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Epidural Bupivacaine–Morphine Analgesia versus *Patient-controlled Analgesia following Abdominal Aortic Surgery*

Analgesic, Respiratory, and Myocardial Effects

John F. Boylan, M.B., Joel Katz, Ph.D.,† Brian P. Kavanagh, M.B.,‡ John R. Klinck, M.D.,§ Davy C. H. Cheng, M.D.,‖ Wilfrid C. DeMajo, M.B.,# Paul M. Walker, M.D., Ph.D.,** K. Wayne Johnston, M.D.,†† Alan N. Sandler, M.B.‡‡*

Background: **The efficacy and effects of epidural analgesia compared with patient-controlled analgesia (PCA) have not been reported in patients undergoing major vascular surgery. We compared the effects of epidural bupivacaine-morphine with those of intravenous PCA morphine after elective infrarenal aortic surgery.**

Methods: **Forty patients classified as American Society of Anesthesiologists physical status 2 or 3 received general anesthesia plus postoperative PCA using morphine sulfate (group PCA; n = 21) or general anesthesia plus perioperative epidural morphine–bupivacaine (group EPI; n = 19) during a period of 48 h. During operation, EPI patients received 0.05 mg/kg epidural morphine and 5 ml 0.25% bupivacaine followed by an infusion of 0.125% bupivacaine with 0.1% morphine (0.1 mg/ml); group PCA received 0.1 mg/kg intravenous morphine sulfate. Continuous electrocardiographic monitoring (V4 and V5 leads) was performed from the night before surgery until 48 h afterward. Respiratory inductive plethysmographic data were recorded after tracheal extubation. Visual analog pain scores at rest and after movement were performed every 4 h after extubation.**

Results: **Nurse-administered intravenous morphine and time to tracheal extubation were less in group EPI, as were visual analog pain scores at rest and after movement from 20 to 48 h. Complications and the duration of intensive care unit and hospital stay were comparable. There was a similar, low incidence of postoperative apneas, slow respiratory rates, desaturation, and S-T segment depression.**

Conclusions: **Epidural morphine–bupivacaine is associated with reduced early postoperative intravenous opioid requirements, more rapid tracheal extubation, and superior analgesia after abdominal aortic surgery, with comparable respiratory effects. (Key words: Apneas; continuous monitoring; epidural local anesthetics; epidural opioids; outcome.)**

BOTH systemic intravenous opioids and epidural analgesia using opioids either alone or in combination with local anesthetic agents provide good-quality analgesia after major surgery, but little comparative data exists on their efficacy and adverse effects in high-risk patients. Epidural opioids have a significant incidence of respiratory depression after major surgery, and their risk–benefit relationship is not clear.[1] Patient-controlled analgesia (PCA) has emerged as the standard technique for which no contraindications exist, but adverse respiratory effects have been reported, especially in elderly patients.[2] Epidural opioid–local anesthetic combination analgesia

* Research Fellow, Department of Anaesthesia.

† Associate Professor, Departments of Public Health Sciences and of Anaesthesia, University of Toronto; Psychologist-in-Chief, The Toronto Hospital.

‡ Assistant Professor, Departments of Anaesthesia, University of Toronto, The Toronto Hospital, and Mt. Sinai Hospital.

§ Staff Anaesthetist, Department of Anaesthesia.

‖ Associate Professor, Departments of Anaesthesia, University of Toronto, The Toronto Hospital, and Mt. Sinai Hospital.

Assistant Professor, Department of Anaesthesia, University of Toronto.

** Professor, Department of Surgery, University of Toronto; Surgeon-in-Chief, The Toronto Hospital.

††Professor, Department of Surgery, University of Toronto, and Division of Vascular Surgery, Department of Surgery, The Toronto Hospital.

‡‡Professor, Department of Anaesthesia, University of Toronto; Anaesthetist-in-Chief, The Toronto Hospital and Mount Sinai Hospital.

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Address reprint requests to Dr. Sandler: Anaesthetist-in-Chief, Department of Anaesthesia, BW 4-643, The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4. Address electronic mail to: asandler@torhosp.on.ca

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may provide superior analgesia to epidural opioids given alone,[3] but the respiratory effects of such combinations have not been described.

The primary aims of this study were to compare the efficacy and respiratory effects of perioperative epidural administration of morphine–bupivacaine relative to a standard regimen of intravenous nurse-administered morphine, followed by intravenous PCA morphine. The effects of both analgesic regimens on respiratory function were compared using respiratory inductance plethysmography and pulse oximetry. A secondary aim was to investigate the daily incidence of S-T segment depression and its relationship to analgesic technique.

