

# Effect of Spinal Anesthesia on Adrenergic Tone and the Neuroendocrine Responses to Surgical Stress in Humans

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In order to quantitate the effect of spinal anesthesia on adrenergic tone, plasma levels of norepinephrine (NE) and epinephrine (EPI) were measured by radioenzymatic assay in 24 patients prior to elective lower body surgical procedures. The subsequent neuroendocrine responses to surgical stress of 16 of these patients were then compared to those of 10 patients receiving inhalation anesthesia (halothane-nitrous oxide). High thoracic dermatome spinal anesthesia caused suppression of both arterial plasma NE and EPI and a fall of mean arterial pressure (MAP); in contrast, no changes of NE, EPI, or MAP were observed in patients receiving low spinal anesthesia. Overall, there was a relationship between the sensory dermatome anesthesia level and changes of both plasma NE ( $r = 0.71$ ,  $P < 0.001$ ) and EPI ( $r = 0.52$ ,  $P < 0.02$ ). In the inhalation anesthesia group, plasma NE increased during the operation and plasma levels of NE, EPI, growth hormone, and cortisol were elevated during the postoperative recovery period. These neuroendocrine responses to surgical stress were not observed in patients receiving either low or high spinal anesthesia. Thus, the effect of spinal anesthesia on adrenergic tone depends on the cord level of anesthesia and can be quantitated by measurement of plasma catecholamines. The neuroendocrine responses to surgical stress were prevented in patients who received low spinal anesthesia and who had no suppression of efferent adrenergic tone. These findings indicate that neural afferents from the site of tissue injury, which were blocked by low spinal anesthesia, mediated both the adrenergic and the hormonal responses to surgical stress in the inhalation anesthesia group. (Key words: Anesthetic techniques: spinal. Hormones: adrenal; growth. Sympathetic nervous system: catecholamines, epinephrine, norepinephrine.)

SPINAL ANESTHESIA is utilized clinically to block afferent neural signals from the site of tissue trauma during surgical procedures. One drawback of spinal anesthesia is that it may also block sympathetic nervous system efferent pathways, resulting in loss of vasomotor tone and the development of hypotension. The

degree of such efferent sympathetic blockade should theoretically be related to the level of spinal anesthesia obtained.<sup>1</sup> However, assessment of the relationship between efferent adrenergic tone and the level of spinal anesthesia in humans has been limited by the lack of a quantitative method for measuring sympathetic nervous system activity. The recent development of sensitive and specific radioenzymatic methods for measurement of plasma catecholamines<sup>2,3</sup> has now made it possible to accurately assess the degree of sympathetic nervous system activity.<sup>4,5</sup> We have used this approach to study the relationship between the sensory dermatome level of spinal anesthesia and the effects of the anesthesia on adrenergic tone in patients about to undergo minor elective surgical operations. In addition, since neural afferent signals appear to be an important mechanism mediating the endocrine responses to surgical stress,<sup>6-10</sup> we sought to determine whether blockade of such signals with spinal anesthesia would also inhibit the increases of plasma norepinephrine (NE) and epinephrine (EPI) which occur during surgical procedures.<sup>11,12</sup>

## Materials and Methods

### STUDY SUBJECTS

Thirty-four adult patients who required anesthesia for elective operations on the lower half of the body were studied. The subjects ranged in age from 21-64 yr, and in body weight from 59-116 kg. All but two of the patients were men. All subjects were unpremedicated and fasted for 12 h prior to study. They were all in good health and had not been taking any medication chronically. Informed consent was obtained from each patient after the nature of the procedures had been fully explained. The protocol was approved by the Human Subjects Review Committee of the University of Washington.

