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Test Doses: Optimal Epinephrine Content with and without Acute Beta-adrenergic Blockade

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The authors studied the optimal epinephrine content of an epidural test dose, and determined criteria to identify intravascular injections in subjects with or without β-adrenergic blockade. Nine healthy nonpregnant subjects 25–36 years of age were given intravenous infusions of saline or esmolol in random order. During each infusion, they received a series of five injections (3 ml each) of either saline, 1% lidocaine or 1% lidocaine containing 5, 10, or 15 μg of epinephrine. Thirty minutes after completing these two infusions, propranolol was administered as a bolus injection, and the series of five injections repeated. All injections were double blind and randomized. During saline infusion, all injections containing epinephrine significantly increased heart rate (HR) by an average of 31–38 beats/min when compared with that following plain lidocaine ($P < 0.05$), and increased systolic blood pressure by an average of 17–26 mmHg ($P < 0.05$ for the 15-μg dose only). During esmolol infusion, epinephrine injections increased HR by an average of 23–31 beats/min ($P < 0.05$), and increased systolic blood pressure by an average of 18–30 mmHg ($P < 0.05$ for 10 and 15 μg). After propranolol injection, epinephrine injections caused a decrease in HR by an average of 21–28 beats/min ($P < 0.05$), whereas systolic blood pressure increased by an average of 22–35 mmHg ($P < 0.05$ for 10 and 15 μg only). Without β-adrenergic blockade, an increase in HR ≥ 20 beats/min was 100% sensitive and specific for intravascular injection of 10 or 15 μg of epinephrine. After selective and nonselective β-adrenergic blockade, HR changes were not reliable, but an increase in systolic blood pressure (SBP) of ≥15 mmHg was diagnostic of injection of 10 or 15 μg of epinephrine. Hemodynamic changes occurred within 2 min after intravascular (iv) injections, and lasted at least 35 s. Injection of 5 μg of epinephrine did not produce reliable hemodynamic changes in any group. The authors conclude that in young, nonpregnant, individuals: 1) a test dose containing at least 10 μg epinephrine is a reliable marker of intravascular injection; 2) intravascular injection can be reliably detected by an absolute variation in HR of ≥20 beats/min in non–β-blocked subjects, and by an increase in SBP of ≥15 mmHg in the presence of β-adrenergic blockade. (Key words: Anesthesia, regional: epidural. Anesthetic techniques: epidural; test dose. Sympathetic nervous system, β-adrenergic blockade: propranolol; esmolol. Sympathetic nervous system, catecholamines: epinephrine.)

SINCE THE REPORT of Moore and Batra in 1981,[1] the use of a test dose containing 15 μg of epinephrine to detect intravascular (iv) placement of a needle or catheter has become standard practice before epidural anesthesia. These authors described an increase in mean heart rate (HR) from 79 ± 14 to 111 ± 15 beats/min when 15 μg epinephrine, mixed with local anesthetics, was injected in healthy premedicated patients. Despite widespread acceptance, neither the sensitivity and specificity nor the optimal epinephrine content (lowest effective dose) of this test dose has been determined. Another concern is the inability of epinephrine to increase the HR in some patients receiving β-adrenergic blocking drugs.[1] This observation has subsequently been documented by two case reports,[2]‡ and a preliminary study conducted at our institution.[3] Criteria for identification of intravascular epinephrine injections have not been determined in patients receiving β-adrenergic blocking drugs.

To address these questions, we designed a study to: 1) determine the "optimal" epinephrine content of an epidural test-dose in healthy young volunteers, 2) determine the "optimal" epinephrine content in the presence of β-adrenergic blockade, and 3) develop simple criteria for detection of intravascular injection of test doses that contain epinephrine.

Materials and Methods

This study was approved by the Institutional Review Board of the Virginia Mason Medical Center. Informed written consent was obtained from each subject. Nine nonpregnant, unmedicated volunteers were studied, all free of cardiovascular or pulmonary disease, and taking no medications. The subjects were encouraged to empty their bladders before the study session, and rested supine.

