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Intra-Renal Reflux

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Summary. A new model for the study of intra-renal reflux (IRR) is proposed. The renal pelvis of human kidneys, either obtained from cadavers or removed surgically, was injected, at increasing pressures, with dye solutions to investigate intra-renal reflux. To reproduce physiological conditions as closely as possible, arterial perfusion was performed, either continuously or by means of a peristaltic pump, so that a predetermined pressure in the vascular system could be obtained. Comparison was made between results obtained by this technique and the results reported in the literature and previously recorded by the present authors without any perfusion of the vascular system. Our results show significant diffsion of the vascular system. Our results show significant differences in the threshold of IRR compared to data from experiments in which vascular perfusion was not simultaneously performed. It can be concluded that, under physiological conditions, intrarenal flux occurs at pressures of 40 cm H_2O, and pyelovenous reflux at pressures of 60–70 cm H_2O.

Key words: Intra-renal reflux, Kidney, Papilla, Reflux-nephropathy.

Due to the recent increase in endourologic techniques, there is a renewed interest in the physiopathology of distension of renal pelvis, in the laws governing the flowback of fluid from the pyelocalycial cavities at various pressures, in the modalities with which such a backflow occurs (pyelotubular, pyelolymphatic, pyelovenous reflux) and in the severity and distribution of the ensuing pathological lesions of the kidney. In the past, the study of pyelo-renal reflux had been focused mainly on the consequences of spontaneously occurring events, such as ureteric obstruction or vesico-ureteral reflux.

Intra-renal reflux (IRR) defined as the reflux of urine from the renal pelvis to the parenchyma, represents an abnormal condition which often causes renal deterioration. Several cases of so-called "reflux nephropathy" are caused by this mechanism. In the case of ascending infections, bacteria are brought to the mucosa lining the pyelo-caliceal cavities, but can only penetrate the kidney if IRR occurs. When pressure within the renal pelvis is particularly high, bacteria can even penetrate into the circulatory stream and give rise to bacteraemia and endotoxic shock.

Since 1954, when Gigon observed for the first time backflow of material injected through the ureter in the renal vein, various other authors (Ludwig and Zawarikin 1853; Poirier 1891; Marcus 1903; Hampton 1920; Minder 1930; Olsson 1948; Hodson 1959; Mailing and Rollston 1974 have investigated this subject. Olsson carried out a careful clinical radiographic assessment whereas Hodson described the rôle played by IRR in various renal diseases.

Del Maschio et al. [6] have recently employed microradiographic and histopathological methods, classifying IRR into tubular, sinusal, interstitial, lymphatic and venous. Pyelolymphatic reflux was observed by Hodson [9] using barium sulphate infusion in the ureter. Pyelo-venous reflux from hydronephrotic kidneys can be preceded by polypoid hernations into the intrarenal veins [1–7]. Infection is often associated with this phenomenon. Typically, such changes are found in obstruction of rapid onset (5–60 days) and not in chronically distended kidneys.

In 1979, Bhagavan et al. [3] studied the pathogenesis of urine reflux in 4 kidneys removed because of obstructive uropathy and in 50 cadaver kidneys. Plastic jellies of different colours were injected into the renal pelvis and into the venous system. The communication between the pelvocalyceal cavities and the venous system was commonly due to forniceal rupture into a small vein. Bhagavan et al. observed that pyelo-venous reflux was more likely to occur with increasing intrapelvic pressure. In particular, when the intrapelvic pressure exceeded 70 mmHg, all kidneys showed pyelovenous reflux. The method of Bhagavan et al. is not physiological in terms of intrarenal blood flow. Therefore, recorded pressure levels are very high and presumably they are not indicative of the real threshold at which RPV occurs. Significantly enough, these authors observed some pyelo-

tubular reflux at pressure levels lower than 70 mmHg. This was probably due to the inadequacy of the compounds used.

In 1975, Hodson carried out in-vivo studies in pigs, and concluded that intrarenal reflux rarely occurs at pressure levels lower than 35 mmHg, while above 45 mmHg, IRR becomes evident.