### PROTOCOL

Operations included in this study were orthopedic and urologic procedures, inguinal hernia repairs, and other minor procedures in the perineal area. Since the method of anesthesia for each patient was randomly selected, the distribution of operations was similar in

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the inhalation and spinal anesthesia groups. Ten patients receiving general inhalation anesthesia were induced with thiamylal (3–8 mg/kg) and muscle relaxation was achieved with intravenous *d*-tubocurarine (5 mg) and succinylcholine (100 mg). Following endotracheal intubation, anesthesia was maintained with inhaled halothane (0.5–1.5 per cent) and nitrous oxide–oxygen (50/50). Intravenous pancuronium (0.05 mg/kg) was used to maintain muscle relaxation. Controlled ventilation (tidal volume = 15 ml/kg at a rate to maintain  $P_{aCO_2}$  at 30–40 torr) was accomplished with a volume-controlled anesthesia ventilator. Twenty-four patients receiving subarachnoid (spinal) anesthesia were placed in the left lateral recumbent position, and tetracaine (10–20 mg) without vasopressor was administered using a L3–L4 paramedian approach and a 22-gauge needle. Sensory dermatome levels of spinal anesthesia ranging from T2 to T12 were obtained by horizontal manipulation of the surgery table plus use of a hyperbaric anesthesia solution (tetracaine in 5 per cent glucose). The anesthesia level was defined as the dermatome below which there was a lack of sensory response to pinprick.

Intravenous fluid therapy for all patients consisted of isotonic saline solution at a rate of approximately 10 ml/kg during the first hour, 7.5 ml/kg over the second hour, and 5.0 ml·kg<sup>-1</sup>·h<sup>-1</sup> thereafter. All patients had an uncomplicated operative procedure with minimal blood loss. No drug was used to supplement spinal anesthesia in the operating room, and studies were completed in the anesthesia recovery room prior to administration of postoperative medication.

An indwelling catheter was inserted into a radial or brachial artery of each study subject for monitoring blood pressure and obtaining blood samples. This catheter was kept patent with heparinized saline. An intravenous line was inserted into an antecubital vein in all subjects for administration of medications (inhalation anesthesia group only) and maintenance fluids. After insertion of the arterial and venous catheters, a 30-min rest period was allowed prior to obtaining two baseline arterial blood samples 5 min apart for measurement of catecholamines, blood gases, and *pH*. Eight subjects were studied to assess the time course of the effects of spinal anesthesia on plasma catecholamines and were sampled before and then 15, 30, and 60 min after anesthesia (T2 to T8 sensory level), but prior to surgical stimulation. In all of the other study subjects, after obtaining baseline samples, subsequent samples were obtained 30 min after induction of anesthesia but prior to surgical

stimulation, 30 min after the surgical incision, and in the postoperative recovery room at least 60 min after discontinuing inhalation anesthesia or when pinprick sensation and leg motor function had returned to the spinal anesthesia patients. The mean interval between the time of the operation blood sample and that of the recovery sample was longer in the spinal group, but the difference was not statistically significant (194 ± 19 min *vs.* 152 ± 10, mean ± SEM, *P* = NS). Samples were obtained for measurement of growth hormone and cortisol at the above times in all of the inhalation anesthesia group and in the first ten spinal patients studied.

Core body temperature was monitored with tympanic membrane and esophageal (general anesthesia only) thermistors.‡ These temperature devices were calibrated in a waterbath against a mercury thermometer.§ Arterial pressure and cardiac rate were obtained from a cardioscope with digital readout utilizing an arterial line pressure transducer and standard lead electrocardiogram. Mean arterial pressure (MAP) was calculated as the diastolic pressure plus 1/3 (systolic–diastolic). Arterial blood-gas and *pH* analyses were performed with a Radiometer BMS-3, MKII blood-gas analyzer, with appropriate corrections for body temperature. Values obtained from measurement of tympanic temperature, blood pressure, pulse, *pH*, and blood gases demonstrated that neither hypotension (systolic blood pressure < 90 torr), tachycardia or bradycardia (pulse < 55 or > 110 beats/min), plasma acidosis (*pH* < 7.3), arterial hypoxemia ( $P_{aO_2}$  < 60 torr), or core body cooling (typanic temperature < 36°C) was present in any inhalation anesthesia patient when arterial blood was sampled for neurohormones.

