on the abscissa) and NE values 1 h postoperatively (shown on the ordinate). Each point represents an individual patient. Line fit by method of least squares.

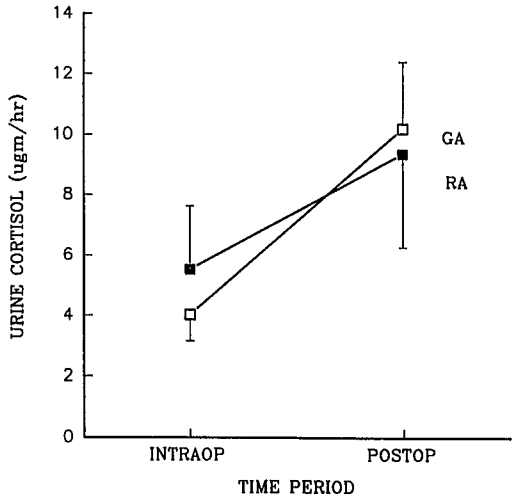

Fig. 4. Cortisol excretion data. Patients receiving general anesthesia (GA) and regional anesthesia (RA) manifest similar values intraoperatively (intraop) and postoperatively (postop). Data are mean ± SEM.

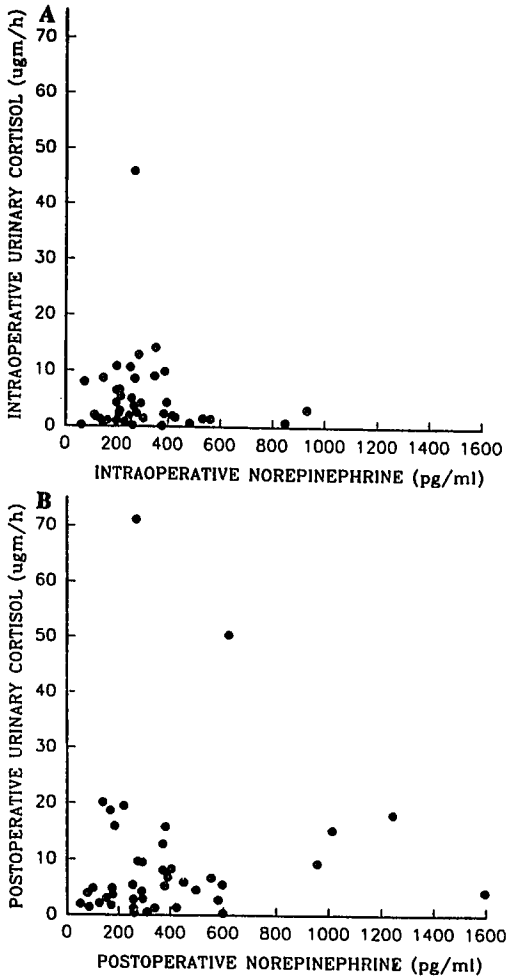

Fig. 5. Relationship between (*A*) intraoperative urinary cortisol excretion and average intraoperative norepinephrine (NE) plasma concentration and (*B*) postoperative cortisol excretion and average postoperative NE plasma concentration. Each point represents an individual patient.

This relationship indicates that there is individual variability in sympathetic reactivity and, with a given stimulus, this variability is an important determinant of the observed catecholamine increase. Alternatively, early activation of the sympathetic nervous system may potentiate subsequent responses in a manner analogous to the "windup" phenomenon postulated for pain.[21]

Pain scores predicted plasma norepinephrine levels in the early postoperative period. Prior studies demonstrating lower catecholamines in patients receiving neuraxial opioids have attributed this effect to superior analgesia. However, central effects on sympathetic nervous system outflow have also been postulated. Although the association between pain scores and catecholamines observed in our study indicates that pain may be a stimulus for postoperative norepinephrine secretion, pain may be only a marker for more severe tissue injury. There was no relationship between pain scores and catecholamines 6, 12, and 18 h postoperatively. However, the use of aggressive analgesic paradigms resulted in very low pain scores at these times.

Other investigators have reported that regional anesthesia combined with neuraxial opioids attenuates the cortisol response to major surgery.[12,14,15] We speculate that similar cortisol excretion in the two groups in our study is related to the small increase that occurs in response to lower extremity revascularization; intraoperative cortisol excretion was in the range noted in normal individuals.[22] Neither univariate nor multivariate analysis found patient or perioperative variables that predicted perioperative cortisol excretion. Although a recently published report indicates that surgically elicited increases in circulating cytokines contribute to perioperative increases in cortisol, this relationship was not thought to apply to patients having peripheral surgical procedures.[19]

Epinephrine and norepinephrine concentrations were correlated during the perioperative period, but cortisol and catecholamines were not. Historically, the stress response has been viewed as a generalized increase in stress hormone secretion. Our data indicate that this is not the case. Whether differential activation of the two systems reflects differences in afferent stimuli or variations in central nervous system integration is not known, and warrants further investigation.

In conclusion, the current study provides data indicating that patient factors, such as age and inherent sympathetic responsivity, are as important in predicting postoperative increases in plasma catecholamines as issues related to anesthetic management. Regional anesthesia/analgesia can modulate the postoperative catecholamine response to surgery, although lower early postoperative catecholamines appears to be caused, in part, by superior analgesia. Cortisol secretion is poorly correlated with catecholamine levels, and is not related to the patient and perioperative variables examined in this study. The poor correlation between increases in catecholamines and cortisol indicates that the stress response does not represent diffuse activation of all systems involved in stress adaptation, but, rather, consists of discrete systems responding to different stimuli.

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