Important pathophysiological background material for managing pneumoperitoneum

Bezold-Jarisch reflex
The Bezold-Jarisch reflex consists of the excessive shallow respiration or abnormally low breathing rate, hypotension and bradycardia in response to certain stimuli. This reflex was originally described in response to chemical agents but it can be elicited by a sudden severe drop of venous return.\textsuperscript{1,2} It results in low heart rate in order to allow enough time for ventricular filling.\textsuperscript{1,2} This effect can be partly or totally attenuated by the baroreceptor reflex, which is the main regulatory hemodynamic mechanism.\textsuperscript{1}

Renal interstitial pressure
Renal interstitial pressure is an important contributor of AKI. Peritubular capillary pressure – which influences the effectiveness of the countercurrent multiplier mechanism – is normally around 7 mmHg.\textsuperscript{3} As the kidney is surrounded by a tight capsule, a ‘dedicated’ renal compartment syndrome can easily evolve.\textsuperscript{4,5} The renal interstitium can be drained through three pathways: through the urinary, the venous and the lymphatic systems. The measurement of venous pressures and flow in the urinary systems is easy to perform, but the pressure or flow of lymphatics can only be estimated, except under experimental conditions. Rather than determining each of them individually, the estimation of net renal perfusion pressure is the clinical tool which can be applied in clinical care (Table 1).

Carbon dioxide: a Janus-faced molecule
The intra-arterial administration of carbon dioxide angiography has been proven to be a safe and non-nephrotoxic method for investigating renal vasculature in human clinical practice.\textsuperscript{6–8} The contradiction can be resolved if one considers the tremendous difference between a few seconds to minutes of blood flow cessation by CO\textsubscript{2} angiogram vs the extrarenal pressure by CO\textsubscript{2} compromising renal perfusion, for up to hours.

Oxidative stress and remote ischemic preconditioning
Elevated IAP results in a temporary deterioration of renal perfusion, flattening the pulsatile arterial wave and diminishing endothelial shear stress.\textsuperscript{9} However, diminished RBF and the subsequent oxidative stress to the kidney tissues remains a significant contributor of AKI. The warm ischemic time over 25-28 minutes during robotic surgery causes a significantly greater drop in GFR in the operated kidney compared to the non-operated kidney during partial nephrectomy.\textsuperscript{10–12} The effect can persist and results in progressive disease up to a stage IV CKD.\textsuperscript{12,13} Comparisons between robotic and open surgeries revealed some uncertainty, since the elimination of pneumoperitoneum did not result in better kidney function in all cases.\textsuperscript{10} In
addition, the length of warm ischemia will largely depend on the proficiency of the operating team.

Under physiologic conditions, approximately 1-2% of human albumin has an altered capacity of binding transitional metals (cobalt, copper, nickel) in its N-terminus called as ischemia-modified albumin (IMA). When ischemia occurs, the Co$^{2+}$ and Ni$^{2+}$ ion binding capacity of albumin decreases rapidly and dramatically due to the ischemia-induced structural changes of the protein. The serum level of IMA reported to be increased during gynecological laparoscopy (0.37 ± 0.06 vs 0.31 ± 0.09, p<0.005; n=33).

The oxidative stress can be aggravated by the endothelial shear stress and can be worsened or alleviated depending of the involvement of nitric oxide synthesis (Supplementary Figure 1). The deleterious effect of reactive oxygen species can effectively be attenuated by (1) intermittent reperfusion (ischemic postconditioning) to allow the protective mechanisms to cope with (mainly through superoxide dismutase, catalase, thioredoxin peroxidase systems, glutathione and glutathione peroxidase family); and (2) increasing the antioxidant capacity (ischemic preconditioning). Surprisingly, remote ischemic preconditioning is also helpful. During ischemic preconditioning, an external compression pressure 30 mmHg above systolic blood pressure is established for 5 minutes, which is followed by a 5-minute deflation period. Three inflation-deflation cycles are recommended before ischemic kidney insult commence.

Intraoperative urine output, as a predictor of AKI

The course of diuresis showed a U-shaped curve in morbidly obese patients reaching its lowest point at 1 hour into the procedure with no notable differences between patients below and above a BMI of 50 kg/m$^2$. Intraoperative urine output generally starts to increase after 150-180 minutes in the non-AKI group, but the urine output continued to decline intraoperatively in those diagnosed with KDIGO defined AKI postoperatively. In major abdominal (mostly liver, colorectal and gastric) surgeries, a urine output of 0.3 ml×kg$^{-1}$×h$^{-1}$ was identified as the critical threshold for increased incidence of postoperative AKI (Odds Ratio [OR]: 2.65, 95% confidence interval, 1.77–3.97; P<0.001). Patients at risk for AKI are those with higher preoperative AKI risk indexes, those that undergo laparoscopy and suffer from intraoperative hemodynamic instability, e.g. more blood loss (over 10 mL/kg) and those with a need for colloid infusion and vasopressor administration. When liver surgery is performed, the risk of renal failure is further increased. Interestingly, blood loss being less than 10 mL/kg in 93% in the oliguric group draws our attention to the importance of a multifactorial approach. Perioperative goal-directed fluid as well as vasoactive and transfusion strategies are recommended for hemodynamic optimization and AKI prevention.

Anesthetic agents and acute kidney injury

Fluoride ion liberated during metabolism of inhalative anesthetic agents may cause nephrotoxicity. This effect is dose dependent, has not been proven for newer agents, and it was minimal in renal transplant recipients.
Sevoflurane can react with the CO₂ absorber producing trifluoro methyl vinyl ether, which is called Compound A. Compound A can cause tubular necrosis and a severe deterioration of renal function in rats.²⁷ This is also dose dependent, but it has never been described in humans, neither during living donor nephrectomy.

References


Supplementary Figure 1. The relevant reactive oxygen and nitrogen radicals contributing to the oxidative stress.