◇ This Month in

ANESTHESIOLOGY

■ Predicting Postoperative Cardiac Events following Coronary Artery Bypass Surgery. Fellahi *et al.* (page 270)

To evaluate both the short- and long-term prognostic value of cardiac troponin I (cTnI) concentrations measured after coronary artery bypass graft procedures, Fellahi *et al.* recruited 202 consecutive patients undergoing elective coronary artery bypass surgery at their institution. Blood samples were collected preoperatively and 24 h postoperatively. A technician unaware of the patients' clinical and electrocardiographic data performed cTnI assays. Study participants were divided into two groups according to the peak level of cTnI postsurgery: group 1 included patients with low levels of cTnI (< 13 ng $\cdot$ ml^{-1}) and group 2 included those with high cTnI: ≥ 13 ng $\cdot$ ml^{-1}).

To analyze patients' in-hospital outcomes, the investigators recorded time to discharge from hospital, length of stay in the intensive care unit, Simplified Acute Physiologic Score, nonfatal cardiac events, and in-hospital death. Causes of death were classified as cardiac or noncardiac. The authors also followed the discharged patients for 2 yr after their procedures, evaluating them at 6, 12, and 24 months. Follow-up visits included physical examination, electrocardiography, and transthoracic echocardiography to determine left ventricular ejection fraction.

At 24 h postsurgery, 174 (86%) of the study participants had a low cTnI (range, 1.1–12.6) and 28 (14%) had a high cTnI (range, 13.4–174.6). Four patients from group 1 and one patient from group 2 died in the hospital, all from noncardiac causes (sepsis and acute respiratory failure). Twenty-nine patients were lost to follow-up. Of the 169 patients in group 1 and the 27 in group 2 available for final evaluation, more patients in group 2 had died from cardiac causes within 2 yr of coronary artery bypass surgery. In addition, high cTnI concentrations postsurgery were associated with delayed extubation and prolonged length of stay in the intensive care unit. The authors suggest that the observed short- and long-term associations between cardiac events and cTnI concentrations might indicate that more aggressive measures should be taken to restore or improve the energetic myocardial balance in the subgroup of patients with high cTnI.

■ Developmental Changes in Behavioral Responses to Mechanical and Thermal Stimuli Examined in Rats. Ririe *et al.* (page 443)

To better understand developmental responses to pain stimuli, Ririe *et al.* used a model of acute incisional pain in rats ranging in age from 2 to 16 weeks. Using von Frey filament testing, mechanical withdrawal thresholds were determined before and after surgery. Withdrawal latency to hind-paw radiant heating was also measured before and after surgery at various time intervals.

Under halothane anesthesia, rats received incisions in one hind paw. Animals were allowed to recover from general anesthesia, and withdrawal thresholds to mechanical and thermal stimuli commenced at 4 h postsurgery. As expected, withdrawal threshold to von Frey filament testing decreased significantly after surgery in animals of all ages, with a peak decrease 5 h after the incision. The duration of reduced withdrawal threshold to tactile stimulation varied as a function of age. The median time until the withdrawal threshold of the injured paw returned to within 80% of the contralateral paw was 2 days in the 2-week old rats, 5 days in the 4-week olds, and 8.5 days in the 16-week olds.

In control animals without incisions, withdrawal latency to thermal stimulation was greater in 2-week-old rats than in 4- or 16-week-olds. As with the mechanical testing, paw incisions resulted in hypersensitivity to thermal stimulation, peaking 5 h after surgery in all age groups of rats. Unlike mechanical testing, however, recovery of the injured paw to within 80% of the contralateral paw to thermal testing occurred with a similar time course in all age groups. The more rapid recovery of younger animals from mechanical allodynia, but not thermal hypersensitivity, suggests the presence of developmental differences in modulation of A-fiber sensitization postoperatively. Lack of age difference in recovery to thermal hypersensitivity suggests that sensitization of C-fiber input has a similar time course of resolution of pain over the ages studied in this model. More study is needed to understand postnatal development of pain pathways.

■ Characterizing the Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids. Bernards *et al.* (page 455 and page 466)

In two studies included in this issue, Bernards *et al.* used microdialysis techniques to sample the epidural and intrathecal spaces of immature pigs in a series of experiments to characterize the epidural, intrathecal, and plasma pharmacokinetics of opioids with and without epinephrine.

In the first set of experiments (Part 1), the team administered the study opioids intravenously with and without intramuscular epinephrine, in an effort to determine whether epinephrine influenced opioid pharmacokinetics. In the second set of experiments (Part 2), conducted 1 week after the first, the same doses of opioids were administered epidurally with and without epidural epinephrine. Twenty-eight pigs were given general anesthesia and intubated, and central venous catheters were placed for obtaining blood samples. Each animal was studied twice, once with intramuscular epinephrine and once without (in varied order). Following the collection of baseline blood samples, animals were given intramuscular injections of either saline or saline and epinephrine, to mimic epidural epinephrine injection. Five minutes later, the animals received an IV bolus of two study opioids (one of which was morphine, and the second of which was alfentanil, fentanyl, or sufentanil). Blood samples were then collected at set intervals for 4.5 hours and were stored for later analysis. The experiment (*i.e.*, intramuscular injection of saline or saline with epinephrine, followed by IV opioids) was repeated, and the animals were returned to the vivarium to recover.