Each volunteer had two 20-G Teflon® catheters inserted after local anesthetic infiltration (maximal total dose equal to 10 mg of plain lidocaine) in different veins of the dorsum of one hand. One catheter was used for bolus injections of the test doses via a minimal dead space port into the iv tubing. The other catheter was used for infusion of saline, esmolol, and propranolol. Three series of five injections of test doses were made in each subject after infusion of either saline, esmolol, or propranolol.

Esmolol and saline loading and infusions were double blind and alternated in random order. Esmolol was administered as a loading dose consisting of 1,500 μg/kg infused over 1 min followed by an infusion at a rate of

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150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the end of data collection for the series of five test injections.[4] Identical volumes of saline were used for the loading dose and infusion during the saline infusion series of five injections. Lastly, 0.066 mg/kg of propranolol was infused over 5 min and followed by the final series of five injections. No maintenance infusion was used for propranolol. We waited at least 30 min after discontinuing the previous infusion before starting the next loading dose.

Each subject received five test injections during the saline infusion, five during the esmolol infusion, and five after the propranolol injection. The series of test injections consisted of 3 ml of: saline, 1% lidocaine, or 1% lidocaine with 5, 10, or 15 μg of epinephrine. These injections were double blind and randomized in each series, for each subject. The first injection started 10 min after completion of the loading dose, and subsequent injections were separated by 10 min in each series.

The hemodynamic changes resulting from intravascular injection of each test solution were monitored with a standard 3-lead ECG, and a Finapres™ monitor (Model 2300, Ohmeda, BOC. Inverness, UK) connected to a two-channel graphic recorder (Model 8373-20, Cole Palmer Instruments company, Chicago, IL). The Finapres was located on a finger of the same hand as the intravenous infusions. Baseline blood pressure recordings were confirmed at the start of each injection and 4 min after each injection by auscultation with a standard manual blood pressure cuff by an observer blinded to the Finapres readings. The cuff was placed on the opposite arm and did not interfere with the infusions or the Finapres. Systolic blood pressure (SBP) and heart rate (HR) were recorded before drug loading, before the first injection, and continuously for 5 min after each test injection. Data were analyzed at 10-s intervals.

We defined the following "parameters" with regard to the hemodynamic changes during the first 2 min after an injection. "Extreme HR" = the highest or lowest HR observed after injection of the test solution; "Maximal change in HR" = the absolute value obtained by subtracting the preinjection (baseline) HR from the "Extreme HR"; "Onset of Maximal change in HR" = the elapsed time between injection and time of "Maximal change in HR"; "Duration of HR Variation ≥20 beats/min" = the duration of time when the HR is more than 20 beats/min different from the baseline HR. Similar terms, "Extreme SBP," "Maximal change in SBP," "Onset of Maximal SBP," and "Duration of SBP Variation ≥15 mmHg" were defined for SBP.

TABLE 1. Hemodynamic Characteristics Before and 10 Min After Infusion of Saline or Esmolol, or Injection of Propranolol

	Loading or Infusion		
	Saline	Esmolol	Propranolol
SBP before (mmHg)	104 ± 9	114 ± 13	110 ± 9
SBP after (mmHg)	106 ± 9	108 ± 12†	104 ± 8*
HR before (bpm)	71 ± 13	67 ± 12	70 ± 7
HR after (bpm)	71 ± 13	61 ± 9‡	61 ± 9†

Data are means ± SD.
* Significant difference before/after loading at $P < 0.05$
† Significant difference before/after loading at $P < 0.01$.
‡ Significant difference before/after loading at $P < 0.001$.

TABLE 2. Systolic Blood Pressure (mmHg) with a Blood Pressure Cuff and a Finapres®

	Loading or Infusion		
	Saline	Esmolol	Propranolol
At start of injection			
BP cuff	111 ± 8	110 ± 7	109 ± 7
Finapres®	112 ± 10	110 ± 10	107 ± 10
4 min after injection			
BP cuff	111 ± 8	109 ± 7	107 ± 7
Finapres®	112 ± 10	110 ± 9	108 ± 9

Data are means ± SD. Pooled data for all doses.
Measurements made at the start and 4 min after injections of epinephrine.

