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The effects of remifentanil or acetaminophen with epidural ropivacaine on body temperature during labor

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Abstract
Purpose. Epidural analgesia is associated with hyperthermia during labor and presumably causes it, although no convincing mechanism has been postulated. It seems likely that fever associated with pyrogenic factors related to labor is suppressed by opioids, whereas it is expressed normally in patients given epidural analgesia. We examined this hypothesis and the possible etiology of temperature elevation in labor.
Methods. In this prospective, randomized, controlled study, we assessed 201 parturients during spontaneous labor. Analgesia was randomly provided with one of four treatment groups: (1) epidural ropivacaine alone, (2) IV remifentanil alone, (3) epidural ropivacaine plus IV remifentanil, and (4) epidural ropivacaine plus IV acetaminophen. At randomization, patients were normothermic. Intrapartum hyperthermia (≥38°C) was correlated to the analgesic technique.
Results. The maximum increase in oral temperature was greatest in the ropivacaine group (0.7 ± 0.6°C) and least in the remifentanil group (0.3 ± 0.4°C; $P = 0.013$). The percentage of patients who became hyperthermic (≥38°C) during the first 6 h of labor was greatest in the ropivacaine group (14%) and least in the remifentanil-alone group (2%), but the difference was not statistically significant. The maximum forearm-finger gradients were lower (less vasoconstriction) in the remifentanil group when compared to the gradients in patients with epidural analgesia (1.4 ± 1.8 vs 3.0 ± 1.7, respectively; $P < 0.001$).
Conclusion. Our results are consistent with the theory that low-dose opioids inhibit fever in patients not given epidural analgesia. However, in view of the negative results, the hypothesis of epidural-induced hyperthermia may be questionable.

Key words Hyperthermia · Labor · Epidural · Acetaminophen · Remifentanil

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Introduction

Hyperthermia is reported to frequently complicate epidural analgesia for labor and delivery [1–4]. Consequently, women receiving epidural analgesia are given antibiotics more often than those treated conventionally and their offspring are treated more frequently for sepsis [1,2,5,6], although there is no evidence of a causal relationship between hyperthermia with epidural analgesia and maternal or neonatal infection [7]. Other risk factors identified for fever in labor are prolonged duration of labor and increased interval of rupture of membranes to delivery [3]. It has been suggested that the increase in maternal temperature with epidural local anesthetics in labor may be caused by diminished sweating caused by the sympathetic block produced by the epidural, decreased hyperventilation as a result of pain control, and reactive vasoconstriction in the upper part of the body [8]. Specifically, the epidural local anesthetics and opioids reported to be associated with increased maternal temperature are bupivacaine with or without sufentanil [3], bupivacaine with or without fentanyl [9], and ropivacaine with or without fentanyl [10].

Implicit in all discussions of hyperthermia associated with epidural analgesia is the assumption that the technique *causes* hyperthermia [11]. It is important, though, to recognize that the control patients in these observational studies were not given a placebo. Instead, their pain was usually treated with opioids. This is a critical factor, because even low concentrations of intravenous opioids attenuate fever [12]. Thus, it seems likely that fever associated with infection, tissue injury, atelectasis, etc. is suppressed by opioids in the control patients, whereas it is expressed normally in patients given epidural analgesia. When fever was induced in volunteers by interleukin 2, it was found that intravenous fentanyl halved the febrile response to this pyrogen, while

epidural ropivacaine and epidural ropivacaine-fentanyl did not [10]. This finding supports the hypothesis that hyperthermia during epidural analgesia should not be considered a complication of the anesthetic technique [10]. Opioids cause an impairment of thermoregulatory control. For example, alfentanil [13] and meperidine [14] decrease the vasoconstriction and shivering thresholds. This effect may be severe when opioids are combined with local anesthetics [15]. Negishi et al. [12] have demonstrated that opioid-induced inhibition of fever is mediated centrally rather than by a reduction in the peripheral concentration of pyrogens. The same authors [10] have shown that epidural fentanyl has no detectable influence on the febrile response. A cardinal feature of fever is that it is mediated by endogenous pyrogens via a prostaglandin-dependent mechanism; therefore, true fever can thus usually be treated with prostaglandin inhibitors, such as acetaminophen.