A week later, the animals were again anesthetized and instrumented for blood sampling and blood pressure monitoring. A second femoral arterial catheter was placed to allow spinal cord blood flow measurements *via* fluorescent microspheres (injected into the left atrium), and microdialysis probes were placed in the lumbar (L5) and thoracic (T12) epidural spaces, as well as intrathecally at L5. The same opioids, doses, and order of the epinephrine-containing injection were used as for the IV study. The epidural opioids contained radiotracers to facilitate later determination of dialysate concentrations. Samples of epidural fat were also removed from sites adjacent to the dialysis probes at the end of the experiment.

In fluid obtained from the epidural space, the investigators found that the terminal elimination half-life of morphine was shorter than that for any of the other opioids, and that the half-life of sufentanil was the longest. The shorter terminal elimination half-life held true for morphine sampled from the thoracic space as well. However, mean residence time did not different significantly among the different opioids in the thoracic epidural space. In central venous sampling, the dose-normalized peak concentration and area under the concentration–time curve were significantly greater for alfentanil than for the other three opioids.

The investigators also found a strong linear relationship between the hydrophobic character of the opioids and their concentration in epidural fat. For instance, at the lumbar level, the fentanyl content of epidural fat was approximately 32-fold greater than the morphine content. The authors believe that hydrophobic opioids are sequestered in lipoidal environments surrounding the epidural space. Their slow release back into the extracellular fluid of the epidural space results in prolonged elimination half-life and an increased mean residence time. Interestingly, epidural pharmacokinetics did not predict the pharmacokinetics of cerebrospinal fluid, reflecting the complex kinetics of these different compartments. It is not possible to infer drug behavior in one compartment by measuring its concentration in another, note the authors.

Part 2 addresses the effect of epinephrine on epidural pharmacokinetics—and what accounts for its ability to improve the efficacy of epidurally administered drugs. For this primarily descriptive study, the authors drew on the data obtained from sampling opioids in the epidural space, central venous plasma, and epidural venous plasma to calculate relevant pharmacokinetic parameters.

Essentially, the authors found that the pharmacokinetic effects of epinephrine varied by opioid and sampling site. The mean residence time of morphine in the lumbar epidural spaces was increased by epinephrine, whereas the drug decreased the mean residence time of fentanyl and sufentanil. Epinephrine had no effect on the terminal elimination half-life of morphine in the epidural space, but it decreased that of fentanyl and sufentanil. In the lumbar intrathecal space, epinephrine had no effect on the pharmacokinetics of alfentanil, fentanyl, or sufentanil, but it increased the area under the concentration-time curve and decreased the elimination half-life for morphine. As in Part 1, the authors reiterate that the effects of epinephrine on spinal pharmacokinetics of opioids are complex. It is not possible to predict the pharmacokinetic effects of epinephrine in spinal compartments from the measurements of drug concentration in plasma.

■ Interrelationship of Hormonal Status and Pain Sensitivity. Flood and Daniel (page 476)

Flood and Daniel compared the pain-enhancing effects of isoflurane in intact male and female mice to those of castrated male mice and oophorectomized female mice. Mice were tested for withdrawal latency to heat with and without isoflurane before castration or oophorectomy, and intact female mice were tested at each stage of the estrus cycle. An investigator blinded to the treatment group measured the latency from the onset of heat application to the time the mouse moved its hind paw.

The animals in the experimental group were also given steroid treatment (estrogen and testosterone injections) to measure the effects on withdrawal latency during administration of isoflurane. Intact female mice had significantly shorter withdrawal latency while breathing isoflurane concentrations up to 0.4%, whereas intact male mice did not have a pronociceptive response to 0.25% isoflurane under the same testing conditions. After castration or oophorectomy, pain thresholds increased significantly in both genders, with an associated enhancement in the pronociceptive effects of isoflurane.

At stages of the estrus cycle when estrogen levels were low, the female mice showed greater pain enhancement from isoflurane than at high estrogen levels. Treatment with exogenous estrogen in oophorectomy mice reduced isoflurane-induced pain sensitivity. Exogenous testosterone treatment had a similar effect, which did not occur when enzymatic conversion to estrogen was prevented. These findings suggest that estrogen treatment induces a physiologic condition that is resistant to isoflurane pronociceptivity. If the results in mice are shown to be similar in humans, the hormonal status of a patient may interact significantly with residual anesthetic to influence postoperative pain sensitivity.

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