

## Limitations of Epinephrine as a Marker of Intravascular Injection in Laboring Women

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Verification of proper epidural catheter placement is important, since intravascular injection of local anesthetic during epidural anesthesia may be fatal.<sup>1</sup> One may not be able to aspirate blood through an intravascular epidural catheter; therefore, the importance of injecting an effective intravascular marker into epidural catheters has been stressed.<sup>2-4</sup> Although epinephrine 15  $\mu$ g iv causes a predictable tachycardia in unpremedicated volunteers and premedicated patients awaiting surgery,<sup>2</sup> this has not been demonstrated in laboring pregnant patients. Unanesthetized laboring patients have fluctuating heart rates;<sup>5</sup> the chronotropic effect of exogenous epinephrine may be more difficult to detect under these circumstances. We designed this randomized, double-blind study to evaluate the safety and efficacy of an epinephrine 15  $\mu$ g iv test dose prior to epidural analgesia in laboring patients.

## METHODS

Twenty unanesthetized, healthy parturients who were between 37 and 42 weeks gestation and carrying single fetuses gave written, informed consent before participating in this study, which was approved by our institutional review board. All patients were in active labor (between 3 and 6 cm cervical dilation), and were taking no medications. Pre-injection continuous fetal heart rate tracings were normal (fetal heart rate  $\geq 120$  and  $\leq 160$  beats/min with long-term variability present, 5-10 beats/min short-term variability and no decelerations). Left uterine displacement was maintained while an HP8040A<sup>®</sup> monitor continuously recorded electrocardiographic maternal

heart rate, ultrasonographic fetal heart rate, and tocodynamometric uterine contractions. A Criticon Dinamapp B45XT<sup>®</sup> measured maternal arterial blood pressure every minute. These measurements were recorded for 10 min before and after each patient randomly received either 3 ml normal saline (NS group; n = 10) or epinephrine 15  $\mu$ g in 3 ml normal saline (EPI group; n = 10) iv 30 s after a uterine contraction. The data-collecting investigator, who was unaware of the treatment group, then attempted to guess which solution had been administered.

We determined maternal heart rate from these tracings at 10-s intervals for 120 s and at 30 s intervals between 120 and 240 s after the injection. Each maternal heart rate and mean arterial blood pressure value was expressed as a percentage of that patient's heart rate or blood pressure at the time of the injection ( $T_0$ ). Group values are expressed as the mean  $\pm$  standard deviation of the normalized values. The effect of uterine contractions on the maternal heart rate, which we called maternal heart rate variability, is expressed as the maximum minus the minimum maternal heart rate during the 120 s before injection. An obstetrician unaware of the solution administered to the patient analyzed fetal heart rate tracings for signs of fetal distress (short-term fetal heart rate variability  $\leq 5$  beats/min, more than one late deceleration within 10 min after  $T_0$ , or a change in baseline fetal heart rate to  $\leq 120$  beats/min or  $\geq 160$  beats/min).

We first analyzed our data using a baseline-to-peak criterion for iv epinephrine injection based on Moore and Batra's data.<sup>2</sup> Baseline-to-peak criterion was a  $\geq 25$  beats/min maternal heart rate increase over the maternal heart rate at the time of drug injection occurring within 120 s of drug injection and lasting  $\geq 15$  s.

Retrospective inspection of our data led us to derive a peak-to-peak criterion for iv epinephrine injection. Peak-to-peak criterion was a  $\geq 10$  beats/min increase in the maximum maternal heart rate during the 2 min after the injection over the maximum maternal heart rate during the 2 min before the injection.

Analysis of variance for repeated measures and Duncan's multiple range test determined the significance of post-injection maternal heart rate and blood pressure differences between the groups. Fisher's exact test determined the significance of differences between the groups in the incidence of fetal distress and in the efficacy of the two criteria. One-way analysis of variance determined the

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significance of demographic differences between the groups.  $P < 0.05$  indicated significance.

### RESULTS

Maternal age, height, weight, gravidity, parity, and gestational age did not differ significantly between the groups.

We found considerable maternal heart rate variability in the 2 min before drug injection:  $33 \pm 12$  beats/min in the NS group and  $27 \pm 8$  beats/min in the EPI group ( $P = N.S.$ ). Six NS group and nine EPI group patients had a uterine contraction within 60 s of the drug injection ( $P = N.S.$ ). Changes in maternal heart rates of EPI group patients were significantly greater than those of NS group patients at 40 s ( $P < 0.05$ ); they were significantly less than those of NS group patients at 110 s ( $P < 0.01$ ), 120 s ( $P < 0.01$ ), and 210 s ( $P < 0.05$ ) after drug injection (fig. 1). Changes in maternal arterial blood pressure were significantly higher in EPI group patients than in NS group patients at 1 and 2 min after drug injection ( $P < 0.05$ ; fig. 2).