Against this background, we decided to test the hypothesis whether labor can induce hyperthermia during epidural analgesia, and we assessed the effects of analgesic doses of the intravenous opioid remifentanil or antipyretic doses of acetaminophen in the prevention of hyperthermia during labor.

Patients, materials, and methods

The study was conducted at the Wolfson Medical Center Affiliated to Tel-Aviv University. With the approval of the local institutional committee of human research and the patients' written informed consent, 213 healthy women with singleton cephalic presentation at term and presenting in spontaneous active labor were enrolled. Patients were excluded from the study if they initially had a fever (oral temperature ≥38°C), signs of infection, or ruptured membranes for more than 24 h. Patients were also excluded if cesarean delivery was anticipated. Patients were invited to participate in the study as early as possible, typically well before they began to experience severe pain.

Protocol

The delivery ward staff followed a written protocol for the management of the parturients. Fetal membranes were usually ruptured during active labor when the fetal head reached the cervix. Internal fetal monitoring was used in those parturients with nonreassuring fetal heart rate tracing, meconium-stained amniotic fluid, or unsatisfactory progression of labor. Pelvic examinations were performed every 2 h. Oxytocin augmentation was applied when the rate of cervical dilatation was less than 1 cm·h^{-1}, and hypotonic contractions (<180 Montevideo units) were recorded via an intrauterine pressure transducer. Per routine in our labor unit, ambient temperature was maintained near 22°C with relative humidity near 45%.

We randomized 213 parturients to receive one of four treatment regimen groups: (1) epidural ropivacaine alone (ropivacaine); (2) IV remifentanil alone (remifentanil); (3) epidural ropivacaine and IV remifentanil (ropivacaine and remifentanil); and (4) epidural ropivacaine and IV acetaminophen (ropivacaine and acetaminophen). Randomization was based on computer-generated codes that were maintained in sequentially numbered opaque envelopes until just prior to use. The randomization envelopes were opened and the designated treatment started when the visual analogue pain score (VAPS) reached 30 mm. The treatment regimen was blinded for the evaluator anesthesiologist by using two patient-controlled analgesia machine devices (PCIA and PCEA) for every patient. A "dummy" IV saline infusion (PCIA) was attached to parturients with patient-controlled epidural analgesia (PCEA) and the other was a "dummy" epidural catheter attached superficially to the skin and connected to a PCEA syringe in the group with patient-controlled IV analgesia (PCIA) with remifentanil.

Epidural analgesia was administered after prehydration with 500 ml Ringer's lactate solution. A test dose of 3 ml lidocaine (2% without epinephrine) was followed by increments of 5–10 ml of 0.2% ropivacaine; maintenance was provided with the same solution via patient-controlled epidural analgesia (PCEA) with a background infusion of 10 mg·h^{-1} and a 10-mg patient-activated bolus with 20-min lockout. The maximal dose of ropivacaine was 20 ml·h^{-1}. The same ropivacaine dose was administered to patients in all epidural groups.

Parturients randomized to PCIA with remifentanil (group 2) initially received a basal infusion of 0.025 μg·kg^{-1}·min^{-1} combined with 20-μg bolus doses with a lockout of 3 min. The dose was increased by 25% every 15–20 min as required. The same remifentanil doses were administered to patients in group 3 (ropivacaine and remifentanil). Acetaminophen was administered by continuous infusion 30 min after the initiation of epidural analgesia with the PCIA machine device at a rate of 0.47 mg·kg^{-1}·min^{-1} to a maximal dose of 2 g.

Patients with breakthrough pain (VAPS > 30 mm) were given rescue analgesia: (1) patients in the ropivacaine or ropivacaine and acetaminophen groups were given up to four additional boluses of 8 ml ropivacaine (0.2%), even if they had reached the maximum dose specified above; and (2) patients in either remifentanil group had their baseline infusion and bolus doses increased, as necessary, in 25% increments. If four increases proved insufficient, patients assigned to IV remifentanil were switched to epidural analgesia.