#### ANALYTICAL METHODS

For measurement of plasma NE and EPI, blood was collected in prechilled glass tubes containing EGTA and glutathione (final concentration, 5 mM) and immediately placed on ice. Within 45 min, the plasma was separated at 4°C and then frozen at –20°C for subsequent analysis. The double isotope derivative enzymatic assay of Engelman *et al.*<sup>2</sup> as modified by Christensen<sup>13</sup> required 30-ml blood samples and was used for all of the inhalation anesthesia studies and the first 11 spinal anesthesia studies. In the remaining 13 spinal anesthesia studies, 2.5-ml blood samples were obtained for measurement with the

‡ Surg-A-Temp, Arlbrook, Inc., Arlington, Texas.

§ Van Waters and Rogers, Seattle, Washington 98134.

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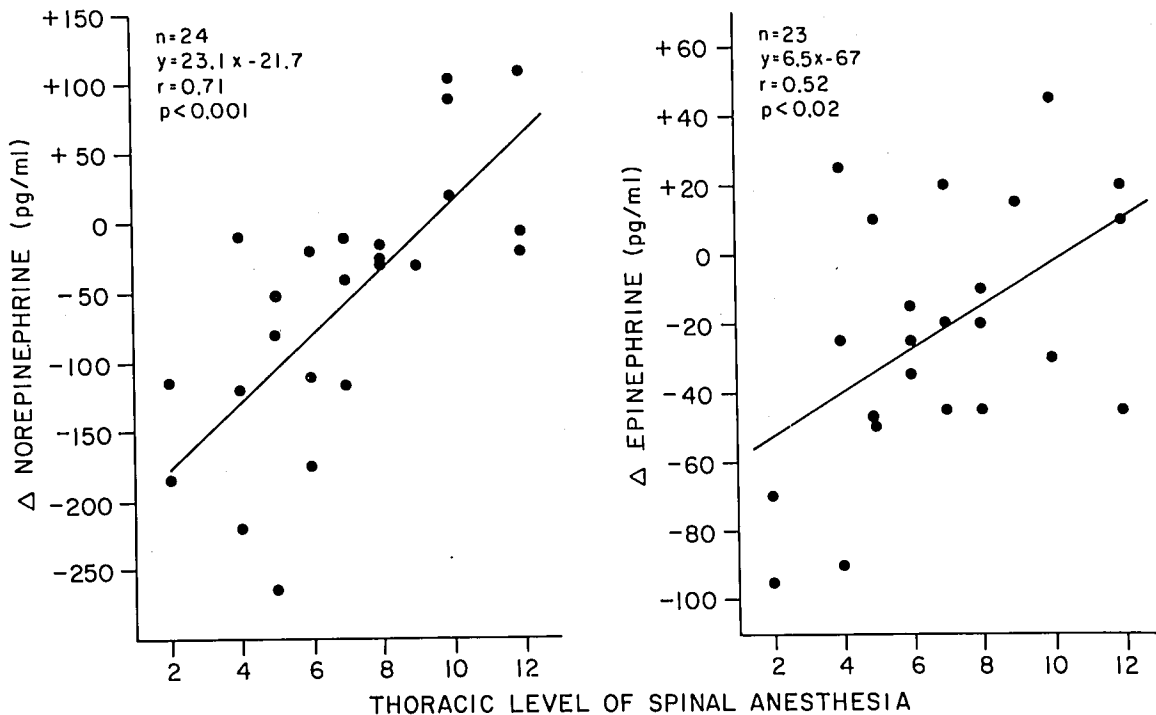


FIG. 1. Regression analysis of the relationship between changes of plasma norepinephrine and epinephrine from preanesthesia baseline levels and the thoracic dermatome level of spinal anesthesia 30 min after subarachnoid injection of tetracaine. The data point in parentheses (high epinephrine level) was not included in the calculation of the regression line. The correlation between anesthesia level and  $\Delta$  epinephrine is significant even when this data point is included (Spearman's rho = 0.56,  $P < 0.01$ ).