The baseline-to-peak criterion identified 2/10 NS group and 5/10 EPI group patients as having received epinephrine ( $P = N.S.$ ; fig. 3). The peak-to-peak criterion identified 0/10 NS group and 9/10 EPI group patients as having received epinephrine ( $P < 0.001$ ; fig. 3). The data-collecting investigator, utilizing maternal symptoms (palpitations, headache, or anxiety in 4/10 EPI group and 0/10 NS group patients) as well as careful inspection of maternal heart rate and blood pressure changes, correctly guessed the treatment group of all patients.

Fetal distress was present in 0/10 NS group and 2/10 EPI group patients ( $P = N.S.$ ). One fetus had persistent late decelerations for 10 min. The other fetus had mild bradycardia for 4 min, followed by a 7-min period of decreased FHR variability. In both cases, fetal heart rate variability did not return to the pre-injection baseline until 20–25 min after the injection. Both fetuses subsequently had uneventful vaginal deliveries. All infants had Apgar scores of 7 or greater at 5 min, weighed between 2500 and 3500 grams, and were judged to be full-term by a pediatrician.

### DISCUSSION

Recognized intravascular placement or migration of an epidural catheter occurs in 5.2% of obstetric epidural anesthetics;<sup>6</sup> detection of these intravascular catheters can be difficult. Intravascular injection of local anesthetic intended for epidural anesthesia has resulted in seizures, cardiac arrest, and death.<sup>1</sup> Three ways to avoid a massive intravascular injection of local anesthetic are now advocated: 1) careful aspiration of the catheter for blood,<sup>7</sup> 2) fractionation of the local anesthetic dose,<sup>7</sup> and 3) injection

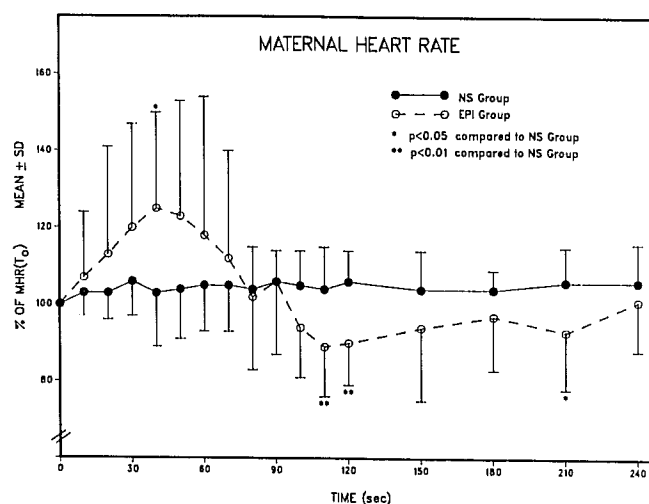


FIG. 1. Maternal heart rate after epinephrine 15  $\mu\text{g}$  iv (○ --- ○) or normal saline iv (● — ●) in unanesthetized laboring patients. We normalized all values for a given patient by expressing them as a percentage of that patient's heart rate at the time of drug injection (MHR [T<sub>0</sub>]). Group values are expressed as the mean  $\pm$  SD of the normalized values.

of a test dose containing epinephrine 15  $\mu\text{g}$ .<sup>3-5</sup> Careful aspiration by itself is insufficient; in a review of 4,003 obstetric epidural anesthetics, 65 of 194 intravascular catheters were not detected by aspiration.<sup>6</sup> Fractionation was also an insensitive test, for the fractionated administration of "rather large quantities" of local anesthetic through an intravascular epidural catheter produced no symptoms in 12 of 51 of these patients.<sup>6</sup> Although the sensitivity and specificity of epinephrine 15  $\mu\text{g}$  as a test