Materials and Methods

Patient Selection

The study protocol was approved by The Toronto Hospital Committee for Research on Human Subjects. Forty patients classified as American Society of Anesthesiologists physical status 2 and 3 who were undergoing elective infrarenal aortic aneurysm repair or aortobifemoral bypass grafting gave written informed consent to participate. Exclusion criteria included coagulopathy or anticoagulant therapy precluding randomization to epidural analgesia; preoperative chronic analgesic use or substance dependence; previous adverse reactions (other than nausea) to narcotic analgesics; and documented cerebrovascular disease or other neuropsychiatric illness, including a history of postoperative confusion. Patients with preoperative left bundle-branch block, cardiac glycoside use, or those with indwelling pacemakers were excluded from S-T segment monitoring.

Patient Allocation

Because we were precluded ethically from epidural placebo administration in patients scheduled for intraoperative heparinization, the study followed a randomized open design. After recruitment, patients received instruction in visual analog score (VAS) pain assessment and were randomly assigned to receive analgesia *via* (1) intraoperative and postoperative nurse-administered epidural morphine–bupivacaine (group EPI) or (2) intraoperative morphine sulfate, followed by nurse-administered morphine sulfate and then PCA morphine (group PCA).

Preoperative Management and Anesthesia

Beginning the evening before surgery, eligible patients underwent continuous S-T segment recording with a clinically validated[4,5] real-time S-T trend monitor (Monitor One; Q-Med Inc., Milwaukee, WI), with modified bipolar V4 and V5 chest leads placed as previously described.[6] S-T depression was defined as horizontal or downsloping S-T segment depression of 1 mm or more extending at least 60 ms beyond the J-point and lasting >60 s. Hard copy records of S-T depression were verified by an investigator (D.C.H.C.) who was blinded to the anesthetic technique.

Patients received premedication with 1 or 2 mg sublingual lorazepam 2 h before surgery together with routine prescription medications as appropriate. Before induction of anesthesia in patients in group EPI, an epidural catheter was placed at the L2–L3 or L3–L4 interspace, and a 3-ml dose of 2% lidocaine plus 1/200,000 epinephrine was injected. An additional 7 ml of 2% lidocaine was injected over 20 min. Anesthesia was induced in all patients with fentanyl (10–15 μg/kg) and sodium thiopental (1 or 2 mg/kg) and maintained using isoflurane, nitrous oxide, and oxygen. After tracheal intubation, patients in group EPI received 10 ml 0.25% bupivacaine over 20 min. After aortic unclamping and hemodynamic stabilization, EPI patients received 0.05 mg/kg epidural morphine and 5 ml 0.25% bupivacaine, whereas PCA patients received 0.1 mg/kg intravenous morphine sulfate. An epidural infusion of 0.1 mg/ml preservative-free morphine, and 0.125% bupivacaine was begun at 4 ml/h in all EPI patients. At completion of surgery, neuromuscular blockade was reversed with neostigmine-glycopyrrolate, and patients were transferred, with endotracheal tubes in place, to the surgical intensive care unit (SICU), as was routine practice when this study was performed.

Postoperative Monitoring

After patients were admitted to the SICU, mechanical ventilatory support was continued until their temperatures were normal and they were hemodynamically stable, awake, cooperative, and able to generate an adequate vital capacity and negative inspiratory force. Nurse-administered morphine sulfate was permitted in both groups for early postoperative analgesia. A four-point, patient-rated, numeric rating scale was used to assess pain while patients were still mechanically ventilated (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Sedation was scored by an experienced observer using a six-point scale[7] at hourly intervals until tracheal extubation. The sedation scale consisted of the following scores: 1 = patient anxious and agitated or restless or both; 2 = patient cooperative,

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oriented, and tranquil; 3 = patient responds to commands only; 4 = patient responds briskly to a light glabellar tap or loud auditory stimulus; 5 = patient responds sluggishly to a light glabellar tap or loud auditory stimulus; 6 = patient does not respond at all to a light glabellar tap or loud auditory stimulus.

Decisions concerning weaning from ventilation were made by SICU staff uninvolved in the study, guided by the unit protocol.

