

## ANESTHESIOLOGY

### ■ Do Proinflammatory Cytokines Play a Role in Renal Dysfunction after Bypass? Gormley *et al.* (page 1210)

Gormley *et al.* recruited 20 patients scheduled to undergo coronary artery bypass grafting with use of cardiopulmonary bypass to measure changes in proinflammatory and antiinflammatory cytokines during surgery. Their aim was to determine whether there was a correlation between the magnitude of the plasma proinflammatory response and perioperative proximal tubular damage as measured by urinary *N*-acetyl- $\beta$ -[scap]d-glucosaminidase (NAG)/creatinine and  $\alpha_1$ -microglobulin/creatinine ratios.

Baseline blood samples were obtained before induction of anesthesia, after aortic cross-clamp release, and 2 and 24 h after termination of cardiopulmonary bypass. Urine samples were obtained at baseline, after aortic cross-clamp release, and 2, 6, 24, 48, and 72 h after termination of cardiopulmonary bypass. Plasma and urinary samples were assayed for the proinflammatory cytokines interleukin (IL)-1 $\beta$ , tumor necrosis factor (TNF)  $\alpha$ , and IL-8 and for the antiinflammatory cytokines IL-10, IL-1 receptor antagonist (IL-1ra), and TNF soluble receptor 2 (TNFSr2). Urine also was assayed for NAG, creatinine, and  $\alpha_1$ -microglobulin.

After cardiopulmonary bypass, concentrations of plasma IL-8, IL-10, IL-1ra, and TNFSr2 were increased significantly compared with concentrations measured at baseline. Urinary IL-1ra, TNFSr2, NAG/creatinine and  $\alpha_1$ -microglobulin also were increased. The study showed a positive correlation between plasma TNF $\alpha$  concentrations at 2 h postoperatively and urinary NAG/creatinine ratios at 2 and 6 h postoperatively. Simultaneous with the increase in urinary IL-1ra and TNFSr2, there was a significant increase in proximal tubular dysfunction as indicated by increased urinary NAG/creatinine and  $\alpha_1$ -microglobulin/creatinine ratios. Although a direct causal relation is unlikely, what is likely is that a common mechanism may contribute both to the antiinflammatory cytokines in the urine and to the evidence of renal dysfunction. The authors suggest that the plasma proinflammatory cytokines, once filtered by the glomerulus, not only induce a degree of proximal tubular injury, but also trigger an intense intrarenal antiinflammatory response to allow the safe disposal of the proinflammatory cytokines. Thus, the kidney may be damaged by the inflammatory response it seeks to control.

### ■ Is Use of Patient-triggered Ventilation Feasible in Infants? Takeuchi *et al.* (page 1238)

In seven infants, aged 1-11 months, who had undergone cardiac surgery to repair congenital heart disease, Takeuchi *et al.* randomly applied five levels of pressure control to determine if patient-triggered ventilation could reduce their respiratory workloads before extubation. Baseline data were obtained when the infants recovered spontaneous breathing in the surgical intensive care unit and met weaning criteria, which included, among other indicators, respiratory rate of less than 50 breaths/min and a backup ventilatory rate of 6 breaths/min and pressure control of 7 cm H<sub>2</sub>O. Infants were hyperventilated for 2-3 min to lessen their inspiratory efforts, at which time ventilation settings were switched to T1 of 1.5-2 s, respiratory rate of 10 breaths/min, and pressure control of 16 cm H<sub>2</sub>O. Five levels of pressure control (0, 4, 8, 12, and 16 cm H<sub>2</sub>O) were applied in random order with assist-control mode. Positive end-expiratory pressure was 3 cm H<sub>2</sub>O continuous flow at 20 l/min, and triggering sensitivity, 1.0 l/min. After establishing steady-state conditions, airflow, airway pressure, esophageal pressure (*via* balloons inserted intranasally), and rib cage and abdominal signals of inductive plethysmography were recorded. No sedatives or opioids were administered during measurements, although fentanyl and midazolam were administered during surgery.