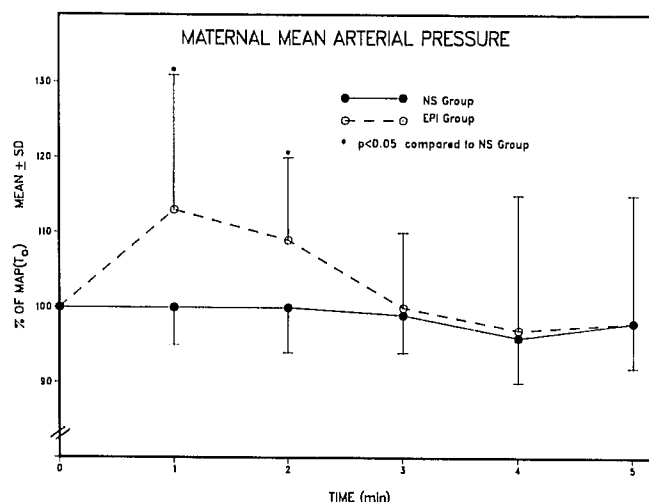


FIG. 2. Maternal mean arterial pressure after epinephrine 15  $\mu\text{g}$  iv (○ --- ○) or normal saline iv (● — ●) in unanesthetized laboring patients. We normalized all values for a given patient by expressing them as a percentage of that patient's mean arterial pressure at the time of drug injection (MAP [T<sub>0</sub>]). Group values are expressed as the mean  $\pm$  SD of the normalized values.

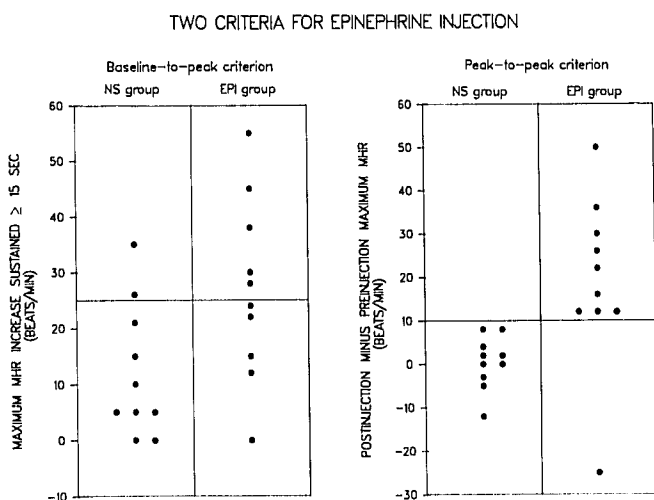


FIG. 3. Analysis of the maternal heart rate changes following the intravenous administration of epinephrine 15  $\mu$ g or normal saline to unanesthetized laboring patients according two criteria for epinephrine injection. Baseline-to-peak criterion: a maternal heart rate increase of  $\geq 25$  beats/min over the maternal heart rate at the time of drug injection that occurred within 120 s of drug injection and lasted  $\geq 15$  s indicated epinephrine injection. Peak-to-peak criterion: a  $\geq 10$  beats/min increase in the maximum maternal heart rate during the 2 min after injection as compared to the maximum maternal heart rate during the 2 min before injection indicated epinephrine injection. The baseline-to-peak criterion was prospectively evaluated; the peak-to-peak criterion was retrospectively derived from our data.

of iv injection has not been tested in parturients, the use of an epinephrine-containing test dose is recommended before every epidural drug dose in obstetric patients.<sup>4</sup> Participation in this study exposed our patients to the same risks encountered by laboring women with intravascular epidural catheters who receive a test dose containing epinephrine 15  $\mu$ g; therefore, we felt that determining the efficacy and safety of such a test dose was both clinically and ethically indicated.

While developing an epidural test dose, Moore and Batra<sup>2</sup> found a  $31.6 \pm 7$  beats/min heart rate increase lasting 3 min that started 20–40 s after epinephrine 15  $\mu$ g iv in unmedicated non-pregnant volunteers. Since Moore and Batra did not precisely define their criteria for determining that an intravascular injection had occurred, we used their data to derive our baseline-to-peak criterion. In contrast to their results, we found that our baseline-to-peak criterion was neither specific nor sensitive; it identified 20% of NS group and 50% of EPI group patients as receiving epinephrine. Changing the cutoff parameters for the magnitude and duration of maternal heart rate changes did not improve the sensitivity and specificity of this method.