As far as the site of IRR is concerned various Authors [8, 9, 14, 15] have shown that it occurs more readily in the renal poles, where the papillae are of the complex type. It has been maintained that in this type of multiple papillae the direction of the ducts of Bellini is parallel to the axis of the pyramid; whereas in the papillae draining one single pyramid of Malpighi the outlets of collector ducts are somewhat oblique thereby preventing reflux.

Recently Del Maschio et al. [5] studied intrarenal reflux with micro-radiographic techniques examining normal kidneys of children and adults removed at autopsy. By trans-ureteral injection of barium sulphate, they demonstrated pyelo-tubular reflux at the polar papillae constantly appearing at 10–15 cm H_2O. When the injection pressure reached 30–35 cm H_2O, the intra-renal pyelo-tubular reflux became generalized and interstitial reflux appeared as well. Interstitial reflux became more evident at 50–55 cm H_2O, visualising lymphatic channels along the venous tree, thus bringing about an appearance of "pyelo-sinus-venous" reflux. Following Rocca Rossetti's suggestions (1981), we have adopted a new experimental model which simulates physiological conditions more closely. Different pressures in the vascular system and in the pelvis were generated by continuous perfusion or by a peristaltic pump.

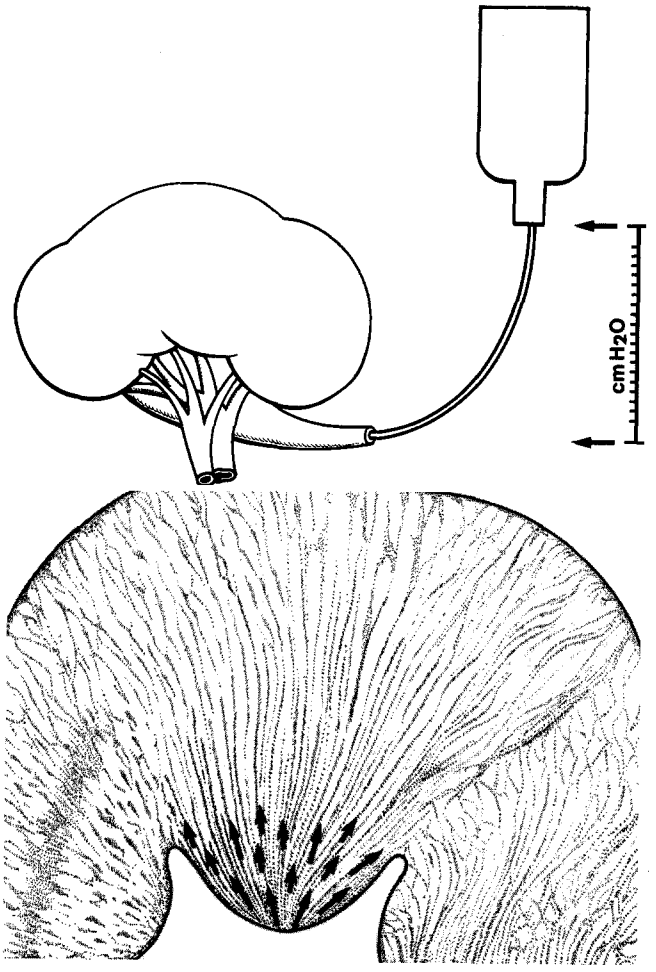

Fig. 1. The *arrows* show reflux in the distal portions of Bellini's tubules with pelvic perfusion of 15 cm H_2O

Material and Methods

This study was carried out on 38 apparently helathy human kidneys removed, at post mortem examination, not later than 24 h after death, and on 5 surgically removed kidneys, three of which were affected by tumour and two by hydronephrosis secondary to long standing obstruction from ureteric stones.

Each kidney was first perfused through the renal artery with 1,000 cc of lactated Ringer's solution with 10 ml of heparin and thereafter with normal saline solution, till a clear liquid flowing from the vein was obtained, thus indicating that no blood was still present in the vascular system.