Forceps or vacuum delivery was used per the judgment of the attending obstetrician. Forceps-assisted deliveries were usually indicated when the head descent was arrested or fetal heart rate was nonreassuring at the head station of SP+2. Cesarean delivery, similarly, was used per the judgment of the attending obstetrician, based on maternal or fetal indications.

Measurements

Routine demographic and morphometric characteristics were recorded, as were previous pregnancies and deliveries. Cervical dilation at analgesic administration, duration of ruptured membranes, vaginal examinations, duration of labor, and other routine obstetric variables were also recorded. Invasive monitoring and oxytocin administration were performed as clinically indicated.

Oral temperatures were recorded every 30 min, with an electronic thermometer positioned under the tongue; the patients were asked to keep their mouths closed during each measurement. Intrapartum hyperthermia was defined as an oral temperature of 38°C or more. Skin temperatures were measured on the radial side of the forearm, halfway between the elbow and wrist; index fingertip temperature was also recorded. Skin-temperature gradients (forearm minus fingertip temperatures) exceeding 0°C were considered evidence of arteriovenous shunt vasoconstriction [16]. Skin temperatures were measured with an infrared thermometer (Dermatemp; Model DT – 1001; Exergen, Watertown, Boston, MA, USA). Patients were asked to rate their pain on a 100-mm-long VAPS; a new scale was used for each measurement.

All neonates born to parturients with hyperthermia were evaluated (as per routine) for sepsis by complete blood count and cultures, followed by antibiotic administered for 48 h. Heart rate, blood pressure, and oxygen saturation were recorded every 30 min. If necessary, oxygen was given via a nasal cannula to maintain oxygen saturation above 95%. The babies' rectal temperatures were recorded, along with Apgar scores at 1, 5, and 10 min. Umbilical blood gases were not obtained purely for study purposes, but the values were recorded when they were obtained for clinical indications.

Data analysis

The primary comparisons of interest were between ropivacaine alone and the other three treatment groups (remifentanil; ropivacaine and remifentanil; and ropivacaine and acetaminophen). Our sample size was based on an incidence of hyperthermia (oral temperature ≥38°C) of 46% in patients given epidural analgesia versus 20% in those give intravenous opioids [17].

Only patients with at least 2 h of labor were included in the analysis. Change in temperature from baseline was also a primary analysis variable. As stated previously, we defined hyperthermia as an oral temperature of 38.0°C or more.

Potential confounding factors were compared among the four treatment groups with one-way analysis of variance (ANOVA) or χ^2 tests, as appropriate. Analysis of temperatures and pain was done with an ANOVA, and if ANOVA indicated that a significant difference existed between the groups, a Dunnett's posttest was used to restrict the comparisons to the three a priori comparisons defined above. Furthermore, we used multivariate regression, which included randomization group and duration of labor as covariates and the maximum increase from baseline temperature as a response. Values for Results are presented as means ± SDs unless otherwise indicated; $P < 0.05$ was considered statistically significant.

Results

Among the 213 women recruited to the study, 201 completed it. The remaining 12 completed the delivery quickly and did not require any analgesia. All patients ($n = 192$) with at least 2 h of labor were included in the data analysis. None of the patients initially assigned to remifentanil alone subsequently required epidural analgesia.

The morphometric and demographic variables were similar among the groups, as were the factors that might have been associated with the development of intrapartum fever. The incidence of instrumental delivery was similar, and the cesarean delivery rate in the remifentanil group was higher than that in the other groups, but with only slight statistical significance ($P = 0.08$; Table 1). Cervical dilation at the time treatments were started averaged 2.8 ± 1.0 cm and, although the difference between the groups (range, 2.5 to 3.1 cm) was statistically significant, we did not consider these differences clinically important (Table 1).