All seven infants were extubated successfully 90 min after completion of the final measurements. After extubation, the research team waited 60 min to confirm that the infants were breathing quietly and then repeated esophageal pressure and rib cage and abdomen signal recording of inductive plethysmography and arterial blood gas analysis. The researchers found that, when the level of pressure control was decreased, tidal volume decreased, respiratory rate increased, and minute ventilation and arterial carbon dioxide tension remained constant. The work of breathing and modified pressure-time product at 4 cm H<sub>2</sub>O pressure control and after extubation were significantly greater than at pressure control of 16, 12, and 8 cm H<sub>2</sub>O. Although extrapolation of these results directly to other infant populations is not advised, the authors maintain that pressure-control patient-triggered ventilation with flow triggering could be a feasible strategy for ventilator weaning in infants.

■ Analgesic Effects of Morphine in Healthy Male and Female Volunteers. Sarton *et al.* (page 1245)

In most studies comparing analgesic effects of opioids in men and women, gender comparisons are not the primary focus of investigation. Accordingly, Sarton *et al.* designed a prospective study to compare analgesic effects of a bolus and a short infusion of morphine in healthy male ( $n = 10$ ) and female ( $n = 10$ ) volunteers. Pain was induced by an electrical current *via* two electrodes placed on the skin overlaying the tibia of the left leg. The intensity of the noxious stimulus (pulses of  $0.2 \mu\text{s}$  at 2 Hz) was increased in steps of 10 mA, from the lowest of 10 mA to the maximum of 80 mA, at 6-s intervals. Participants were instructed to state "pain" when the stimulus became painful (pain threshold) and "stop" when the pain became intolerable (pain tolerance). This sequence of increasing stimulus intensity was performed twice at fixed intervals before, during, and after morphine administration. Men were tested by a male researcher, and women were tested by a female researcher.

The researchers observed that baseline pain threshold and pain tolerance currents were similar in both sexes. With intravenous administration, morphine had a greater potency in the women, as well as a slower onset and offset. The causes for sex differences in effect-site morphine concentrations ( $k_{e0}$ ) in the plasma samples obtained in this study were not clear, although the value of  $k_{e0}$  observed in women parallels the  $k_{e0}$  estimate for morphine-induced pupil constriction. These data agree with observed gender differences in morphine-induced respiratory depression and may explain higher postoperative opioid consumption in men compared with women.

■ Mechanisms of Pain Caused by Surgical Incision Investigated in a Rat Model. Vandermeulen *et al.* (page 1294)

Sensitization of the dorsal horn of the spinal cord *via* surgery (termed central sensitization) is not well-defined. Hypothesizing that a surgical incision would produce activation and enhanced responsiveness of single dorsal horn neurons, Vandermeulen *et al.* used a previously developed rat incisional pain model to study spontaneous and evoked activity from individual dorsal horn neurons in the lumbar spinal cord directly. After performing laminectomy in halothane-anesthetized rats, dorsal horn neurons from the lumbar enlargement were identified antidromically and characterized as low threshold, wide dynamic range, or high threshold based on their responses to brush and pinch of the animals' paws. The receptive field for each neuron also was mapped. Then an incision was made within the receptive field. Changes in background activity, punctate mechanical thresholds, receptive field size, and stimulus-response functions were recorded for up to 1 h after incision.

In all cells, incisions produced a strong response and an increase in background activity, which remained increased in 3 of 9 high-threshold neurons and 16 of 27 wide-dynamic-range neurons 1 h later. The mechanical responsiveness was enhanced in 10 of 27 wide-dynamic-range neurons and in 2 of 8 high-threshold cells after incision. Wide-dynamic-range neurons may be the most important for pain signaling, and the increased background activity in these dorsal horn neurons may signal pain at rest after surgery. The receptive field size also expanded beyond the initial area around the incision, indicating a mechanism for amplification of dorsal horn response *via* surgery.

Gretchen Henke