Green or violet Kohinoor ink diluted in normal saline, was then infused into the renal pelvis through a 8–12 Fr. Nélaton catheter introduced in the ureter.

The ureters were tied around the catheters to prevent leakage. Free flow of fluid was allowed to run by gravity till pressure within the pyelo-caliceal cavities was equal to that of the inflow system, thereby preventing further penetration of fluid.

By regulating the height of the bottle above the kidney, different pressures were obtained and monitored by a venous pressure measurement set. A control group, without concomitant arterial perfusion, was formed by 14 cadaver kidneys, whose pyelo-calyceal cavities were filled by gravity at pressures ranging from 10 to 70 cm H_2O.

A second group was composed of 14 cadaver kidneys; in addition to gravity infusion of the renal pelvis with ink solutions at pressures ranging from 15 to 70 cm H_2O, the arterial tree was simultaneously perfused by gravity with Ringer's solution at a pressure of 100 mgHg. In a third group, of 10 autopsy specimens the same method of infusion of the renal pelvis was supplemented by pulsing vascular perfusion at the pressure of 120/80 mmHg using a peristaltic pump [2].

In order to verify whether a significant difference existed between kidneys harvested at autopsy and kidneys free from post-mortem phenomena, parallel investigations were also carried out on five surgically removed kidneys, using the same experimental technique employed for the second group of cadaver kidneys. In all kidneys, pelvic infusion was continued till a balanced pressure was obtained, or until an outflow of dye into the renal vein revealed an effusion into the venous system. The kidneys were then fixed in a 10% formalin solution for 24 h; thereafter, by a bivalve nephrotomy, they were cut and kept in a 10% formalin solution for at least further 24 h.

All the pyramids of each fixed kidney were studied through longitudinal and transversal sections. The presence and the extent of reflux, was revealed by the presence of the dye solution in the tubules and, sometimes, in the fatty tissue of sinus and in the venous system.

Results

In the control group, tubular reflux appeared when pressure values were about 15 cm H_2O (Fig. 1), and venous reflux began when the pelvic pressure values were higher than 40 cm H_2O. At 15 cm H_2O, a retrograde migration of the dye

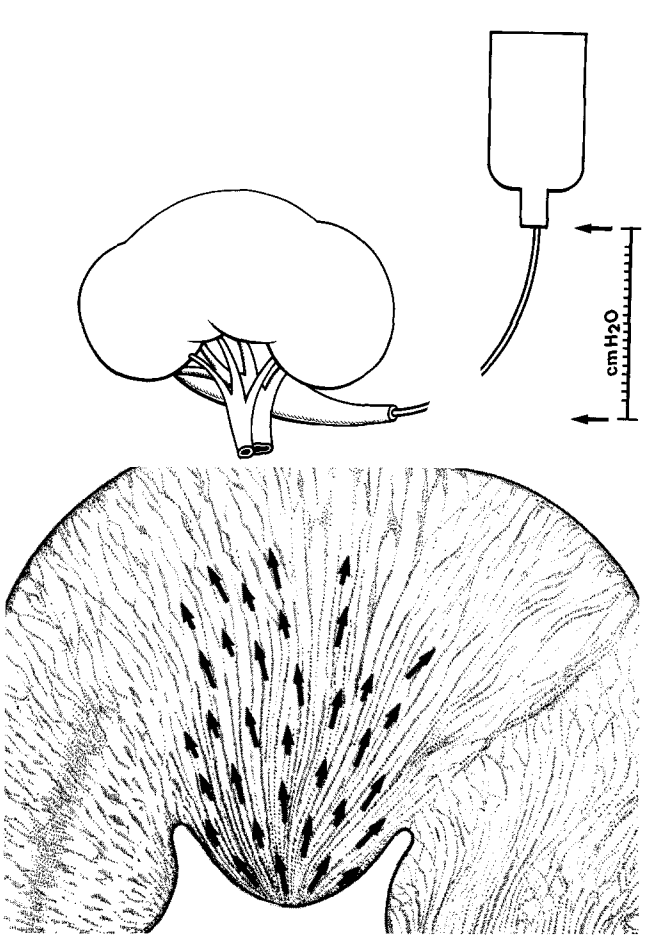

Fig. 2. The *arrows* show that pyelo-tubular reflux extends throughout the pyramid at pelvic pressure of 30–40 cm H_2O