At enrollment, no patients reported VAPS exceeding 30 mm on a 100-mm visual analogue scale. Averaged over the duration of the study, though, patients assigned to remifentanil reported more pain (49 ± 12 mm) than those in the other groups (≈27 mm; $P < 0.001$). Unsurprisingly, patients assigned to remifentanil alone required much more opioid: $8.5 \pm 2.2\,\mu g \cdot kg^{-1} \cdot h^{-1}$, as compared to the epidural groups, $4.2 \pm 1.8\,\mu g \cdot kg^{-1} \cdot h^{-1}$ ($P < 0.001$). Maximum skin temperature gradients were significantly lower (i.e., showing more vasodilation; 1.4 ± 1.8°C) in patients assigned to remifentanil alone than in all the other study groups (≈3°C; $P < 0.001$; Table 2). We designed our study so that the multiple comparisons

Table 1. Potential comfounding factors

Patients with at least 2 h of labor ($n = 192$)[a]	Ropivacaine 50	Remifentanil 44	Ropivacaine and remifentanil 49	Ropivacaine and acetaminophen 49	P —
Patients with at least 6 h of labor; n (%)	26 (52)	12 (24)	20 (44)	13 (27)	0.009
Age (years)	28 ± 5	29 ± 7	27 ± 5	27 ± 4	0.153
Weight (kg)	79 ± 14	75 ± 11	78 ± 10	74 ± 14	0.277
Height (cm)	159 ± 25	157 ± 33	159 ± 25	161 ± 24	0.853
Gravida (1/2/3/≥4)	28 / 12 / 5 /5	20 / 7 / 11 / 11	25 / 9 / 4 / 7	29 / 13 / 4 / 3	0.100
Membrane rupture duration (h)	8 ± 6	7 ± 5	9 ± 6	8 ± 5	0.299
Cervical dilation at study entry (cm)	2.5 ± 1.1	3.1 ± 1.0	2.7 ± 0.9	3.0 ± 0.8	0.010
Forceps delivery; n (%)	3 (6)	1 (2)	3 (7)	3 (6)	0.752
Cesarean delivery; n (%)	5 (10)	4 (8)	11 (24)	3 (6)	0.048

Data values are presented as means ± SD or numbers (n) and percentages (%). The groups were compared with a one-way ANOVA
[a] Patients with labor duration of less than 2 h were excluded from the statistical analysis

Table 2. Major study results

	Ropivacaine	Remifentanil	Ropivacaine and remifentanil	Ropivacaine and acetaminophen	P
Maximal forearm—finger gradient temperature (°C)	3.3 ± 1.7	1.4 ± 1.8*	3.0 ± 1.7	3.1 ± 1.6	<0.001
VAPS (mm)	26 ± 13	49 ± 12*	24 ± 12	25 ± 11	<0.001
Temperature at baseline (°C)	36.6 ± 0.4	36.5 ± 0.4	36.6 ± 0.4	36.6 ± 0.5	0.671
Maximum increase from baseline temperature (°C)	0.7 ± 0.6	0.3 ± 0.4***	0.5 ± 0.6	0.5 ± 0.5	0.013
Hyperthermic patients; n (%)	7 (14)	1 (2)	4 (8)	4 (8)	0.175

Data values are presented as means ± SD or numbers (n) and percentages (%). VAPS, visual analogue pain scale, 0–100 mm; pain scores in each patient were averaged over the study period and then averaged among patients in each treatment group. The groups were compared with one-way ANOVA or χ^2 test. For a significant ANOVA, Dunnett's posttest was used to compare each of the three treatment groups against the control group (ropivacaine alone). Significant differences are denoted with single asterisks (*). Using multivariate regression, which included randomization group and duration of labor as covariates and the maximum increase from baseline temperature as a response, we found a significant difference between the remifentanil and ropivacaine groups (marked by **)

with a control group (ropivacaine) would be tested using Dunnett's method. We believe that the post-hoc hypothesis using Dunnett's method for other control groups was not statistically valid. The maximum forearm-finger gradients were lower in the remifentanil group (1.4 ± 1.8°C) than in patients who received regional anesthesia (3.0 ± 1.7°C; $P < 0.001$; Table 2). To analyze the maximal forearm-finger gradient, we used Tukey's all pairwise comparison method to compare all groups to one another. With this test, we found that the remifentanil group differed significantly from all other groups. However, we chose to abandon this analysis, because it was not included during the study design.

