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Editorial

Understanding intrarenal backflow: Intrarenal pressure during ureteroscopy and beyond

The number of ureterorenoscopic procedures for upper urinary tract stone management has increased dramatically during recent years worldwide [1]. Developments in flexible ureteroscope and laser technology have made it possible to successfully address larger and more complex stone scenarios retrogradely. On the other hand, this means that more and more patients are exposed to the potential adverse effects of ureteroscopy [2]. In general, ureteroscopy is considered a safe procedure. However, serious complications and even deaths do occur, and these events are most likely underreported [3,4]. Therefore, it is of utmost importance to focus on the safety aspects of the procedure itself.

Sepsis is considered the most dangerous complication to retrograde ureteroscopic procedures since sepsis is associated to high morbidity and mortality rates. In a recent study of 120 consecutive patients undergoing ureteroscopy for stones or diagnostic purposes, the intrarenal pressure (IRP) was measured using a pressure guidewire (COMET™ II, Boston Scientific, Marlborough, MA, USA) [5]. None of the patients included had urinary tract infection. The mean baseline IRP was found to be 16 mmHg (1 mmHg=0.133 kPa), and the mean IRP during gravity irrigation was 27 mmHg compared to 67 mmHg during pressurized irrigation, which are in line with initial findings by our group [6,7]. Patients were followed for 30 days, and six (5%) patients developed postoperative urosepsis. Worth noting is that in this prospective study, sepsis patients had significantly higher IRPs (mean 82 mmHg) compared to controls (mean 39 mmHg) [5], highlighting the importance of keeping the IRP low during ureteroscopy. On the other hand, not all patients exposed to high IRPs develop infectious complications; therefore, patient specific and procedure-related issues seem to be important as well.

The exact relation between the IRP and septicemia is insufficiently understood, although the most logically event immediately preceding sepsis seems to be intrarenal backflow (IRB) [1,2]. IRB is backflow of urine and irrigation fluid from the collecting system to (1) the renal tubules (pyelotubular backflow), (2) the renal and peri-renal venous system (pyelo-veneous backflow), and (3) the renal and perirenal lymphatic system (pyelo-lymphatic backflow) [1,2]. Additionally, urine and irrigation fluid may escape the collecting system due to rupture, which most often happens at the peri-papillary fornices (forniceal rupture). IRB is thought to be a compensatory mechanism established during fetal development, protecting the growing kidney cells from high pressures when the developing upper urinary tract transiently experiences obstruction. These compensatory mechanisms are transferred to the adult kidney, which is the reason that obstruction with infected urine (pyonephrosis) and ureteroscopy in patients with active urinary tract infection quickly may lead to septicemia. While data on the IRP during human endourological procedures are extensive [8], knowledge on IRB is sparse and mainly generated from animal studies. However, in the latter mentioned studies, interesting data of importance for understanding IRB during ureteroscopy may be emerged.

The medulla of the kidney is divided in several (usually more than eight and less than 20) cone-shaped structures, called the renal pyramids. The base of the pyramids originates at the cortico-medullary junction and ends in the renal papilla that projects into the calyces. The pyramids contain the tubules that transport urine from the cortex to the calyces. The nipple-shape of the normal renal papilla is thought to protect against intrarenal reflux by compression of the ducts of Bellini (medullary collecting ducts), when pressure increases around the papilla. Kidney stone patients often present with abnormal renal papillary anatomy. We found in a consecutive unselected kidney stone population that 25% of patients had compound papillae [9]. In the classic studies [10,11], it was observed that surgically induced vesicoureteral reflux resulted in intrarenal reflux, but only into those segments whose renal collecting ducts exited at compound papillae, in which the anti-reflux