After tracheal extubation, pain was assessed using a 10-cm VAS with 0 and 10 labeled as "no pain" and "worst pain imaginable," respectively.[8] The VAS scores were obtained at four hourly intervals at rest (VAS-R) and on movement (VAS-M) until 48 h after admission to the SICU. In group EPI, epidural bupivacaine–morphine infusions (0.125% bupivacaine, 0.1 mg/ml morphine) were continued at 4 ml/h and adjusted in response to patient status. Inadequate analgesia (VAS-R >4) was treated by a 5-ml bolus of epidural 0.25% bupivacaine and 0.05 mg/kg morphine followed by an increase in the infusion rate by an increment of 2 ml/h. To minimize unnecessarily high dosages, sustained low pain scores (VAS-M ≤3 for 4 h) mandated a decrease in the infusion rate by 2 ml/h to a minimum of 4 ml/h. Patients in group PCA received nurse-administered morphine sulfate for analgesia until they were deemed able to use a PCA infusion device (Life Care II Infuser, Abbott, Chicago, IL) programmed to deliver intravenous morphine sulfate (1-mg bolus), with a 6-min lock-out period, a 4-h maximum dose of 30 mg, and with no continuous background infusion. No other analgesic agents were used.

Postoperative Assessment

Immediately after tracheal extubation, respiratory monitoring was begun using respiratory inductance plethysmography (NIMS, Miami Beach, FL) and pulse oximetry (model N-100; Nellcor, Hayward, CA). After a setup and calibration procedure,[9] the average respiratory rate was recorded continuously in 5-min epochs, and episodes of apnea (15-s intervals with no tidal volume >100 ml) and slow respiratory rate (any 5-min interval with an average respiratory rate <10 breaths/min) were recorded. All episodes of oxygen saturation <90% were noted.

Patients were monitored continuously for 48 h by a trained research observer who verified data and revalidated respiratory inductance plethysmography function when necessary. Adverse effects (pruritus, nausea, motor blockade) were recorded if present. All patients had indwelling urinary catheters for the duration of the study.

Withdrawal of Patients from the Study

Withdrawal criteria included (1) failure of surgery to proceed as planned and (2) development of postoperative complications limiting assessment. In cases of withdrawal, data collected up to the time of discontinuation were retained for analysis.

Statistical Analysis

Before the study was begun, a sample size calculation was performed. Based on anticipated control (PCA) VAS-M scores of 6 ± 2.5 (mean ± SD), we calculated a sample size such that a between-group mean difference in postoperative VAS-M of 2, with reduced pain scores in group EPI, would (1) permit a type 1 error rate of one-tailed $\alpha = 0.05$, and (2) under the alternate hypothesis retain the null hypothesis with a type 2 error of $\beta = 0.20$ (*i.e.*, power equal to 0.80). Therefore we estimated that a total sample size of 40 patients would be required.

Demographic data were analyzed using one-way analysis of variance or Fisher's exact test as appropriate. Sedation scores, numeric rating scale pain scores, and nurse-administered morphine during ventilation were compared between the groups using the Mann-Whitney U test. The Bonferroni type 1 error rate adjustment (alpha/number of tests) was used to correct for multiple tests of significance. The VAS pain scores were analyzed by three-way analysis of variance, with group as the between-group factor and pain type (VAS-R, VAS-M) and time after surgery as the two repeated-measures factors. Respiratory variables were analyzed by two-way analysis of variance, with group as the between-group factor and time after surgery as the repeated measures factor. Significant interaction effects were analyzed by simple main effects using a pooled mean square error and Satterthwaite's adjusted degrees of freedom.[10] Continuous data are presented as mean ± SD or median ± interquartile range (Q1–Q3) as appropriate; categorical data are presented as frequencies. Initial data analysis was by intention to treat for all variables. Statistical significance was inferred for $P \leq 0.05$.

Results

Demographic and Surgical Variables

Table 1 summarizes demographic and surgical data for the two groups (EPI = 19, PCA = 21). Treatment groups

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Table 1. Demographic Characteristics and Surgical Variables for the Two Groups

	EPI (n = 19)	PCA (n = 21)
Age (yr)	69.9 (8.4)	68.1 (9.2)
Weight (kg)	77.6 (10.6)	75.4 (11.0)
Height (cm)	173 (8.8)	174 (13.2)
Sex (M/F)	17/2	16/5
Procedure (n): AAA/ABF	15/4	12/9
β-Blocker (n)	6	3
Diuretic (n)	2	3
Calcium channel blocker (n)	4	1
Nitrate (n)	1	3
ACE inhibitor (n)	4	2
Previous MI/CAD	2/8	4/10
Smoker (n)	11	15
Pack-years of cigarettes	43 (5)	51 (6)
Duration of surgery (min)	188 (12)	227 (13)
Estimated blood loss (ml)	1,017 (844)	1,610 (1,155)
Fentanyl (μg)	800 (180)	895 (317)
Cross-clamp (min)	51 (26)	50 (18)
Fluid balance (ml)	3,282 (1,250)	3,202 (1,831)
Postoperative hemoglobin (g/L)	108 (8.8)*	99 (9.2)
Survival (n)	19	21

Values are mean (SD) or frequency (n).