Baseline hemodynamic values, and hemodynamic changes defined by the preceding "parameters" were compared by analysis of variance (ANOVA). When significant, differences between groups were identified with the Scheffe F-test. Heart rate and SBP before and after saline and before and after the loading dose of β-adrenergic blocking drugs were compared by paired t test. Null hypothesis was rejected in all tests with $P < 0.05$. Baseline and 4-min data are reported as mean ± standard deviation (SD). Others results are expressed as mean values with 95% confidence intervals (CI).

Results

Nine subjects completed the first two series of injections during saline and esmolol infusions. There were five men and four women, averaging 31.3 years of age (±3.3), 72 (±14.1) kg in weight, and 171 (±7.6) cm in height. Eight received the series of five test injections following propranolol.

Baseline SBP and HR were not different before the three series of infusions (table 1). Saline infusion did not alter the SBP and HR, but acute β blockade with esmolol and propanolol decreased both these parameters ($P = 0.003$ and $P = 0.0008$, respectively, with esmolol; and $P = 0.01$ and $P = 0.006$, respectively, with propanolol). Following injection of each test solution, all hemodynamic values were approaching baseline within 2 min, and no differences from baseline values were observed at 4 min after injection (table 2). Thus, we report the analysis of

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HR and SBP changes that occurred during the first 2 min after each injection.

There were no differences in responses to injection of saline or plain lidocaine, and neither produced significant changes in HR or SBP. Subsequent comparisons are made only between plain lidocaine and lidocaine plus 5, 10, and 15 μg epinephrine.

Saline Loading Dose and Infusion

Addition of epinephrine to lidocaine caused a significant increase in HR ($P < 0.05$), as reflected by the values for "Extreme HR" and "Maximal change in HR." The same trend was observed for SBP, but the only difference reaching statistical significance was observed in "Maximal change in SBP" after injection of 15 μg epinephrine.

Maximal changes in SBP occurred significantly later than maximal HR changes ($P < 0.001$). For example after 10 and 15 μg of epinephrine, the maximal increase in SBP occurred 26 and 41 seconds, respectively, after the maximal increase in HR. HR changes were prolonged after 10 and 15 μg epinephrine, as reflected by the significant increase in "Duration of HR Variation ≥ 20 beats/min." Systolic blood pressure changes lasted progressively longer with increasing doses of epinephrine, but only 15 μg produced a statistically significant increase in "Duration of SBP Variation ≥ 15 mmHg." There was no difference between the duration of HR and SBP changes (table 3)

Esmolol Loading Dose and Infusion

After an initial transient slowing, the maximal change in HR was always an increase after all epinephrine injections. Heart rate increased significantly after all epinephrine injections when compared with that following plain lidocaine. An initial increase in SBP was followed by a decrease and then a larger increase in SBP after all doses of epinephrine. Larger epinephrine doses produced progressively larger "Maximal Change in SBP," which attained statistical significance for the 10- and 15-μg doses.

Although the time of "Onset of Maximal Change in SBP" did not differ between injections, maximal changes in SBP occurred 15–30 s later than maximal HR changes ($P < 0.05$). Ten- and 15-μg doses of epinephrine induced significantly longer "Duration of HR and SBP Variations" than plain lidocaine. Although there was a trend for changes in SBP to be more prolonged than changes in HR, this difference did not reach statistical significance (table 3).

Propranolol Load

Significant decreases in HR occurred after all epinephrine injections. After 10 μg epinephrine, a mean 26 beats/min (95% CI, 22–30) decrease in HR was observed, with "Extreme HR" equal to 34 beats/min (95% CI, 30–39). In two subjects HR decreased to 28 beats/min for more than 10 s after the 15 μg dose of epinephrine. Neither subject showed signs or symptoms of hypoperfusion.

"Maximal change in SBP" were significantly increased after the 10- and 15-μg doses of epinephrine only. Time of "Onset of Maximal SBP and HR Variations" were similar, and did not differ between injections. Fifteen micrograms of epinephrine significantly prolonged the "Duration of HR Variation ≥ 20 beats/min." Systolic blood pressure changes did not last significantly longer than HR changes. (table 3).

