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-β-scopolamidase (NAG)/creatinine and α₁-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)-1β, tumor necrosis factor (TNF) α, 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 α₁-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 α₁-microglobulin also were increased. The study showed a positive correlation between plasma TNFα concentrations at 2 h postoperatively and urinary NAG/creatinine ratios at 2 and 6 h postoperatively. Simultaneously 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 α₁-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.
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 µs 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 28 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.

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