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Histopathologic effects of extracorporeal shock wave lithotripsy on rabbit kidney

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Summary. Despite the widespread clinical use of the lithotriptor, the margin of safety for the kidney during shock wave application is substantially unknown. Although a series of pilot studies have been performed in laboratory animals, long-term follow-up is mandatory to establish the effect of extracorporeal shock wave lithotripsy (ESWL) and subsequent dose-dependent changes on the kidneys. An experimental study was performed in 45 rabbits; to define and compare the early and late complications of ESWL in the kidneys. The rabbits were divided into three groups of 15 animals each that received 1000, 1500 or 3000 shock waves respectively at 15–20 kV. The rabbits in each group were killed and necropsy performed within 24 h for the first 5 animals, 1 week for the second 5 animals and 2 months post-ESWL for the last 5 animals. Dose-dependent moderate damage (subcapsular hemorrhage, interstitial hemorrhage, capsular tension and perirenal hemorrhage) were noted in all kidneys at 24 h after treatment. Evidence of permanent changes (some fibrosis, tubular and glomerular damage, chronic inflammatory alterations) was noted in long-term follow up. Complete necrosis of the treated kidney was not encountered in this study.

Key words: Extracorporeal shock wave lithotripsy (ESWL) – Kidney damage

Extracorporeal shock wave lithotripsy (ESWL) has introduced a new dimension into the treatment of urolithiasis. Although on a clinical basis only a few side effects have been reported, the margin of safety for the kidney remains unknown. Most experimental studies with lithotriptors have demonstrated limited pathologic changes with the conventional number of shock waves [6, 7, 9].

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An animal model was developed using Dornier lithotriptor MPL 9000 to demonstrate the side effects of ESWL on rabbit kidneys and to elucidate the dose- and time-dependency of these effects.

Materials and methods

Forty-five adult New Zealand white rabbits were used, of body weight 2800–3900 g. The animals were divided into three groups (1, 2 and 3), each consisting of 15 animals, which were exposed to 1000, 1500 or 3000 shock waves, respectively. A second group of 5 rabbits constituted the sham groups. All of the animals in this group underwent the entire procedure, including anesthesia and opacification of the kidneys with contrast agent, except for shock wave administration.

Anesthesia was by intramuscular ketamine at an initial dose of 1 mg/kg, increased when needed. To opacify the kidney 5 ml 76% Urografin (Schering AG) was given intravenously before the procedure. The animal was placed in the supine position on the platform of the lithotriptor and fixed through its thorax and hip to permit direct entry of the waves through abdominal wall into the right kidney. A pad was used to compress the abdomen and thus induce a dilation of the pelvis to provide better visualization. The fur on the abdomen was shaved to avoid a reduction of the shock wave effect.

Shock waves were generated with Dornier lithotriptor MPL 9000. The X-ray localization system of the lithotriptor was used and the ellipsoidal focal point (F2) of the system was 7×48 mm at about 530 bar pressure with an efective treatment depth of 0–155 mm. An 80 nanofarad capacitance was used and the maximum electrical discharge value was 26 kV.

By means of the intravenous opacification the kidneys of the animal were positioned in the focal point of the lithitriptor and all of the shock waves applied to the pelvis of the right kidney at a rate of 100–120 shock waves per minute.

The electrical discharge was gradually increased from 15 to 20 kV. Each group was subdivided into three groups of 5 animals each which were sacrificed 24 h, 1 week and 2 months after shock wave treatment respectively. The animals were killed with intravenous pentothal before histopatholgic examination. Tissues were fixed in 10% buffered formalin and embedded in paraffin. Sequential 5–6 μm sections were stained with hematoxylin and eosin and examined under the light microscope.