single isotope enzymatic assay described by Peuler and Johnson.<sup>3</sup> These two assay methods give virtually identical results for measurement of NE and EPI, and have similar interassay coefficients of variation.<sup>14</sup> Results of analysis of samples from the present study with both methods were closely correlated both for NE ( $r = 0.88$ ,  $n = 22$ ,  $P < 0.001$ ) and EPI ( $r = 0.90$ ,  $n = 17$ ,  $P < 0.001$ ). For measurement of plasma cortisol and growth hormone, 5 ml of blood was collected in EDTA, then separated at 4°C, and frozen at -20°C for subsequent analysis. Plasma cortisol assays were completed with the use of gamma coat ( $I^{125}$ ) cortisol radioimmunoassay kit.¶ Plasma growth hormone values were also obtained by use of a radioimmunoassay method.<sup>15</sup> Statistical methods included paired and nonpaired Student's *t* tests, Spearman's rank correlation, and linear regression analysis.<sup>16</sup> Due to variability of individual responses, the nonparametric Wilcoxon signed rank test<sup>16</sup> was used for analysis of the study of the time course of spinal anesthesia.

## Results

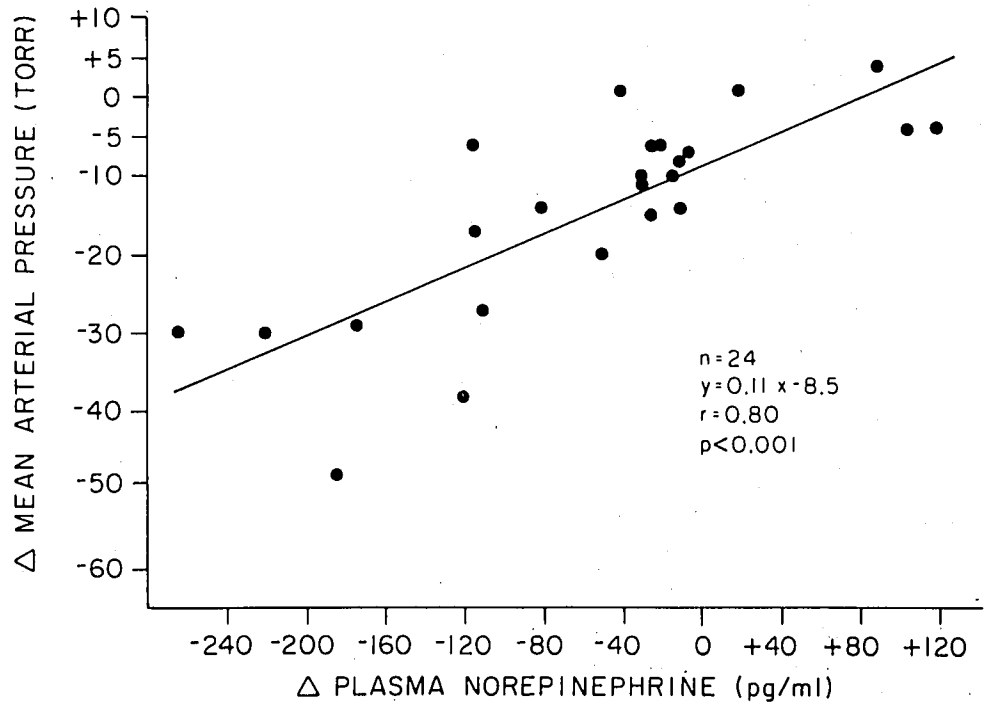
### EFFECTS OF SPINAL ANESTHESIA ON ADRENERGIC TONE

As illustrated in figure 1, there was a significant relationship between the thoracic dermatome sensory level in 24 patients receiving spinal anesthesia and the changes from control values 30 min after induction of anesthesia of both plasma NE ( $r = 0.71$ ,  $P < 0.001$ ) and EPI ( $r = 0.52$ ,  $P < 0.02$ ). Patients receiving high levels of anesthesia showed a marked suppression of plasma NE and EPI, whereas those receiving low block had little or no change of catecholamine levels when compared with control. The degree of suppression of plasma NE and the fall of MAP accompanying spinal anesthesia were closely correlated ( $r = 0.80$ ,  $P < 0.001$ , see fig. 2).