MI = myocardial infarction; CAD = coronary artery disease; AAA = abdominal aortic aneurysm; ABF = aortobifemoral repair; ACE = angiotensin-converting enzyme.

* $P = 0.02$.

were similar with regard to age, sex, procedure, preoperative medication, intraoperative fentanyl dosage, and perioperative fluid balance. Time to tracheal extubation was shorter in patients in group EPI. Postoperative hemoglobin concentrations were significantly higher in group EPI.

Table 2 summarizes the duration of hospital stay and complications. Durations of SICU and hospital stay were comparable for the two groups. Two patients in group EPI had their infusions discontinued because of severe refractory pruritus. One patient was switched to epidural bupivacaine-fentanyl 20 h after admission, whereas a second patient received PCA with meperidine at 30 h. One group EPI patient received 0.08 mg naloxone with temporary discontinuation of his infusion because of an elevated arterial P_{CO_2} (58 mmHg) and a respiratory rate of 10/min 9 h after SICU admission. One PCA patient received 0.1 mg naloxone 10 h after SICU admission.

No patient died. The incidence of severe perioperative complications was similar in both groups. One patient in each group sustained a nonfatal myocardial infarction. A nonfatal myocardial infarction and cardiogenic shock developed in a patient in group PCA on the second postoperative day; arm pain and elevated cardiac enzymes developed in a patient in group EPI 5 days after surgery. One patient in group PCA experienced postoperative confusion that was later attributed to alcohol withdrawal.

Postoperative Period

Tracheal Extubation. The mean (SD) time to tracheal extubation was significantly ($P = 0.0006$) shorter for group EPI (6.7 ± 4.8 h) than for group PCA (13 ± 8.3 h). Figure 1 shows the cumulative percentage of patients extubated as a function of time after admission to the SICU. By 20 h after SICU admission, all group EPI patients and 14 patients receiving PCA were extubated successfully. By 24 h after SICU admission, all group PCA patients were extubated successfully.

Sedation. As the patients in group EPI were extubated earlier, analyses of early sedation data are limited to the first 6 h because of large divergences in patient sample sizes thereafter. All patients had comparable sedation levels on admission to the SICU and during the following 6 h.

Analgesia. Median nurse-administered intravenous morphine requirements were significantly less in group EPI for the initial 4 h of ICU admission (0 [0 to 0] *vs.* 10 [7.5 to 14], $P = 0.01$). Four of the 19 patients in group EPI received intravenous morphine from the nurse between 0 and 4 h. No further intravenous morphine was administered thereafter. PCA consumption decreased during the study, with usage significantly less for the period 40–48 h compared with 20–28 h.

The quality of analgesia during ventilation was comparable in the two groups across the first 6 h after operation. Visual analog scale pain scores were analyzed initially by intention to treat. The VAS-R (fig. 2, top) and VAS-M (fig. 2, bottom) pain scores were consistently and

Table 2. Hospital Stay and Complications

	EPI (n = 19)	PCA (n = 21)
ICU stay (days)	2 (1–2)	2 (2–2)
Hospital stay (days)	13 (10–17)	14 (13–15)
Nausea/vertigo (n)	1	3
Pruritus (n)	2	0
Opioid antagonist (n)	1	1
Regimen failure (n)	2	0
Confusional state (n)	0	1
Pulmonary edema (n)	2	1
Myocardial infarction (n)	1	1
Pneumonia (n)	2	0
GI hemorrhage (n)	0	1

Values are median (interquartile range) or frequency (n).