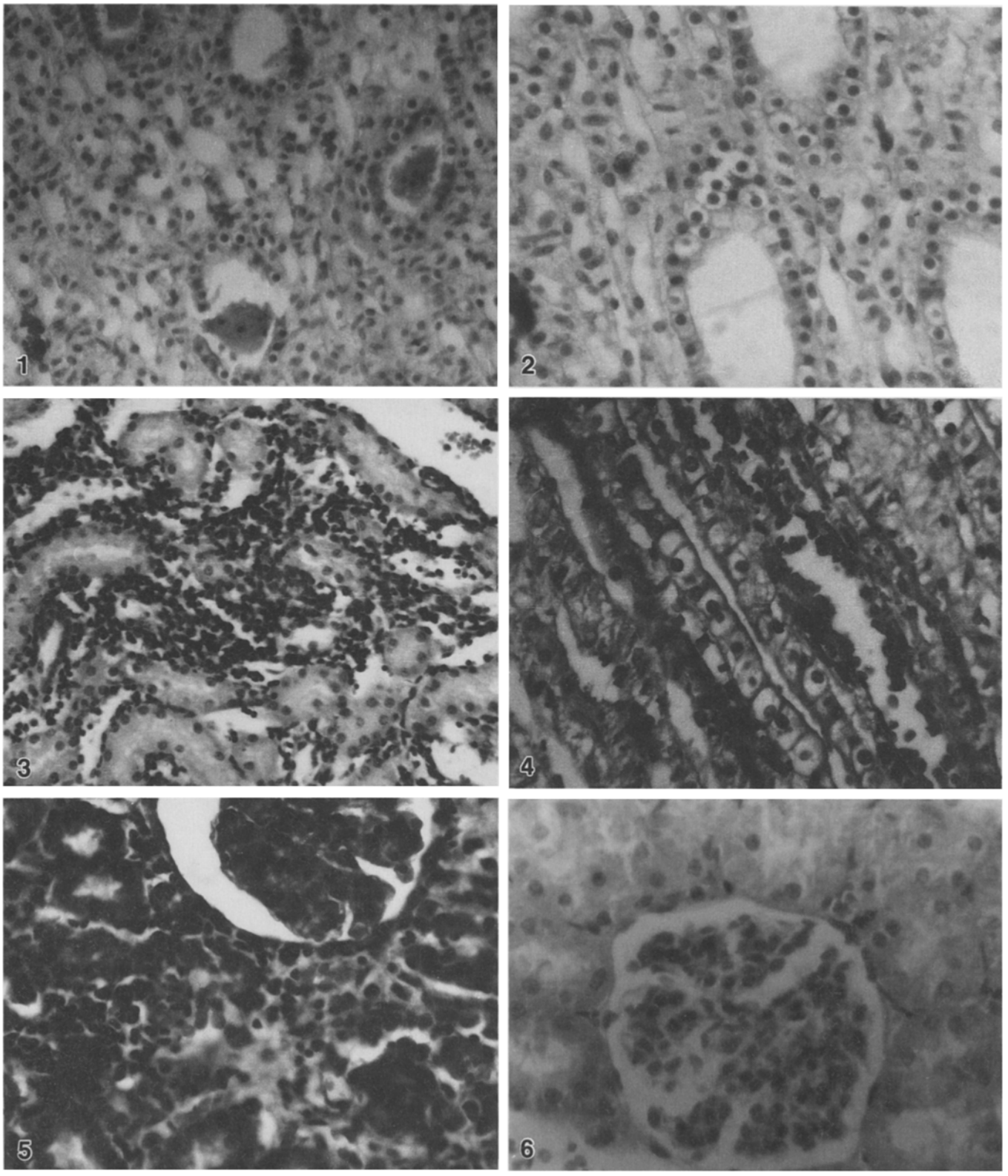

Fig. 1. Free erythrocytes in Bowman's capsule following 1000 SW at 24-h follow-up examination. H&E, ×80

Fig. 2. Protein aggregation following 1000 SW at 1-week follow-up examination. H&E, ×80

Fig. 3. Focal interstitial nephritis following 1500 SW at 2-month follow-up examination. H&E, ×80

Fig. 4. Focal interstitial nephritis following 3000 SW at 2-month follow-up examination. H&E, ×80

Fig. 5. Focal glomerulonephritis following 3000 SW at 2-month follow-up examination

Fig. 6. Normal histopathologic appearance of the kidney from an animal in the sham group following preparation for ESWL without shock wave application. H&E, ×375

Results

During the follow-up period 7 animals died (2 in group 1, 1 in group 2 and 4 in group 3) for different reasons.