In eight patients (sensory dermatome level T2-T8), plasma NE was suppressed below baseline levels by 15 min after spinal anesthesia induction ( $214 \pm 40$  pg/ml vs.  $161 \pm 54$ ,  $P < 0.05$ ) and remained suppressed at 30 min ( $149 \pm 37$ ,  $P < 0.02$ ) and at 60 min ( $177 \pm 30$ ,  $P < 0.10$ ). Concomitantly, MAP fell

¶ Clinical Assays, Division of Travenol Laboratories, Cambridge, Massachusetts 02139.

FIG. 2. Regression analysis of the relationship between changes of plasma norepinephrine from preanesthesia baseline levels and changes of mean arterial blood pressure at 30 min after injection of tetracaine for spinal anesthesia.



from  $87 \pm 4$  torr to  $75 \pm 5$ ,  $71 \pm 3$ , and  $77 \pm 3$  torr at 15, 30, and 60 min, respectively (all  $P < 0.05$ ). Plasma EPI levels did not change significantly in this group of patients.

EFFECTS OF SPINAL ANESTHESIA ON THE NEUROENDOCRINE RESPONSES TO SURGICAL STRESS

A comparison of changes of plasma catecholamines during surgical stress in patients receiving inhalation anesthesia with those receiving spinal anesthesia is shown in table 1. Inhalation anesthesia alone caused a significant suppression of plasma EPI, a finding we

have also observed previously.<sup>11</sup> In the inhalation anesthesia group, significant increases of plasma NE were observed during the operation and of both NE and EPI during the postoperative recovery period. These increases did not occur in the patients receiving spinal anesthesia. Similarly, spinal anesthesia prevented the increases of both plasma growth hormone and cortisol observed during the recovery period in the inhalation anesthesia group (see table 2).

However, although blockade of neural afferents from the site of operation was achieved in all of the spinal anesthesia patients as indicated by pinprick testing, a variable block of sympathetic efferent path-

TABLE 1. Effects of Inhalation and Spinal Anesthesia on Plasma Norepinephrine (NE) and Epinephrine (E) during Surgical Stress

	Baseline (pg/ml)		Change from Baseline (pg/ml)					
			Norepinephrine			Epinephrine		
	Norepinephrine	Epinephrine	Anesthesia	Operation	Recovery	Anesthesia	Operation	Recovery
Inhalation Anesthesia (n = 10)								
Mean	240	86	+53	+153	+80	-51	+9	+118
SEM	35	10	36	40	35	8	34	31
P (vs. baseline)			NS	<0.005	<0.05	<0.001	NS	<0.005
Spinal Anesthesia (n = 16)								
Mean	211	80	-49	-9	+23	+6	+28	+18
SEM	21	12	26	21	18	34	19	14
P (vs. baseline)			NS	NS	NS	NS	NS	NS
P (inhalation vs. spinal)	NS	NS	<0.05	<0.001	<0.02	NS	NS	<0.005

TABLE 2. Effects of Inhalation and Spinal Anesthesia on Plasma Growth Hormone and Cortisol during Surgical Stress

	Baseline	Anesthesia	Operation	Recovery
Growth Hormone (ng/ml)				
Inhalation Anesthesia (n = 10)	4.0 ± 1.8	6.0 ± 1.9	3.4 ± 0.8	9.0 ± 1.9*
Spinal Anesthesia (n = 10)	4.0 ± 2.0	6.0 ± 2.7	3.7 ± 1.0	2.3 ± 1.3
<i>P</i> (inhalation vs. spinal)	NS	NS	NS	<0.01
Cortisol (ng/ml)				
Inhalation Anesthesia (n = 10)	162 ± 13	194 ± 25	177 ± 27	248 ± 30†
Spinal Anesthesia (n = 10)	179 ± 19	194 ± 19	186 ± 26	150 ± 30
<i>P</i> (inhalation vs. spinal)	NS	NS	NS	<0.05

All values are means ± SEM.