Patients were normothermic at the time of randomization, with oral temperatures near 36.5°C. The maximum increase in oral temperature during the study was greatest in the ropivacaine group (0.7 ± 0.6°C) and least in patients assigned to remifentanil alone (0.3 ± 0.4°C; $P = 0.013$). The percentage of patients who became hyperthermic (≥38°C) at any time during the first 6 h of labor was greater in those assigned to ropivacaine alone (14%), than in those assigned to remifentanil (2%), but the difference was not statistically significant ($P = 0.175$). Oral temperature increased slightly more in patients randomized to ropivacaine alone than in those randomized to the three other modes of treatments. However, the difference was only ≈0.2°C and was not statistically significant (Fig. 1). Parturients with increased temperatures had no signs of chorioamnionitis.

Apgar scores of the infants born to patients in each group were similar at 1, 5, and 10 min. Heart rate, blood pressure, and oxygen saturation in the infants were also similar. Neonates delivered to hyperthermic mothers had negative blood cultures.

Discussion

The maximum increase in oral temperature during our study was greatest in the ropivacaine group and least in the remifentanil-alone group. More patients be-

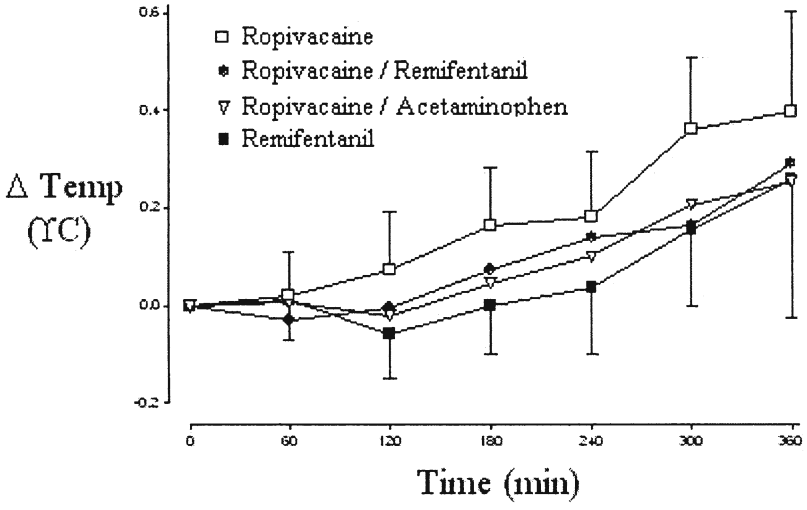

Fig. 1. Changes in oral temperature during 6 h of labor in patients who remained in labor for at least 2 h are presented in this Fig. Baseline temperatures are shown in Table 2 and the number of patients at baseline and after 6 h of labor are shown in Table 1. Values for results are presented as means ± 95% confidence intervals. There were no statistically significant differences among the groups, and only a few of the 201 participating patients became hyperthermic (oral temperature ≥38°C) at any time during the study

came hyperthermic during the first 6 h of labor in the ropivacaine-alone group, as compared to the remifentanil-alone group; however, the difference between the groups was statistically insignificant.

It is well established that epidural analgesia is associated with maternal hyperthermia in laboring women and postoperative patients. For example, Gonen et al. [18] reported that, in a nonrandomized series, 11.8% of 406 women who received epidural analgesia developed hyperthermia (maternal temperature ≥37.8°C) during labor, compared with only 0.2% of 600 women who did not have epidural analgesia. Gross et al. [19] report similar ratios. Philip et al. [1] similarly found that the risk of hyperthermia was increased fourfold by epidural analgesia in a randomized trial. Others, likewise, report that hyperthermia frequently complicates epidural analgesia for labor and delivery [2–4].