Gross morphology

All of the kidneys showed morphological changes after treatment. Subcapsular hematoma, hemorrhage at the corticomedullary junction, capsular tension, renal and perirenal edema and perirenal hematoma were apparent in all of the animals killed 24 h after shock wave administration. The extent and severity of the lesions depended on the number of the shock waves applied. In contrast to the diffuse subcapsular hemorrhage, parenchymal hemorrhage was more limited. Reduction in the extent of these pathologic findings was seen in the animals killed 1 week after the procedure. Organized hematoma in perirenal fat tissue was apparent in 2 animals exposed to 3000 SW and killed 2 months after shock wave application. One animal in the 1500 SW group and 3 in the 3000 SW group had hemorrhagic areas in Gerota's fascia 24 h after shock wave treatment. However, these effects disappeared with time. Two animals exposed to 3000 SW showed thickening of Gerota's fascia after 2 months of follow-up. Hematoma in the renal pelvis was present in 3 animals after 24 h – 1 in the 1500 SW group and 2 in the 3000 SW group. These findings were also absent in the later follow-up period. Perirenal fluid collection that was seen in 2 animals of the 3000 SW group at 24 h was not detectable in the later follow-up period.

Histopathological changes

The extent and severity of the changes seen in almost all of the tissues appeared to be related to the number of shock waves.

Group 1 (1000 SW). At 24 h after shock wave administration there was tubular dilatation with vacuolar and hydropic degeneration. The tubules contained various amounts of blood and protein. Glomerular hemorrhage, free erythrocytes and protein in Bowman's capsule (Figs. 1, 2), hemorrhage in interstitial vessels and mononuclear cell infiltration in the interstitium were also prominent. These finding were considerably reduced at 1 week post-ESWL and had almost completely disappeared at 2 months. However, focal interstitial nephritis had developed in 1 animal in this group examined 2 months post-ESWL.

Group 2 (1500 SW). The same changes observed in the 1000 SW group also developed in group 2 animals, though to a greater extent. While the effects tended to be reduced in later phases, 1 subject developed glomerular atrophy and 1 focal interstitial nephritis (Fig. 3).

Group 3 (3000 SW). All of the findings mentioned above were also prominent in this group of animals, with a greater extent and severity as was expected. In later follow-up, when some of these effects tended to be reduced, tubular degeneration and adherence in Bowman's capsule seemed to be irreversible in some animals. Interstitial hemorrhagic areas were still present in 2 animals.

There was evidence of glomerular atrophy in 2 kidneys. Focal interstitial nephritis in 2, focal glomerulonephritis in 1 (Figs. 4, 5) and tubular necrosis in 1 kidney were prominent during examinations after 2 months. Another important finding was cortical interstitial fibrosis in 2 animals. Capsular fibrosis was observed in 2 cases 1 week after ESWL and in 1 case 2 months after the procedure.

Although these changes were more apparent around the pelvic region of the kidney, the upper and lower poles were also partly involved. Additionally, the evidence of prior damage was more prominent in the cortex than the medulla. Moreover the renal tubules seemed to be more affected than the interstitium and glomeruli. Tubular degeneration usually involved groups of several adjacent collecting tubules, interspersed with some normal appearance. The dilated tubules contained free erythrocytes and hyalinized casts in varying amounts.

In contrast the necropsy material from the sham group of animals which were exposed to all othe procedure except shock wave application revealed, as expected a normal histopathology without any abnormal features (Fig. 6).

Discussion

Despite its clinically and radiologically successful results, ESWL is not free from complications in terms of renal and perirenal morphology and physiology. Our study aimed to elucidate the time- and dose- dependency of these histopathologic changes.