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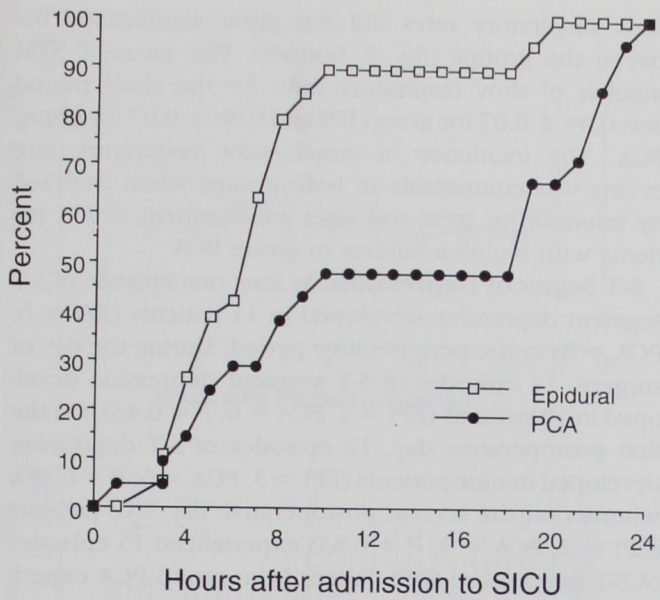
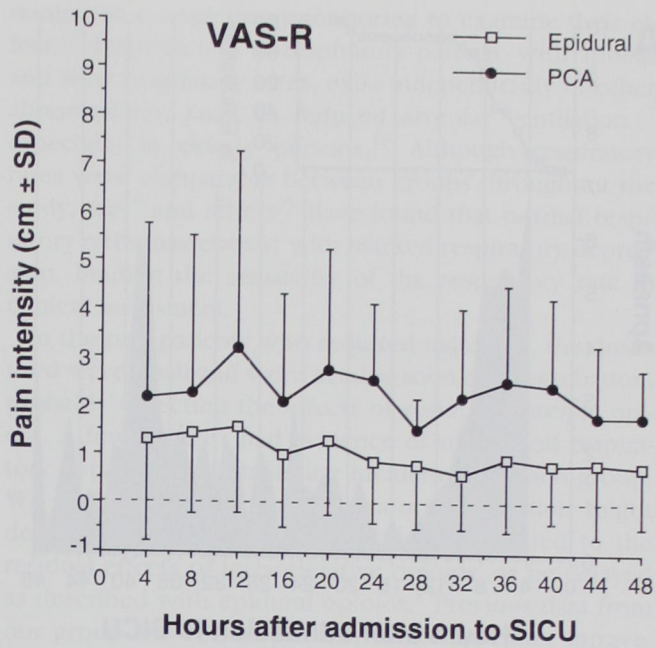


Fig. 1. The cumulative percentage of patients extubated as a function of time after admission to the surgical intensive care unit.



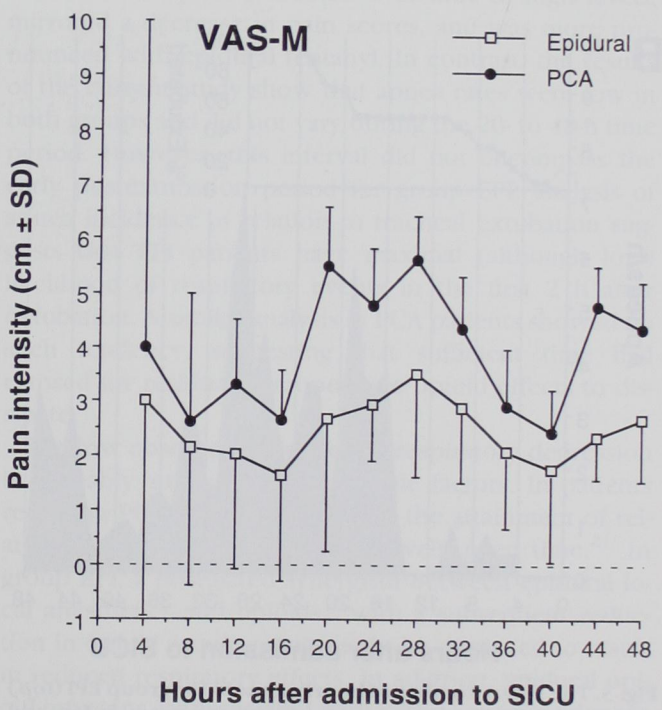


Fig. 2. Visual analog pain scores at rest (VAS-R) and after movement (VAS-M). The VAS-R pain scores were significantly lower in group EPI than in group PCA and did not change significantly with time. The VAS-M pain scores were lower in group EPI and changed significantly over time in both groups, with nadir values at 36–40 h.

significantly less in group EPI compared with those in group PCA across the 48-h period ($P = 0.002$). The VAS-M scores were significantly greater than VAS-R scores for both groups ($P = 0.0001$). Pain scores exhibited different responses over time ($P = 0.0001$); resting pain scores in both patient groups decreased, although not significantly, during the study period, whereas VAS-M scores decreased significantly over time, with nadir values for the period between 36 and 40 h. On reanalysis of VAS data by treatment received, incorporating group EPI patients with regimen failure in group PCA, pain scores and intergroup differences were not significantly changed.