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mechanism is compromised. Thus, stone patients with one or more compound papilla may be at particular risk to infectious complications and fibrosis (renal scarring) due to IRB. Medullary sponge kidney is a relatively rare condition in which the predominant mechanism of stone formation appears to be crystallization due to urinary stasis in dilated inner medullary collecting ducts [9]. Obviously, these patients will experience IRB at lower pressures than patients with normal papillary anatomy [12]. Thus, differences in papillary morphology may—at least in part—explain why some stone patients are more prone to develop complications secondary to increased IRPs during endoscopy. Both compound papillae and medullary sponge kidney can easily be recognized during ureterorenoscopy, and such findings probably should give rise to extra vigilance regarding pressure increases during the procedure. Furthermore, endoscopic evaluations with new high-quality digital ureteroscopes have revealed so-called pitting areas, which appear as crater-like focal erosions of the papillary surface that most likely represent mechanical disruption due to detached stones from Randall's plaques [9,12]. It is conceivable that such lesions also may promote IRB (intrarenal reflux and migration of urine and irrigation fluid into the interstitium). Thus, several morphological papillary changes may contribute to the adverse events of high IRPs during endoscopy [12].

The IRP unequivocally increases during ureterorenoscopy due to irrigation and scope manipulation [1,2]. The physiological IRP is in the range of 0—15 mmHg, equaling 0—20 cmH_2O (1 cmH_2O=0.098 kPa) [1]. As outlined above, threshold for IRB varies with the morphology of the papilla. Based on animal studies and studies during retrograde pyelography in humans, pyelotubular backflow occurs at 20—30 mmHg (27—41 cmH_2O), pyelovenous backflow at 30—50 mmHg (41—68 cmH_2O), and forniceal rupture at 70—200 mmHg (95—272 cmH_2O) [1,2]. Newer studies using dynamic gadolinium-enhanced MRI have suggested, however, that IRB may occur at considerably lower pressures, starting at mean pressures as low as 15 mmHg (20 cmH_2O) [13]. Thus, it seems logic that IRB happens as a continuous function of pressure, initially appearing in the center of the medullary pyramid, where the collecting ducts are less protected against reflux, compared to the peripheral ducts that end on the oblique part of the papillary surface. These findings were in accordance with the pig study by Coulthard et al. [11], showing that damage due to experimental vesicoureteral reflux in some of the less severely affected areas of the kidney, appeared to be limited to the center of the medullary pyramid with normal renal parenchyma at the borders. Additionally, it appears that IRB happens first and at lower pressures in the upper pole [13], which is consistent with compound papillae being more frequently observed in the upper calyces in both human and pig kidneys [11].

In a recent study, histologic changes and fluid extravasation during simulated ureteroscopy in juvenile pig kidneys were examined at various IRPs [14]. Using ink-infused saline irrigation for 30 min at constant pressures ranging from sphygmomanometer settings of 50 mmHg, 100 mmHg, and 200 mmHg with or without ureteral access sheaths, the authors found that increasing irrigation pressure resulted in deeper tissue penetration of ink, and that tissue penetration was higher when a ureteral access sheath was not used. Overall, in kidneys with a ureteral access sheath, a smaller tissue penetration among all pressures were observed, compared to kidneys without an access sheath (6.3% *vs*. 54.5%) [14]. This study was the first to show that ureteral access sheaths not only reduce IRPs during ureteroscopy, but also as a logic consequence of this limit IRB. The limitation of the study is that the experiment was done in *ex-vivo* kidneys, and, thus, data do not consider the dynamics of the system. Recently, for the first time, IRB was documented dynamically *in-vivo* by MRI, using gadolinium-saline solution for irrigation in a pig model [13]. Under controlled irrigation, the IRP was increased while repeating MRI scans until a maximum pressure of 50 mmHg was reached. In all cases, MRI showed early signs of backflow of gadolinium into the renal cortex, and at the end of the experiment (approximately 70 min—equivalent to a standard ureteroscopic stone procedure), a mean of 66% of the cortex was affected by backflow (Fig. 1). IRB was first seen at the renal poles, subsequently spreading to all other areas of the kidney. The mean time to the first visualization of IRB to the cortex was 15 min, and the mean IRP at first visual changes was 21 mmHg, which is considerably lower than previously assumed from *in-vitro* studies [14,15]. The data suggested that IRB is a function of both pressure and time, and it was suggested to use a measure for accumulated ureteroscopy-induced pressure impact on the kidney (IRB multiplied by operation time) to be used for comparison of postoperative clinical outcome in ureterorenoscopic procedures [13]. Subsequent evaluation of renal cortex tissue showed significant up-regulation of the proinflammatory cytokine, monocyte chemoattractant