Given previous reports and our own data of hyperthermia during epidural analgesia, we calculated our study parameters in the expectation of observing hyperthermia in 46% of the patients given epidural analgesia, versus 20% in those given intravenous opioids [17]. Our most remarkable result was, thus, that only 16 of 201 participating patients (8%) became even mildly hyperthermic (i.e., oral temperature ≥38°C) during labor. Hyperthermia in our study population was thus far less common than previously reported.

The rationale behind our observation of such lower incidences of hyperthermia than others reported remains unclear. Our Israeli population differed from the North Americans evaluated in most previous reports, but ethnicity seems an unlikely explanation. A more likely explanation is that the duration of labor in our patients was relatively short, with only about a third of the patients laboring for 6 h after being assigned to one of our four treatments at a cervical dilation greater than 1.5 cm. This is a potentially important factor, because the incidence of hyperthermia is a strong function of epidural analgesia duration [1,3,8,18,19]. We also excluded patients with membranes that had ruptured more than 24 h previously; this would have limited infectious fever [3]. Fusi et al. [8] found that women with labor duration of 5–12 h were seven times more likely to develop fever if they had epidural analgesia. Others [9] found an increase in temperature after 5 h of epidural analgesia. However, potential confounders (i.e., parity or duration of labor) were not analyzed in these two studies. An independent correlation between tympanic temperature and duration of epidural analgesia was reported by Vinson et al. [20], while Herbst et al. [3] found that epidural analgesia, duration of labor, and longer interval from membrane rupture to delivery were independent risk factors for the development of maternal fever during labor. The only significant difference between our study groups was in the number of parturients who had a duration of labor of 6 h or more. However, the differences in the percentages of patients who developed hyperthermia did not reach statistical significance.

The low incidence of hyperthermia in our patients limited our ability to test the hypothesis that patients given ropivacaine alone would have more hyperthermia than patients assigned to remifentanil alone or to ropivacaine combined with remifentanil or acetaminophen. For example, the increase in oral temperature over time was greatest in patients given ropivacaine alone, but the difference was small (≈0.2°C) and not statistically significant. Ropivacaine patients were also more likely to become hyperthermic (14%) than the others (range, 2%–8%), a difference that, again, was not statistically significant. On the other hand, patients given ropivacaine alone had significantly greater maximum oral temperature increases during labor (0.7°C vs 0.3°C–0.5°C; $P = 0.013$) than patients in the other groups.

Our general theory for hyperthermia during epidural analgesia is that hyperthermia is a normal fever in response to peripartum events, such as the release of endogenous pyrogens from the placenta or, presumably rarely, maternal infection. Epidural analgesia per se does not impair febrile responses [10], whereas low-dose opioids do [10,12]. This is the critical point, because control patients in studies evaluating hyperthermia during epidural analgesia are usually given opioids to ameliorate pain. Thus, fever may be inhibited in these patients by the opioids, whereas it is expressed normally in those having epidural analgesia. There have been no definitive conclusive studies regarding the effect of intravenous opioids on thermal regulation during labor analgesia.

Our results are consistent with the theory that low-dose opioids inhibit fever in patients without epidural analgesia: among the four treatment groups, the maximum increase in core temperature and in the fraction of patients becoming hyperthermic was greatest in the ropivacaine-alone group and least in the patients given remifentanil alone. Our observation that remifentanil administration ameliorates hyperthermia contrasts with the report by Gross et al. [19], but is similar to the results reported by Negishi et al. [10]. These authors [10] showed that fever was normally manifested during epidural analgesia, but was suppressed by low doses of intravenous opioids. If the theory that low-dose opioids inhibit fever in patients without epidural analgesia is correct, the incidence of fever among patients receiving systemic opioids alone should be lower than the incidence in those receiving neither epidural nor systemic opioid analgesia. This may not be the case, as shown by Gross et al. [19], who have suggested that systemic opioids do not act as antipyretics; therefore, the concept that fever associated with epidural analgesia is caused by the antipyretic effect of opioids may not be correct. Why the results should so differ remains unclear. But, given the limitation of each study (little hyperthermia in our study, retrospective analysis in the study by Gross et al. [19]), it is clear that additional study is required to find more definitive answers.