The mean ± SD epidural infusion rate (4.3 ± 1.3 ml/h) was constant for the group as a whole for the entire study period (minimum = 3.8 ml/h; maximum = 4.9 ml/h). Ten patients in group EPI required a total of 45 alterations in infusion rate during the study period (26 increases, 19 decreases), a mean of 2.4 adjustments per patient.

Respiratory Effects. There was a comparable, low incidence of apneic events in the EPI group (fig. 3A) and the PCA group (fig. 3B) from 20 through 48 h, with little change over time. The incidence of apneas was reanalyzed as a function of time elapsed since tracheal extubation (fig. 4, top). In group EPI, the mean apnea rate was significantly greater in the first 2 h after extubation compared with the subsequent 10 h. The incidence of

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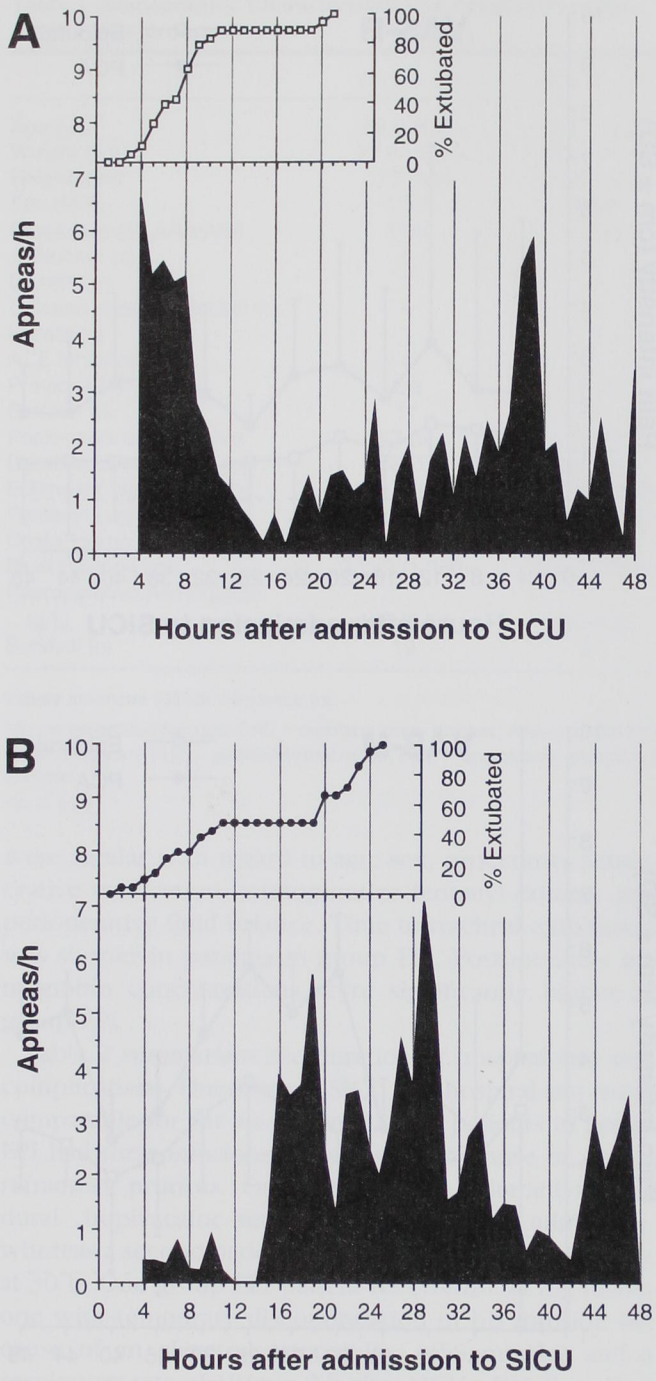

Fig. 3. The mean number of hourly apneas for group EPI (*top*) and group PCA (*bottom*). Apnea rates were extremely low and comparable in both groups. The inset panel in each figure shows the percentage of patients extubated as a function of time to permit a visual inspection of the relationship between the number of respiratory events and the number of patients extubated.

slow respiratory rates did not differ significantly between the groups (fig. 4, bottom). The mean ± SEM number of slow respiratory rates for the study period was 0.09 ± 0.07 for group EPI and 0.08 ± 0.07 for group PCA. The incidence of apneic/slow respiratory rate events was comparable in both groups when analyzed by intention to treat and after reassignment of EPI patients with regimen failures to group PCA.