Experimental animal studies concerning these effects are very limited. Chaussy and Schmiedt [4] reported that gross renal injury, as demonstrated by ultrasound detection of hematoma, developed in approximately 0.6% of all treated cases. However, Caude [8], Baumgartner et al. [2] and Rubin et al. [10] indicated the prevalence of acute gross injury to the kidneys induced by ESWL was much higher (63%–74%) when compared with magnetic resonance imaging or computed tomography.

Early investigations by Chaussy et al. did not reveal pathologic renal damage in dogs. This observations gave rise to the hope that kidney stones could be fragmented with ESWL without causing any damage to the kidneys and perirenal tissues [1, 5, 7, 9]. But the average number of shock waves used was only 500, which is considered a subtherapeutic dose for ESWL treatment. Furthermore, since these animals were killed 14 days after lithotripsy, interpretations of the acute effects of ESWL on renal tissues could not be made reliably. Hematuria, which is observed almost universally after ESWL, suggests that kidneys are damaged to some extent during treatment. Brendel [3] showed the formation of subcapsular hematomas in dog kidneys by using a therapeutic number of shock waves. Gunasekaran et al. [7] demonstrated in their

original study that gross morphologic changes occur 7 days after shock wave application in rabbit kidneys exposed to 3000 SW with an electrical discharge value of 18 kV.

In our trial we attempted primarily to define and demonstrate the adverse effects of an increasing number of shock waves on renal morphology. As another important parameter, the electrical discharge value (kV), might also affect the degree of these morphological changes we kept this in the same range (15–20 kV) for all animals. This is very similar to the range used on patients we have treated in our routine procedures.

The morphological changes we observed in our study were closely related to the number of shock waves applied during the procedure. All of the kidneys demonstrated gross morphologic changes when exposed to 3000 shock waves. Hemorrhage was the most prominent finding. Subcapsular hemorrhagic foci were diffuse in nature whereas parenchymal hemorrhage were generally focal. The changes had disappeared to a large extent by the end of 2 months. However, persistence of thickening of the renal capsule and Gerota's fascia were discouraging findings we observed. The dose dependency of the morphological changes seen in this study was very close to that in Delius and Newman's studies [6, 9].

The microscopic changes noted in our study covered a wide spectrum from tubular hemorrhage to tubular necrosis, from glomerular hemorrhage to atrophy, and from interstitial hemorrhage to focal interstitial nephritis and interstitial fibrosis. Capsular damage up to the degree of fibrosis was also encountered. Most of these findings in groups 1 and 2 disappeared in later follow-up. However, in group 3 (3000 SW) some pathologic findings such as tubular necrosis, glomerular atrophy, focal glomerulonephritis, focal interstitial nephritis, interstitial fibrosis and capsular fibrosis persisted at 2 months follow-up after ESWL. These findings support the suggestion that shock waves may cause some irreversible changes in the kidneys, especially at higher doses.

The more intensive changes seen at hilar region are the natural outcome of the ESWL treatment as the lithotriptor was focused on the renal pelvis, at least in this experimental study. On the other hand, some minimal changes that we observed in the left kidneys examined might be due to the close anatomic relationship of the two kidneys in the rabbit.

Some other studies dealing with the side effects of ESWL on renal function have been reported recently. For example, Kaude et al. [8] found that 14% of their patients treated with ESWL had evidence of diminished renal function. This functional impairment together with hypertension may be explained by the finding of permanent cortical fibrosis.

Although ESWL is the preferred treatment modality for renal stones, it seems from the literature reports that it may cause some irreversible damage to the kidneys. In our study most of the changes seen were reversible, but the renal cortical fibrosis observed at higher doses also suggests that ESWL may be responsible for some irreversible changes in the kidneys. The degree of morphological change varies in relation to the number of shock waves, level of electrical discharge, localization problems, the affected area in the renal parenchyma, and the previous pathologies of the treated kidney. Moreover, the presence of the stone in the kidney may enhance these harmful effects.

There are still a number of unanswered questions regarding the long-term functional and pathologic effects on the kidney subjected to ESWL. Further studies with larger series are needed to define the threshold safety limits for the treatment.

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