\* *P* < 0.02; significantly different from the baseline level.

† *P* < 0.01; significantly different from the baseline level.

ways was also present, as indicated by plasma NE and EPI levels (see fig. 1). In order to determine whether afferent blockade alone prevented the plasma catecholamine response to surgical stress, the NE and EPI levels of the inhalation anesthesia group were compared to those of two subgroups of the patients receiving spinal anesthesia: six patients with high spinals (T2–T6), and six patients who had low spinals (T9–T12). The data from four patients receiving intermediate levels of anesthesia (T7–T8) were not included in this analysis.

As shown in figure 3, high spinal anesthesia resulted in a marked blockade of sympathetic efferents as indicated by falls of plasma NE from baseline levels of  $215 \pm 4$  to  $67 \pm 22$  pg/ml (*P* < 0.005), and of EPI from  $62 \pm 14$  to  $15 \pm 7$  pg/ml (*P* < 0.01). However, in this group plasma NE had returned to  $215 \pm 4$  pg/ml by the recovery period and plasma EPI to  $62 \pm 14$  (both *P* = NS vs. baseline). Plasma levels of both NE and EPI were unchanged by low spinal anesthesia (NE:  $210 \pm 34$  vs.  $218 \pm 45$  pg/ml; EPI:  $82 \pm 23$  vs.  $84 \pm 15$  pg/ml, baseline vs. anesthesia, both *P* = NS), and remained unchanged from baseline during the operation and recovery periods. Plasma NE levels of both the high and low spinal anesthesia groups were significantly lower than levels of the inhalation anesthesia group during the operation (see fig. 3). The mean plasma EPI levels during the recovery period of both spinal groups were lower than those of the inhalation group, although this difference reached statistical significance only in the high spinal group.

### Discussion

The results of this study provide further evidence that afferent nerves from the site of tissue injury provide the major stimulus for the neuroendocrine response to surgical stress in humans. When such afferent nerves were blocked with spinal anesthesia, the operative increases of plasma NE levels and the postoperative increases of plasma NE and EPI which

accompanied surgical stress in patients receiving inhalation anesthesia were not observed (see table 1). Similarly, the postoperative increases of growth hormone and cortisol observed in the inhalation anesthesia group were prevented by spinal anesthesia (see table 2). This prevention of the adrenergic and endocrine responses to surgical stress can be ascribed only to the spinal anesthesia, since these