In our study, there were also fewer patients with hyperthermia (although not significantly so) in those receiving ropivacaine combined with remifentanil than in those given remifentanil alone, even though these patients required little remifentanil. This observation suggests that hyperthermia is inhibited by opioids, rather than being caused by epidural analgesia per se. Similarly, there was also a nonsignificant reduction in hyperthermia in patients given acetaminophen. This observation is consistent with elevated temperatures being a regulated fever rather than passive hyperthermia, but the finding that the magnitude is trivial is consistent with a large randomized trial showing that acetaminophen does not prevent fever during epidural analgesia for labor [4]. The interpretation of the additive effects of simultaneous administration of remifentanil or acetaminophen on epidural analgesia is difficult due to our small patient population. It is speculated that the simultaneous administration of acetaminophen may attenuate a febrile reaction.

The scores on the visual analogue pain scale (VAPS; which is a linear function calculation of pain intensity) [21] in the remifentanil-alone group were nearly twice those of the patients in the other groups. Remifentanil alone, therefore, provided notably inferior pain relief compared with epidural analgesia. It is unlikely that pain per se influences core temperature; but if anything, it would cause vasoconstriction via sympathetic activation and, therefore, hyperthermia. That pain relief was so much better with ropivacaine than with opioid alone indicates the importance of epidural analgesia and the need to determine the etiology of epidural-associated hyperthermia.

The maximum forearm-finger gradients were lowest (showing less vasoconstriction) in our remifentanil-alone group. An increase in this gradient is usually produced by vasoconstriction in order to maintain central temperature. Vasoconstriction in hyperthermic parturients may increase the threshold of thermoregulation; therefore, febrile reactions could occur during epidural analgesia. Low doses of opioids have been shown to impair thermoregulatory vasoconstriction in response to cold exposure [13] or fever [10]; but, if that were the sole explanation, we would expect the Ropivacaine and remifentanil and ropivacaine and acetaminophen groups to have had comparable gradients, because the increase in core temperatures was similar. In fact, that was not the case; gradients were reduced only in the remifentanil-alone patients. This result suggests that a nonthermoregulatory factor dominated. Among the likely possibilities is that epidural analgesia causes lower-body sympathectomy vasodilation. To maintain comparable mean arterial pressure, a degree of upper-body vasoconstriction would be required, and this would be manifested as large forearm-minus-fingertip skin-temperature gradients.

There are four reliable core-temperature monitoring sites: the pulmonary artery, nasopharynx, distal esophagus, and tympanic membrane thermocouples or thermistors. (Infrared aural canal thermometers are not generally sufficiently accurate for thermoregulatory research—or even routine clinical care [22]). Among these, only tympanic membrane temperatures could have been used in our patients. However, tympanic membrane probes are tricky to insert correctly and they are a bit uncomfortable. Thus, we elected to carefully record oral temperatures in our patients. Under the circumstances of our study, it is likely that oral tempera-

tures reliably reflected core temperature. Furthermore, various previous reports of hyperthermia during epidural analgesia have been based on oral temperatures [3,19].

In summary, opioids inhibit fever in patients not given epidural analgesia. This result is consistent with the theory that fever associated with pyrogenic factors related to labor is suppressed in patients not given epidural analgesia (who require opioids for pain management), whereas it is expressed normally in patients given epidural analgesia.