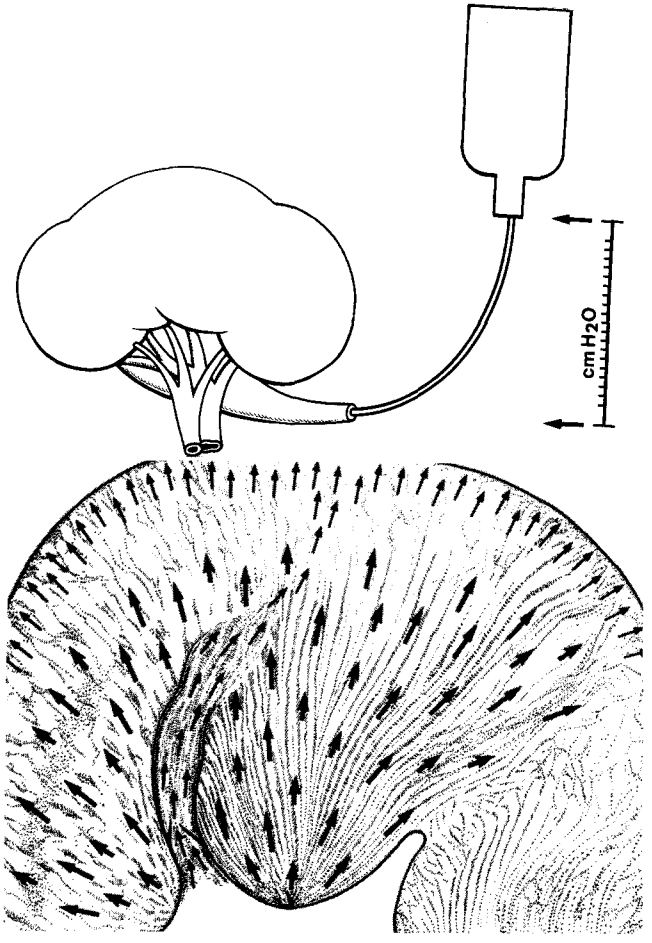

Fig. 3. The *big arrows* show how at pelvic pressures equal to or exceeding 50 cm H_2O, pyelo-tubular reflux is massive. The *small arrows* show that at this pressure breaking of fornix and pyelovenous reflux also appear

Table 1. Control group (14 kidneys)

Pyelic pressure in cm H_2O	Pyelo-venous reflux	evidence of reflux in the		
		upper calix	medium calix	lower calix
1 kidney : 10	–	–	–	–
3 kidneys: 15	–	±	– (±1 case)	±
2 kidneys: 20	–	+	±	+
3 kidneys: 30	–	+++	+	++
3 kidneys: 40	–	+++	++	+++
2 kidneys: 50	+	+++	++	+++

solution in the distal part of Bellini's tubules, especially in both polar regions was recorded; only in one kidney reflux was observed in one of the three pyramids of the central group, which was part of a complex papilla. At pelvic pressures of 30 to 40 cm H_2O (Fig. 2), reflux involved the whole pyramid, and this always occurred in the polar papillae of the complex type, mainly at the upper pole. At pelvic pressures of 50 cm H_2O or above (Fig. 3), pyelovenous reflux was a constant phenomenon (Table 1).