S-T Segment Depression. At least one episode of S-T segment depression developed in 14 patients (EPI = 6, PCA = 8) in the perioperative period. During the day of surgery, 14 episodes of S-T segment depression developed in 10 patients (EPI = 4, PCA = 6; $P = 0.43$). On the first postoperative day, 12 episodes of S-T depression developed in nine patients (EPI = 3, PCA = 6; $P = 0.28$), whereas on the second postoperative day, five patients (EPI = 2, PCA = 3, P = 0.83) experienced 15 episodes of S-T depression. One patient from group PCA experienced 11 episodes of S-T depression during evolution of a non-Q wave myocardial infarct.

Discussion

Epidural analgesia using morphine-bupivacaine was associated with shorter times to tracheal extubation and reduced requirements for nurse-administered morphine sulfate, compared with morphine-based PCA. From 20 h onward, epidural analgesia was associated with superior pain relief compared with systemic morphine. One half of the group EPI patients required adjustments of their infusion rates, but these tended to be short term, and pain scores and analgesic infusion rates were relatively stable over time.

Previous work has examined analgesic efficacy in terms of simple resting VAS scores, whereas more recent data have examined the effect of interventions on pain associated with mobilization. Epidural opioids may provide nearly complete analgesia at rest but suboptimal relief on movement, a state called "differential analgesia."[3] Our data confirm that epidural analgesia using opioid and local anesthetic combinations is highly effective in reducing movement-associated pain, and that regardless of analgesic modality, VAS-M values gradually decreased toward VAS-R levels during the first 48 h after operation. The nadir values for VAS-M at 36 and 40 h have not been reported before and are not preceded by peaks in analgesic usage for either group. They may represent a cumulative effect of analgesic administration up to that point; however, despite analgesic consump-

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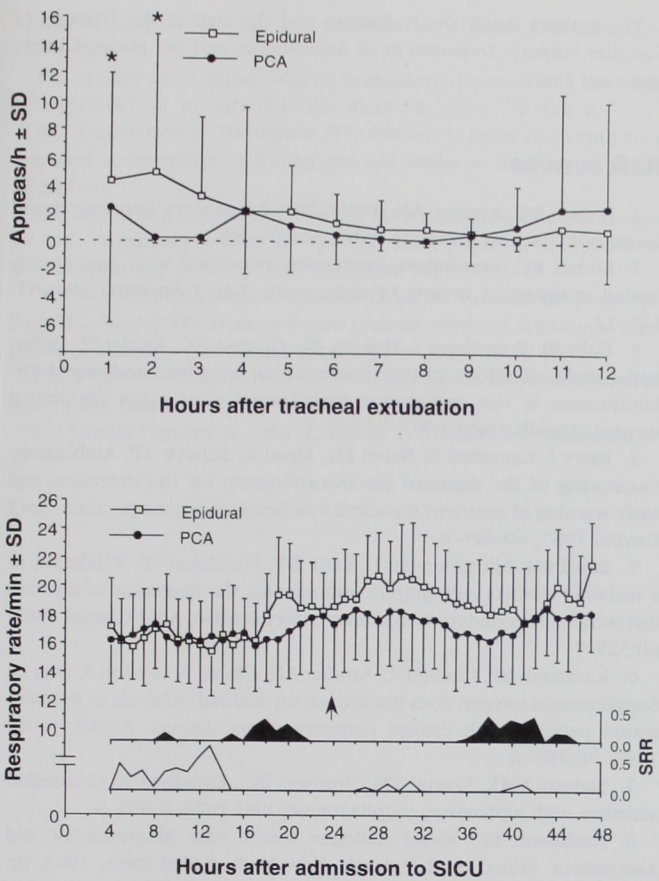

Fig. 4. The mean number of postextubation apneas depicted as a function of time after tracheal extubation (*top panel*). In group EPI, there were more apneas in the first 2 h compared with the remaining first 12 h after extubation (*$P < 0.05$). The mean respiratory rate and mean number of slow respiratory rates are shown for the two groups (*bottom*). The respiratory rate and number of slow respiratory rates did not differ significantly over time or between groups. The arrow refers to the point when all patients were extubated.

tion continuing at similar levels, VAS-M values subsequently increased again. Because this time interval corresponds to the period between midnight and 4:00 A.M., it is possible that lowered scores during this time reflect an interaction between sleep state and analgesia, or they may represent some form of nondiurnal cyclical variation in pain score, as previously described for intramuscular opioids (although absent for PCA) in orthopedic surgery.[11]