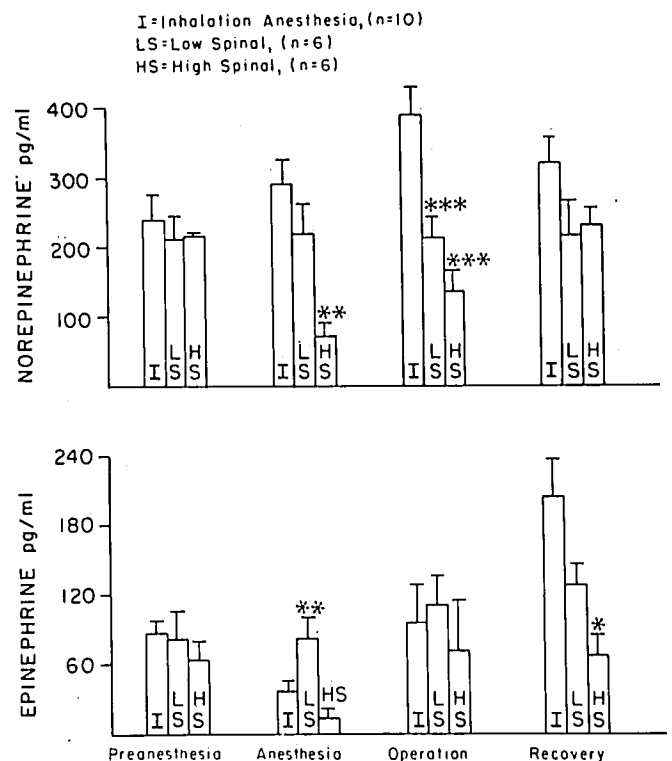


FIG. 3. Comparison of plasma epinephrine and norepinephrine levels (mean ± SEM) before and during surgical stress in patients receiving inhalation anesthesia (halothane–nitrous oxide), low spinal anesthesia (dermatome level T9–T12), or high spinal anesthesia (dermatome level T2–T6). \**P* < 0.02, \*\**P* < 0.01, \*\*\**P* < 0.001 are levels of significance of difference between indicated value and corresponding value for the inhalation anesthesia group.

patients received no other medication during the study. Previous studies in humans and in dogs have also found that the hormonal response to surgical stress can be blocked by interruption of neural afferents from the site of tissue trauma.<sup>6-10</sup> The present study extends this concept to include the regulation of the plasma catecholamine response to surgical stress.

Spinal anesthesia alone had an effect on adrenergic tone that depended on the sensory dermatome level of block. The relationship between the level of spinal anesthesia and the suppression of plasma NE (see fig. 1) is in agreement with the neuroanatomy of the spinal cord sympathetic nervous system efferent pathway.<sup>1</sup> Thus, patients who had blockade of most of the thoracolumbar sympathetic nervous system by high spinal anesthesia demonstrated a marked suppression of plasma NE from baseline levels and a concomitant fall of mean arterial blood pressure. In contrast, there was little change of either plasma NE or blood pressure in patients who had a low spinal block. The close correlation between changes of blood pressure and of plasma NE levels during spinal anesthesia in the present study (fig. 2) is similar to the relationship between blood pressure and plasma NE in other studies in humans in which adrenergic tone has been altered.<sup>11,17</sup> The degree of suppression of plasma EPI by spinal anesthesia also agrees with the known innervation of the adrenal medulla by spinal nerves from cord levels T6-L2.<sup>18</sup> Plasma EPI levels were markedly suppressed in patients who had an anesthesia level of T6 or above, but unchanged in those with a level of T9 or below (see fig. 3).

Thus, inhibition of plasma catecholamine responses to surgical stress could have been due to blockade of sympathetic efferents in some patients who had high spinal anesthesia. However, the operative increase of plasma NE was prevented in low spinal anesthesia patients, who had no evidence of efferent sympathetic blockade (see fig. 3). Furthermore, plasma catecholamines had returned to preanesthesia baseline levels during the recovery period in patients receiving high spinals, suggesting at least a partial wearing off of the efferent sympathetic block. Therefore, the prevention of postoperative increases of plasma NE and EPI in the high spinal group may also have been due to a residual block of neural afferents (although pinprick sensation at the site of operation had returned at the time of postoperative sampling, the patients were not yet complaining of pain).

Although plasma NE increased during the operation in the inhalation anesthesia group, no consistent operative changes of plasma EPI were ob-

served. A similar dissociation of catecholamine responses was also observed previously in patients undergoing abdominal operations.<sup>11</sup> The direct inhibitory effect of halothane-nitrous oxide anesthesia on plasma levels of EPI, but not of NE, observed in this and the previous study provides an explanation for the lack of operative increases of plasma EPI. However, during the postoperative recovery period, when the anesthetic agents had worn off, plasma EPI levels rose consistently (see fig. 3). Similarly, elevations of plasma growth hormone and cortisol were observed during the recovery period in these patients, but not during the operation (see table 2). Others have also found that growth hormone and cortisol levels remain unchanged during minor operations such as inguinal hernia repairs.<sup>19-21</sup>