In the group in which the arterial system was simultaneously perfused with continuous flow at a pressure of 100 mmHg, the endopyelic threshold pressure to induce tubular IRR was 40 cm H_2O (Fig. 4), the polar pyramids always being the most involved. However, when vascular pressure

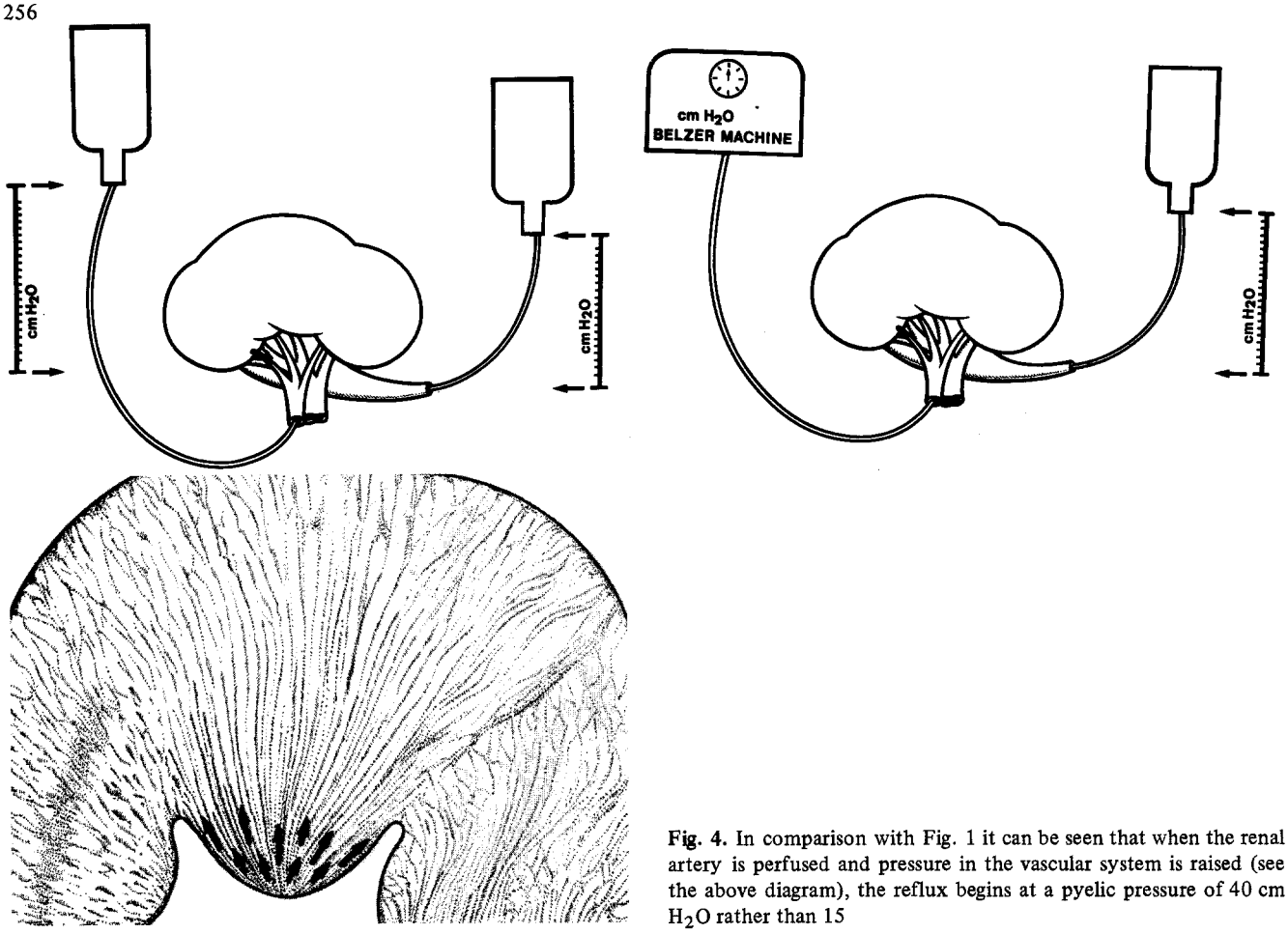

Fig. 4. In comparison with Fig. 1 it can be seen that when the renal artery is perfused and pressure in the vascular system is raised (see the above diagram), the reflux begins at a pyelic pressure of 40 cm H_2O rather than 15