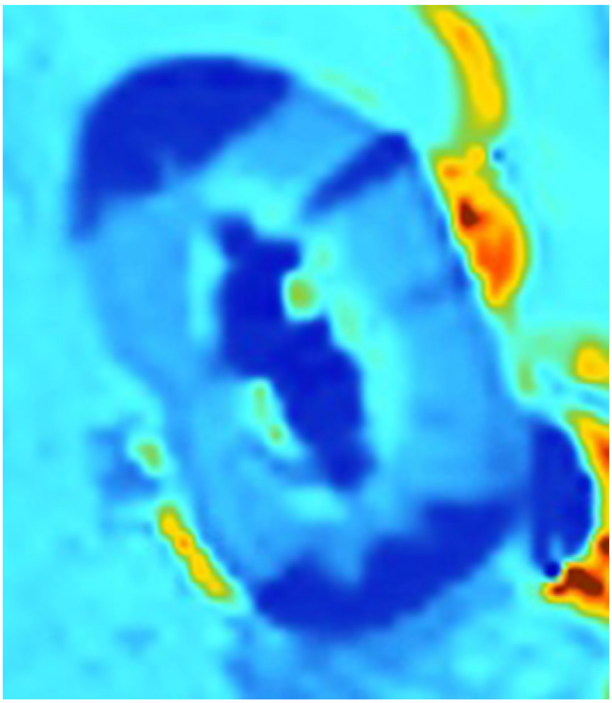

Figure 1 MRI showing intrarenal backflow into the renal cortex during irrigation with gadolinium-saline solution, visualized as pyramid shaped changes first appearing at the upper and lower poles (dark blue).

protein-1, suggesting that early IRB may induce inflammation [13].

Mean IRPs reported during ureterorenoscopy range from 6 mmHg to 146 mmHg (8—199 cmH_2O) [5,7,15], with pressure peaks during forced irrigation as high as 334 mmHg (454 cmH_2O) [5,7]. Consequently, it may be argued that the threshold for IRB is exceeded in almost all ureteroscopies, and in order to reduce potential adverse events of IRB, all measures to reduce the IRP should be taken during the procedures. This includes using as little irrigation as possible and usage of ureteral access sheaths. The ureteral access sheath being a double-edged sword, that on one hand reduces the IRP (and IRB) and on the other hand increases strain on the ureteral wall with potential adverse effects, is presently a controversial issue [16]. As mentioned above, IRB is not only dependable on the IRP but also on papillary morphology. The fact that few studies have been able to directly correlate level of the IRP during ureterorenoscopy to infectious complications and influence on kidney function is probably because papillary morphology and consequently the degree of IRB at a given pressure vary tremendously from patient to patient, further adding to the extreme heterogeneity among kidney stone patients.

In conclusion, data in the literature on IRB during ureterorenoscopy are sparse and come exclusively from animal studies. Nevertheless, IRB is the likely event preceding septicemia following ureterorenoscopy, and IRB seems to be related to the IRP, operation time, and papillary morphology. Thus, morphological features like compound papillae, dilated ducts in medullary sponge kidney and pitting craters must be added to the equation, explaining IRB-related complications in ureteroscopy. Digital ureteroscopes with excellent image quality give us the possibility to acknowledge some of the morphological features that predispose to severe IRB, and, subsequently, we as endourologists can modify the procedures in a personalized stone approach manner, thereby achieving a better balance between efficacy and safety. Furthermore, newer single use ureteroscopes with possibility of the real-time IRP monitoring potentially will give us further knowledge on the relation between the IRP and IRB [17], thus providing us with better tools for preventing adverse events following ureteroscopy. An exciting era in endourology is just around the corner!

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Conflicts of interest

Palle J.S. Osther has been a consultant for Olympus, Copenhagen, Denmark, and Boston Scientific, Copenhagen, Denmark; Helene Jung has been a consultant for Boston Scientific, Copenhagen, Denmark, and Ambu, Copenhagen, Denmark. The other authors declare no conflict of interest.

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