Our baseline-to-peak criterion for iv epinephrine injection lacked specificity because the epinephrine-induced maternal heart rate increase was not larger than the base-

line maternal heart rate variability. Cartwright *et al.* also documented the maternal heart rate variability of unanesthetized laboring patients. They injected plain bupivacaine into epidural catheters and concluded that, had the solution contained epinephrine, iv catheter placement would have been incorrectly assumed in 12% and 24% of their patients if maternal heart rate increases of  $\geq 30$  and  $\geq 20$  beats/min, respectively, were considered diagnostic.<sup>5</sup>

The cardiovascular changes we saw in the epinephrine group, a brief period of tachycardia followed by hypertension and bradycardia, may explain the lack of sensitivity of the baseline-to-peak criterion. We postulate that these changes represent a brief beta-adrenergic followed by a prolonged alpha-adrenergic cardiovascular response to epinephrine 15  $\mu$ g. The magnitude and duration of the initial tachycardia varied greatly among epinephrine group patients. In fact, one epinephrine group patient never developed a tachycardia; she became severely hypertensive (mean blood pressure of 152 mmHg) and bradycardic (heart rate of 46 beats/min) immediately after the injection. Larger epinephrine doses should produce a greater alpha-adrenergic and a lesser beta-adrenergic effect, and, therefore, be less, not more, sensitive as a test of intravascular injection.

After we had determined the lack of sensitivity and specificity of the baseline-to-peak criterion, we examined the continuous maternal heart rate tracings for other potential diagnostic methods. We derived the peak-to-peak criterion after noting that the maximum maternal heart rate achieved during a uterine contraction was fairly consistent for each patient, and that this maximum maternal heart rate increased after epinephrine injection. Since the peak-to-peak criterion was retrospectively derived, it would need to be prospectively evaluated before it could be recommended as a diagnostic tool.

The data-collecting investigator, who observed maternal symptoms and heart rate and blood pressure changes, correctly guessed the treatment group of all patients immediately after each study. However, in clinical practice, maternal cardiovascular changes are generally less carefully monitored than in this study. In several cases, the treatment group was correctly guessed only after careful inspection of the maternal heart rate tracing for differences in the maximum maternal heart rate during a contraction before and after the injection; such subtle changes would not be detected by the "finger on the pulse" method, or even by electronic monitoring instituted immediately before the test dose injection.<sup>2,5</sup>

Intravenous epinephrine causes decreased uterine blood flow, hypertension, and bradycardia in pregnant but nonlaboring females of two species, the guinea pig and the sheep. Uterine blood flow transiently decreases to 87% of the control value within 1 min after epinephrine

0.2 mg/kg iv in pregnant guinea pigs.<sup>8</sup> Uterine blood flow decreases to 63% of the control value, and requires 5 min to recover fully after epinephrine 10  $\mu$ g in pregnant ewes.<sup>9</sup> This decrease in uterine blood flow is more striking and prolonged than the effect of epinephrine on the ovine maternal cardiovascular system, for the elevated blood pressure and decreased heart rate return to control values within 1 min of the epinephrine injection. Despite the decreased uterine blood flow, none of the fetuses in either of these studies became distressed.

In contrast, the fetuses of two of our epinephrine group patients developed distress lasting 10–12 min following the administration of epinephrine 15  $\mu$ g iv. Similarities between our study and previous animal studies<sup>8,9</sup> lead us to suspect that decreased uterine blood flow may have been responsible for this fetal distress. Even though transient decreases in uterine blood flow are well tolerated by normal, healthy fetuses, the response may be different in already stressed fetuses. The difficulty in determining in advance which fetuses may not tolerate a brief period of ischemia is illustrated in our series, for both of the fetuses that developed signs of distress were apparently healthy at the time of drug injection.

Labouring pre-eclamptic patients may have a greater hypertensive response to epinephrine 15  $\mu$ g iv than normal parturients, for pre-eclamptic patients have exaggerated pressor responses to angiotensin II and norepinephrine.<sup>10</sup> Such vasoconstriction might well endanger the mother as well as the fetus.

In summary, we found that epinephrine 15  $\mu$ g iv produced a transient tachycardia followed by hypertension and bradycardia in healthy labouring parturients. Fetal distress occurred in two patients following epinephrine 15  $\mu$ g iv. Our data suggest that, if epinephrine 15  $\mu$ g is

to be an effective test of intravascular injection in labouring patients, then monitoring sophisticated enough to detect a transient 10 beats/min increase in the maximum maternal heart rate is required. However, we question the clinical usefulness of relying on such a subtle and possibly unsafe test dose to detect intravascular catheters and suggest that another marker of intravascular injection should be developed.

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## Resistance to Pancuronium in Patients Receiving Carbamazepine

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Resistance to pancuronium, metocurine, and vecuronium has been demonstrated in patients chronically receiving phenytoin.<sup>1–4</sup> In these patients, resistance was characterized by either an increased hourly requirement

of pancuronium or shorter recovery times after an iv bolus dose of pancuronium. To produce a given level of neuromuscular blockade after metocurine, higher plasma metocurine levels were required in patients receiving phenytoin compared to controls. The mechanism of these

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