Criteria for Positive Test Doses

Criteria for definition of a positive test dose were derived using the 95% confidence intervals for the absolute changes in HR and SBP observed in the subject groups. An increase in HR ≥ 20 beats/min was 100% sensitive and specific in the saline group after a 10- or 15-μg epinephrine injection (table 4). After selective or nonselective β-adrenergic blockade, an increase in SBP ≥ 15 mmHg was 100% sensitive for injection of the same epinephrine doses. A false-positive increase in SBP ≥ 15 mmHg was observed in 1 of 9 and 1 of 8 subjects in the esmolol and propranolol groups, respectively, after plain lidocaine injections (table 5).

Discussion

Intravenous injection of clinical doses of potent local anesthetics can cause seizures, cardiovascular collapse, and even death.[5] To prevent intravascular injections of toxic quantities of local anesthetics during performance of an epidural block, several techniques have been proposed, such as: 1) aspiration through the epidural catheter[6]; 2) rapid injection of 5 ml of plain 0.5% bupivacaine[7] or 100 mg of 2-chloroprocaine[8]; 3) injection of a dye that can be detected by a pulse oximeter§; 4) incremental injections of local anesthetics[9]; or 5) addition of 15 μg epinephrine to the local anesthetic test dose.[1] To date, only the last recommendation has been examined prospectively in a large series of patients. In that study, a significant increase in HR was observed within 3 min following intravenous injection of epinephrine. On the basis of that study, the use of epinephrine to provide a marker of intravascular injections has become common clinical practice.

Our results confirm the findings of Moore and Batra.[1] In the absence of β-adrenergic blockade, intravenous in-

§ Sidi A, Rush WR, Paulus DA, Gravenstein N, Davis RF: Effect of fluorescein, indocyanine green, and methylene blue on the measurement of oxygen saturation by pulse oximetry (abstract). ANESTHESIOLOGY 65:A132, 1986

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TABLE 3. Hemodynamic Variations (means and 95% CI) Produced by Incremental Doses of Epinephrine During Test Infusions

	Extreme HR (bpm)	Extreme SBP (mmHg)	Maximal Change in HR (bpm)	Maximal Change in SBP (mmHg)	Onset of Maximal Change in HR (s)	Onset of Maximal Change in SBP (s)	Duration of HR Variation ≥ 20 bpm (s)	Duration of SBP Variation ≥ 15 (mmHg) (s)
Saline infusion (n = 9)								
Saline	64 (34–94)	109 (103–115)	8 (5–11)	9 (5–14)	64 (34–94)	61 (32–89)	0	0
Lidocaine 1% plain	72 (60–85)	118 (107–128)	7 (6–8)	10 (6–14)	72 (47–96)	86 (60–112)	0	6 (−6–19)
Lidocaine 1% + epinephrine 5 μg	103 (83–122)*	109 (97–121)	31 (20–42)*	17 (9–25)	56 (44–68)	60 (45–74)	21 (9–32)	12 (−3–27)
Lidocaine 1% + epinephrine 10 μg	109 (94–124)*	126 (108–143)	38 (28–49)*	22 (13–30)	56 (41–72)	82 (57–106)	35 (17–53)*	36 (10–62)
Lidocaine 1% + epinephrine 15 μg	108 (97–120)*	140 (128–151)	37 (29–46)*	26 (18–33)*	57 (47–68)	98 (76–121)	35 (24–46)*	44 (28–60)*
Esmolol infusion (n = 9)								
Saline	66 (58–74)	111 (103–118)	6 (4–8)	7 (5–9)	54 (33–75)	62 (27–96)	0	0
Lidocaine 1% plain	68 (57–79)	112 (101–123)	8 (4–12)	9 (7–11)	71 (44–97)	65 (40–91)	0	1 (−1–3)
Lidocaine 1% + epinephrine 5 μg	74 (61–87)	119 (104–135)	23 (15–31)*	18 (13–23)	72 (49–95)	86 (62–110)	16 (3–29)	22 (6–37)
Lidocaine 1% + epinephrine 10 μg	86 (69–103)	127 (107–146)	30 (22–39)*	25 (20–31)*	70 (58–81)	98 (87–110)	27 (9–45) *	47 (26–68)*
Lidocaine 1% + epinephrine 15 μg	82 (60–103)	144 (130–158)*	31 (23–38)*	30 (22–37)*	70 (52–87)	100 (87–112)	27 (9–45)*	55 (35–75)*
Propanolol (n = 8)								
Saline	59 (50–68)	110 (97–123)	8 (4–11)	10 (6–13)	76 (44–107)	63 (38–89)	0	2 (−1–6)
Lidocaine 1% plain	67 (61–73)	109 (95–122)	7 (5–10)	9 (6–12)	61 (36–86)	66 (34–97)	0	1 (−1–4)
Lidocaine 1% + epinephrine 5 μg	40 (36–44)*	129 (123–135)	−21 (−16–26)*	22 (14–29)	55 (47–62)	62 (50–74)	23 (3–44)	35 (14–55)*
Lidocaine 1% + epinephrine 10 μg	34 (30–39)*	137 (125–149)*	−26 (−22–30)*	30 (24–37)*	61 (43–78)	63 (50–77)	33 (17–50)	70 (56–83)*
Lidocaine 1% + epinephrine 15 μg	32 (28–36)*	141 (128–155)*	−28 (−23–33)*	35 (24–46)*	55 (40–69)	66 (46–86)	47 (17–77)*	60 (38–81)*