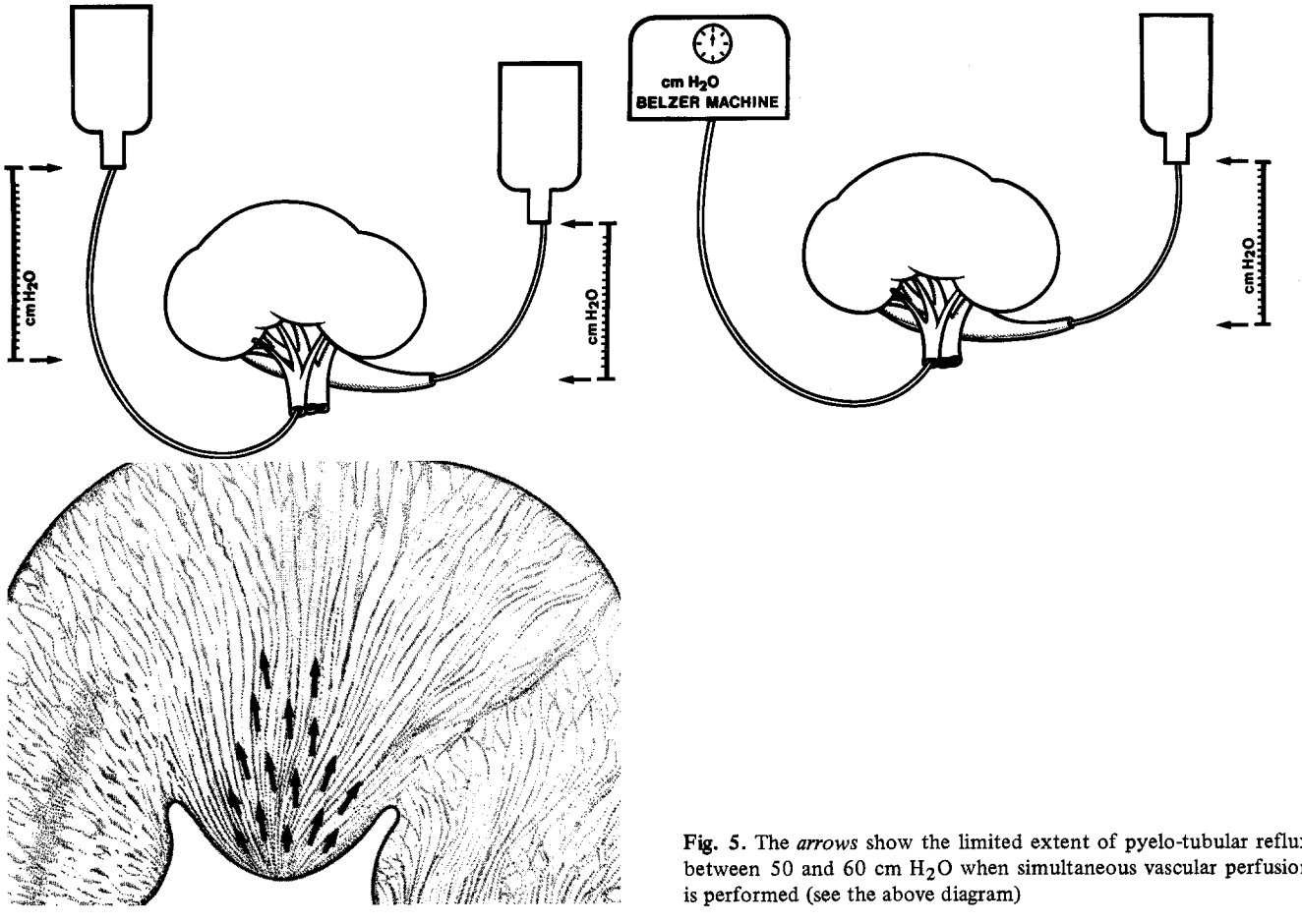

Fig. 5. The *arrows* show the limited extent of pyelo-tubular reflux between 50 and 60 cm H_2O when simultaneous vascular perfusion is performed (see the above diagram)