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References

1. Philip J, Alexander JM, Sharma SK, Leveno KJ, Mc Intire DD, Wiley J. Epidural analgesia during labor and maternal fever. Anesthesiology. 1999;90:1271–5.
2. Lieberman E, Lang JM, Frigoletto F, Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. Pediatrics. 1997;99:415–9.
3. Herbst A, Wolner-Hanssen P, Ingemarsson I. Risk factors for fever in labor. Obstet Gynecol. 1995;86:790–4.
4. Goetzl L, Rivers J, Evans T, Citron DR, Richardson BE, Lieberman E, Suresh MS. Prophylactic acetaminophen does not prevent epidural fever in nulliparous women: a double-blind placebo-controlled trial. J Perinatol. 2004;24:471–5.
5. Lieberman E, Cohen A, Lang J, Frigoletto F, Goetzl L. Maternal intrapartum temperature elevation as a risk factor for cesarean delivery and assisted vaginal delivery. Am J Public Health. 1999; 89:506–10.
6. Goetzl L, Cohen A, Frigoletto F, Ringer SA, Lang JM, Lieberman E. Maternal epidural use and neonatal sepsis evaluation in afebrile mothers. Pediatrics. 2001;108:1099–102.
7. Viscomi CM, Manullang T. Maternal fever, neonatal sepsis evaluation, and epidural labor analgesia. Reg Anesth Pain Med. 2000; 25:549–53.
8. Fusi L, Steer PJ, Maresh MJ, Beard RW. Maternal pyrexia associated with the use of epidural analgesia in labour. Lancet. I. 1989;1250–2.
9. Camann WR, Hortvet LA, Hughes N, Bader AM, Datta S. Maternal temperature regulation during extradural analgesia for labour. Br J Anaesth. 1991;67:565–8.
10. Negishi C, Lenhardt R, Ozaki M, Ettinger K, Bastanmehr H, Bjorksten AR, Sessler DI. Opioids inhibit febrile responses in humans, whereas epidural analgesia does not: an explanation for hyperthermia during epidural analgesia. Anesthesiology. 2001;94: 218–22.
11. Frigoletto F, Lieberman E, Lang JM, Cohen A, Brass V, Ringer S, Datta S. A clinical trial of active management of labor. N Engl J Med. 1995;333:745–50.
12. Negishi C, Kim J-S, Lenhardt R, Sessler DI, Ozaki M, Vuong K, Bastanmehr H, Bjorksten AR. Alfentanil reduces the febrile response to interleukin-2 in humans. Crit Care Med. 2000;28: 1295–300.
13. Kurz A, Go JC, Sessler DI, Kaer K, Larson MD, Bjorksten AR. Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. Anesthesiology. 1995;83:293–9.
14. Kurz A, Ikeda T, Sessler DI, Larson MD, Bjorksten AR, Dechert M, Christensen R. Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. Anesthesiology. 1997;86:1046–54.
15. Vassilieff N, Rosencher N, Sessler DI, Conseiller C. Shivering threshold during spinal anesthesia is reduced in elderly patients. Anesthesiology. 1995;83:1162–6.
16. Rubinstein EH, Sessler DI. Skin-surface temperature gradients correlate with fingertip blood flow in humans. Anesthesiology. 1990;73:541–5.
17. Dashe JS, Rogers BB, McIntire DD, Leveno KJ. Epidural analgesia and intrapartum fever: placental findings. Obstet Gynecol. 1999;93:341–4.
18. Gonen R, Korobochka R, Degani S, Gaitini L. Association between epidural analgesia and intrapartum fever. Am J Perinatol. 2000;17:127–30.
19. Gross JB, Cohen AP, Lang JM, Frigoletto F, Lieberman ES. Differences in systemic opioid use do not explain increased fever incidence in parturients receiving epidural analgesia. Anesthesiology. 2002;97:157–61.
20. Vinson DC, Thomas R, Kiser T. Association between epidural analgesia during labor and fever. J Fam Pract. 1993;36:617–22.
21. Myles PS, Troedel S, Boquest M, Reeves M. The pain visual analogue scale: is it linear or nonlinear? Anesth Analg. 1999;89: 1517–20.
22. Imamura M, Matsukawa T, Ozaki M, Sessler DI, Nishiyama T, Kumazawa T. The accuracy and precision of four infrared aural canal thermometers during cardiac surgery. Acta Anaesthiol Scand. 1998;42:1222–6.