The findings of this study indicate that the plasma catecholamine response to minor surgical stress in humans can be prevented by spinal anesthesia. Low spinal anesthesia does not result in hypotension or suppression of plasma catecholamine levels. Therefore, prevention of the adrenergic response to surgical stress by low spinal anesthesia may be a clinically useful means of preventing cardiovascular complications associated with increased adrenergic activity in high-risk surgery patients with cardiovascular disease during an operation involving the lower half of the body and in the early postoperative recovery period.

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## References

1. Pick J: The Autonomic Nervous System. Philadelphia, JB Lippincott Company, 1979, pp 25-28
2. Engelman K, Portnoy B, Lovenberg W: A sensitive and specific double isotope derivative method for the determination of catecholamines in biological specimens. *Am J Med Sci* 255: 259-268, 1968
3. Peuler JD, Johnson GA: Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci* 21:625-636, 1977
4. Cryer PE: Isotope-derivative measurements of plasma norepinephrine and epinephrine in man. *Diabetes* 25:1071-1085, 1976
5. Lake CR, Ziegler MC, Kopin IJ: Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. *Life Sci* 18:1315-1326, 1976
6. Egdahl RH: Pituitary-adrenal response following trauma to the isolated leg. *Surgery* 46:9-21, 1959
7. Hume DM, Egdahl RH: The importance of the brain in the endocrine response to injury. *Ann Surg* 150:697-712, 1959
8. Gordon NH, Scott DB, Robb IWP: Modification of plasma corticosteroid concentrations during and after surgery by epidural blockade. *Br Med J* 1:581-583, 1973

9. Cosgrove DO, Jenkins JS: The effects of epidural anesthesia on the pituitary-adrenal response to surgery. *Clin Sci Mol Med* 46:403-407, 1974
10. Engquist A, Brandt MR, Alvito F, et al: The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic responses to surgery. *Acta Anaesthesiol Scand* 21:330-335, 1977
11. Halter JB, Pflug AE, Porte Jr D: Mechanism of plasma catecholamine increases during surgical stress in man. *J Clin Endocrinol Metab* 45:936-944, 1977
12. Madsen SN, Fog-Møller F, Christiansen C, et al: Cyclic AMP, adrenaline and noradrenaline in plasma during surgery. *Br J Surg* 65:191-193, 1978
13. Christensen NJ: Plasma noradrenaline and adrenaline in patients with thyrotoxicosis and myxoedema. *Clin Sci Mol Med* 45:163-171, 1973
14. Evans MI, Halter JB, Porte Jr D: Comparison of double- and single-isotope enzymatic derivative methods for measuring catecholamines in human plasma. *Clin Chem* 24:567-570, 1978
15. Schalch DS, Parker ML: A sensitive antibody immunoassay for human growth hormone in plasma. *Nature* 203:1141-1442, 1964
16. Sokol RR, Rohlf FJ: *Biometry*. San Francisco, WH Freeman and Company, 1969, pp 127, 367, 404, 494
17. Metz SA, Halter JB, Porte Jr D, et al: Suppression of plasma catecholamines and flushing by clonidine in man. *J Clin Endocrinol Metab* 46:83-90, 1978
18. Bonica JJ: Autonomic innervation of the viscera in relation to nerve block. *ANESTHESIOLOGY* 29:793-813, 1968
19. Newsome HH, Rose JC: The response of human adrenocorticotrophic hormone and growth hormone to surgical stress. *J Clin Endocrinol Metab* 33:481-487, 1971
20. Noel GL, Suh HK, Stone JG, et al: Human prolactin and growth hormone release during surgery and other conditions of stress. *J Clin Endocrinol Metab* 35:840-851, 1972
21. Wright PD, Johnston IDA: The effect of surgical operation on growth hormone levels in plasma. *Surgery* 77:479-486, 1975