Regardless of the route of administration, continuous infusions of opioids given by either fixed or variable rates are associated with a high incidence of respiratory abnormalities.[12–16] Techniques using patient feedback or adjunctive agents without respiratory depressant effects are attractive, but no studies have used continuous noninvasive respiratory monitoring to examine their effect.[17] Disturbances in respiratory pattern, with apneas and slow respiratory rates, exist independently of other abnormalities, such as reduced alveolar ventilation,[17] especially in elderly persons.[18] Although respiratory rates were comparable between groups throughout the study, we[19] and others[20] have found that normal respiratory rates may coexist with marked respiratory depression, limiting the sensitivity of the respiratory rate in clinical assessment.

In the two patients who required naloxone, the doses used were small and were needed soon after extubation, probably reflecting the effects of residual systemic opioid. A few patients had evidence of subclinical respiratory depression, with similar incidences in each group. We had anticipated that respiratory depression might develop either shortly after extubation, related to the residual effects of intraoperative opioids, or be delayed as described with epidural opioids.[1] Previous data from our group showed in patients receiving either intravenous or epidural fentanyl[15] after thoracotomy that the incidence of apnea increased over time to high levels, mirrored a decrease in pain scores, and was more pronounced with epidural fentanyl. In contrast, the results of the current study show that apnea rates were low in both groups and did not vary during the 20- to 48-h time period. However, this interval did not encompass the early postextubation period for group EPI; analysis of apnea incidence in relation to tracheal extubation suggests that EPI patients have maximal (although low) likelihood of respiratory events in the first 2 h after extubation. A similar analysis in PCA patients showed no such tendency, suggesting that sufficient time had elapsed for residual intraoperative opioid effects to dissipate.

The low observed incidence of respiratory depression is probably attributable to multiple factors. In patients receiving PCA, these may include the attainment of relatively stable systemic opioid levels over time.[21] In group EPI, a postulated synergism between epidural local anesthetics and opioids,[3] with a subsequent reduction in opioid requirement, might be expected to result in reduced respiratory effects. In addition, epidural opioid infusions are associated with lower apnea incidences than intermittent bolus regimens.[22] Finally, the emphasis in our protocol on downward adjustment of infusion rates, maintaining the minimum dosage that can provide good-quality analgesia, may also have contributed to the low incidence of apnea.

Although we anticipated that the use of epidural

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local anesthetic agents might be associated with increased perioperative fluid requirements, the similar fluid balance observed suggests that the autonomic effects of the regimen do not significantly affect usual clinical practice. In the current study, maintenance of epidural local anesthesia was not initiated until after hemodynamic stability was established after aortic unclamping. This is in contrast to the experience of Baron *et al.*,[23] who reported a markedly increased intraoperative use of pressor agents; however, these investigators infused higher doses of local anesthetic agents during operation *via* the thoracic epidural route. Despite similar fluid balance and a nonsignificant difference in intraoperative blood loss, group EPI patients appeared to have higher postoperative hemoglobin values. Putative reductions in blood loss associated with regional anesthesia in the past have been confined mainly to lower body procedures, and previous work[24] does not remark on a relationship during major cavitary surgery. Thus the reason for our *post hoc* observation on postoperative hemoglobin remains unclear.

With one exception, S-T segment depression in this study was sporadic and not associated with clinical complications. Because electrocardiographic data were analyzed off-line, we could not synchronize the occurrence of S-T depression with other data and could not link these events to contemporaneous pain scores or respiratory events. The current study lacked sufficient power to detect altered S-T segment depression incidence as a function of analgesic technique, because to detect a doubling of baseline incidence from 30% (for $\alpha = 0.05$, $\beta = 0.20$) would have required 40 patients per group.[25] A larger trial[26] has also reported similar but high incidences of myocardial ischemia in patients receiving epidural bupivacaine–meperidine or nurse-administered intravenous morphine, suggesting that the mode of analgesia did not influence cardiac morbidity.

We conclude that in patients undergoing abdominal aortic surgery, epidural infusion analgesia using morphine–bupivacaine is associated with reduced early postoperative opioid requirements, earlier weaning from mechanical ventilation, and superior postextubation analgesia both at rest and on movement. With the exception of a slightly increased apnea incidence immediately after tracheal extubation in patients receiving epidural analgesia, comparable and low levels of respiratory depression and other adverse effects are seen with either modality.

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