* Significant difference from lidocaine 1% at $P < 0.05$.

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jections of epinephrine produce tachycardia. Additionally, we have documented the magnitude of the concomitant increase in systolic blood pressure (table 3). These changes are transient, reflecting the short half-life of intravenously administered epinephrine.[10] After injection of 15 μg of epinephrine, maximal increases in HR and SBP occur in the range of 47–68 and 76–121 seconds, respectively.

Although a 15-μg dose of epinephrine has become the standard dose to detect intravascular injection, the rationale for using this dose has never been documented. One reason for selecting a 15-μg dose is based in the tradition of regional anesthesia. Epinephrine is commonly added to local anesthetics to produce a final concentration of 5 μg/ml, and 3 ml of local anesthetics is commonly used to test for subarachnoid blockade. Thus, a 3-ml test dose containing 15 μg of epinephrine is a practical choice, as it should allow simultaneous testing for intravascular and subarachnoid injection. The possibility that a smaller epinephrine dose could be sufficient has not been evaluated.

We have shown that a test dose containing either 10 or 15 μg of epinephrine in 3 ml of 1% lidocaine produces significant changes in HR and SBP (table 3). A test dose containing 5 μg does not produce reliable hemodynamic changes. Increasing the dose of epinephrine from 10 to 15 μg did not appear to produce a statistical nor clinical improvement in the ability to detect these changes. A test dose containing 10 μg of epinephrine should be sufficient in a patient group similar to ours (*i.e.*, nonpregnant and less than 40 years of age). With a standard 1:200,000 epinephrine solution of local anesthetic, a 2-ml test dose could then be used, as recommended by other authors,[6,11] although for different reasons.

A second focus of our study was to evaluate the effect of acute β-adrenergic blockade on intravenous injections of small doses of epinephrine. Different cardiovascular responses may be expected, depending on the β-selectivity of the drug.[12] With nonselective β-adrenergic blocking drugs (like propranolol, timolol, or nadolol), the α-adrenergic stimulation of epinephrine, unopposed by simultaneous β_2-mediated vasodilatation, should induce a significant increase in SBP, and, potentially, bradycardia mediated by simultaneous vagal reflex. With selective β-adrenergic–blocking drugs, only the chronotropic (β_1) effects of epinephrine should be blocked, and cardiovascular variations after epinephrine will depend on the balance between direct β_2 cardiac stimulation,[13] peripheral β_2 vasodilatation, direct α peripheral vasoconstriction, and the degree of reflex vagal response. Metoprolol and atenolol would be expected to act in this manner; we chose esmolol to demonstrate this pattern of activity because its short duration allowed the study of both types of β-blockers in the same subjects.

TABLE 4. Subjects with HR Variation ≥ 20 bpm After Injection of Saline, Lidocaine 1%, or Lidocaine 1% Plus Epinephrine

Injections	Loading or Infusion		
	Saline	Esmolol	Propranolol*
Saline	0/9	0/9	0/8
L	0/9	0/9	0/8
L + E (5 μg)	8/9	6/9	5/8
L + E (10 μg)	9/9	8/9	8/8
L + E (15 μg)	9/9	7/9	7/8

* HR changes with propanolol were bradycardia.
L = lidocaine 1%; L + E = lidocaine 1% + epinephrine.