Table 2. 14 kidneys with arterial continous flow at 100 mmHg

Pyelic pressure in cm H_2O	Pyelo-venous reflux	evidence of reflux in the		
		upper calix	medium calix	lower calix
2 kidneys: 15	–	–	–	–
2 kidneys: 20	–	–	–	–
2 kidneys: 30	–	–	–	–
2 kidneys: 40	–	±+	±	±+
2 kidneys: 50	–	±+	±	±+
2 kidneys: 60	– (+ 1 case)	++	+	++
2 kidneys: 70	+	++	+	++

Table 3. 10 kidneys with arterial peristaltic flow (Belzer machine (at 120/80 mmHg

Pyelic pressure in cm H_2O	Pyelo-venous reflux	evidence of reflux in the		
		upper calix	medium calix	lower calix
2 kidneys: 30	–	–	–	–
2 kidneys: 40	–	±	±	±
2 kidneys: 50	–	+	±	+
2 kidneys: 60	–	++	+	++
2 kidneys: 70	+	++	+	++

Table 4. 5 kidneys from surgery (arterial continous flow at 100 mmHg)

Pyelic pressure in cm H_2O	Pyelo-venous reflux	evidence of reflux in the		
		upper calix	medium calix	lower calix
3 kidneys with tumours: 50	+	++	+	++
1 kidney with hydronephrosis: 50	+	–	–	–
1 kidney with hydronephrosis: 60	+	–	–	–

was simulated, tubular reflux was less extensive compared to the control group studied by endopelvic perfusion only. Under these simulated conditions of vascular perfusion the signs of IRR were less severe even when the endopelvic rose to 10 cm H_2O (Fig. 5). In some kidneys the venous reflux started to appear at 60 cm H_2O but was constant above 70 cm H_2O (Table 2).

In the kidney perfused by the Belzer machine, with a constant pressure of 120/80 mmHg, pyelotubular reflux was observed at an endopyelic pressure of about 40 cm H_2O and was limited to some tubules at the apex of a few papillae. It was necessary to reach pressure levels of 60–70 cm H_2O, in order to obtain reflux involving a wider area, including the whole pyramids and a higher number of papillae, especially in the kidney poles. The threshold pressure to generate pyelovenous reflux was the same as that observed with continuous perfusion, i.e. 70 cm H_2O and above (Table 3). With regard to the kidney obtained at surgery and tested under continuous vascular perfusion a striking difference could be observed between the two groups.

In the 3 kidneys with tumours the distribution of refluent papillae was very similar to that observed in the previous groups although pyelovenous reflux was observed at lower pressure levels (50 cm H_2O).

In the two kidneys with hydronephrosis due to long-standing stone obstruction, where a thin layer of renal parenchyma was present, not even at pyelic pressures of 50–60 cm H_2O, which led to pyelo-venous backflow, was it possible to discover tubular IRR (Table 4).

Discussion

Our results, as far as the kidneys of the control group are concerned, are comparable with those obtained by most authors (pyelo-tubular reflux onset at 15–20 cm H_2O, and pyelo-venous reflux onset at 50 cm H_2O). Contrariwise, in the kidneys in which a continuous or a peristaltic perfusion was performed, pyelo-tubular reflux occurred at pressure levels of 40–50 cm H_2O, and pyelo-venous reflux at levels of 60–70 cm H_2O and above.

These results did not differ in the 3 kidneys surgically removed because of cancer and tested with the continuous perfusion method. The only difference seemed to be that the endopelvic pressure necessary to obtain pyelo-venous reflux, was 50 cm H_2O rather than 60–70 cm H_2O. This may be due to the higher fragility of the venous paracalyceal structures displaced from the neoplastic mass.

Finally, as far as the two surgically removed kidneys due to long-standing hydronephrosis are concerned, no IRR but only pyelo-venous reflux was observed even at pressure levels of 60 cm H_2O. This is in accordance with the observations of Ransley (12–16) who suggested that rearrangement of Bellini's ducts in a scarred kidney prevented IRR event at the polar level.

In conclusion, our study confirmed some of the data reported by other investigators. We feel however, that the simultaneous infusion of the renal vascular tree together with filling of the excretory system, may be a better physiological model for studying intrarenal reflux.

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