TABLE 5. Subject with SBP Increase ≥ 15 mmHg After Injection of Saline, Lidocaine 1%, or Lidocaine 1% Plus Epinephrine

Injections	Loading and/or Infusion		
	Saline	Esmolol	Propranolol*
Saline	0/9	0/9	2/8
L	2/9	1/9	1/8
L + E (5 μg)	4/9	7/9	7/8
L + E (10 μg)	7/9	9/9	8/8
L + E (15 μg)	8/9	9/9	8/8

L = lidocaine 1%; L + E = lidocaine 1% + epinephrine.

In our study, the β_1-selective blocking drug (esmolol) reduced the increase in HR observed after injection of epinephrine such that tachycardia was no longer a reliable sign of epinephrine injection. The nonselective blocking drug, propranolol, completely modified the HR response, producing a bradycardia. Systolic blood pressure increases were increased modestly but significantly during esmolol infusion for 10 and 15 μg epinephrine injections (table 3). In contrast, all three doses of intravenous epinephrine in subjects receiving propranolol provoked sustained hypertension with the bradycardia. Our results suggest that SBP monitoring will be necessary to detect intravascular injection of epinephrine in patients receiving either selective or nonselective β-adrenergic–blocking drugs. However, detection of these transient changes in blood pressure may prove difficult with current noninvasive blood pressure (NIBP) cuffs, as they require a constant arterial pressure over several beats.[3,14] Moreover, some automatic NIBP machines will not determine arterial pressure in the presence of bradycardia, such as we observed in subjects after propranolol. This problem was solved in our study by use of a Finapres™, allowing continuous and reliable noninvasive blood pressure monitoring.[15]

The question of what constitutes a positive response to an intravenous injection of epinephrine has been raised.[16] Also, the sensitivity and specificity as well as range of responses after an epinephrine test dose is unknown. In this study we sought to establish reliable criteria to identify intravascular injection of a test dose containing epinephrine.

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In non–β-blocked subjects, a 20-beats/min increase in HR occurring during the 2 min after an iv injection of 10 or 15 μg of epinephrine was 100% sensitive and specific (table 4). In the presence of β-adrenergic blockade, the HR response is no longer a reliable sign of intravascular injection, but an SBP increase ≥ 15 mmHg is 100% sensitive for epinephrine injections, although with a small incidence of false-positive results (table 5). We suggest that an SBP rise ≥ 15 mmHg in a patient receiving β-adrenergic blocking drugs is probably the best indicator of an intravascular injection of epinephrine. Equivocal results should lead to repetition of the test dose, if not immediate epidural catheter replacement.

One potential criticism of our investigation (and our conclusions about the reliability of NIBP measurements) is that the changes seen on the Finapres™ are not accurate measurements of central blood pressure changes, but exaggerated responses in peripheral circulation. This may reflect an exaggerated sensitivity of the finger plethysmograph in the presence of vasoconstrictors. The Finapres™ technology has been shown to be reliable when compared with invasive monitoring in other clinical situations, including measurements over a wide range of pressures during major surgical procedures, as well as in the presence of peripheral vasoconstriction.[15,17] We have no reason to question the Finapres™ reliability in healthy young subjects with no evidence of peripheral vascular abnormalities. Furthermore, a close correlation between NIBP and Finapres™ measurements was observed before injection of the test dose and during stable control measurements (table 2).

The small sample size and healthy subjects of our study may be considered limitations to its interpretation. Significance is enhanced by our study design, which uses subjects as their own control, for each series of infusions and injections. Hemodynamic variations are of sufficient magnitude to reach statistical significance. Care must be taken in extrapolating these hemodynamic patterns seen in young healthy subjects to the usual patient population on chronic β-blockade. Elderly subjects may have other alterations of their responses that further interfere with adrenergic responsiveness.

The absence of preanesthetic medication may have affected the hemodynamic changes in our subjects. Many anesthesiologists consider some kind of preanesthetic medication useful before performance of an epidural block. But no agreement exists on what constitutes an optimal or even standard medication in such cases.[18] We elected not to administer preanesthetic medication to our subjects, on the basis of previous data showing no difference in maximal changes in HR, the time of onset of maximal changes, or the duration of HR changes between unmedicated volunteers and sedated patients.[1]

Moore and Batra[1] reported a delay of 20–40 s for the *onset* of HR rise after a test dose, with an average return to baseline within 3 min.[1] Here, we report the delay to *maximum* HR and SBP changes within the first 2 min after the test dose injection. This obviates the risk for confusion with random physiologic HR or SBP variations, or transient initial changes observed during saline and esmolol infusion. Maximal changes in HR and SBP occur within 60–90 s after epinephrine injections in most subjects. The slight time differences from the previous report may be due to injection through a smaller catheter at a more peripheral site. To our knowledge, venous return time to the heart from the epidural space has never been compared with venous return time from the hand or antecubital fossa. Extrapolation of the delays we observed to epidural injections should be made with care.

Another criticism is that we have no assurance that our subjects were "adequately β-blocked." The employed dosages are standard regimen to attain acute β-adrenergic blockade with intravenous administration.[4] Our subjects had significant decreases in both SBP and HR after receiving esmolol or propranolol (table 1). Although there is wide variation in responsiveness to β blockade, we felt that our subjects represented a degree of blockade that may be equivalent to the range of variation seen in patients presenting for surgery, for whom no accurate assessment of degree of blockade is available. Although we did not assess degree of blockade in our subjects, our findings support our basic conclusion that any degree of β blockade in any patient should be presumed to interfere with the reliability of the standard epinephrine test dose.

Another question is whether the response to epinephrine may differ in patients who are chronically receiving β-adrenergic–blocking drugs. In such patients, epinephrine test doses have nevertheless been reported to induce an SBP increase ≥ 15 mmHg (and often much more), easily fulfilling our criteria for a positive test dose.[1,2] Care must be exercised in applying these criteria to elderly patients until this pattern can be confirmed in that patient population.

One other potential objection to our study is the possibility that lidocaine and/or epinephrine will accumulate with repeated injections. Our subjects received an average total dose of 5 mg/kg of lidocaine. Although a residual blood concentration of lidocaine surely developed, we believe it would be insignificant for two reasons: First, lidocaine was injected in 12 separate doses over at least 4 h. The cumulated serum concentration then would be expected to be extremely low.[19] Second, the peak concentration of lidocaine immediately after each bolus injection would be at least an order of magnitude greater than the concentration expected to result from accumulation over the duration of the study. Because the peak concentration of lidocaine did not provoke significant changes in HR or SBP, the residual concentrations would

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not be expected to affect the response to epinephrine injections. Likewise, in the dosages and time intervals employed in our study, neither tachyphylaxis nor residual effect was expected or observed with epinephrine, owing to its short half-life.[10]

Several questions remain unanswered.

No prospective study has conclusively demonstrated that test doses, whatever their content, improve the margin of safety for epidural anesthesia. A prospective study, using the criteria we define, is needed in a larger patient population.

Parturients and small children anesthetized with halothane have been shown to have diminished cardiovascular responses to intravenous injection of epinephrine.[9,20] Our results may therefore not apply to these patients.

A diminished responsiveness of β-adrenoceptors to both agonist and antagonist drugs has been described with advancing age.[21] It takes ten times the dose of isoproterenol to raise the HR 25 beats/min in a 70-year-old patients compared with a 20-year-old. No data are available for epinephrine. In older patients, the HR increases we observed in our subjects may be absent. Moreover, the SBP response in elderly subjects chronically receiving β-adrenergic–blocking drugs has not been studied.

In conclusion, we found that:

1) a test dose containing 10 or 15 μg epinephrine is a sensitive and specific marker of intravascular injection in young, nonpregnant, healthy subjects;
2) a positive response can be reliably detected by an absolute increase in HR $\geq$ 20 beats/min;
3) in the presence of acute selective or nonselective β blockade, tachycardia is no longer a reliable sign of intravascular injection;
4) an increase in SBP $\geq$ 15 mmHg is a sensitive, although not entirely specific, indicator of intravascular injection of epinephrine during acute β-adrenergic blockade.

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