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Morphological Changes in Canine Kidneys Following Extra-Corporeal Shock Wave Treatment

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Summary. Extracorporal shock wave lithotripsy has rapidly become established world wide as a routine method for treatment of nephro- and ureterolithiasis. Although initial studies showed no tissue damaging effect by the shock waves, we found in an animal experiment using canine kidneys, the ESWL induced damage to the renal parenchyma is more marked than originally assumed. The damage is limited to the area that was focused on, and heals relatively rapidly by connective tissue encapsulation with final cicatrisation without any further residual effects being observed until now. This parenchymal damage is probably also the cause of the macrohaematuria that is always observed during therapy. The resulting tissue damage is not extensive enough to cause demonstrable reduction of function as measured by the usual methods (serum creatinine, creatinine clearance, isotopy renography, i/v-urography). The main clinical complication is the large subcapsular haematoma which, according to present knowledge, could well result from a lesion of the larger peripheral vessels. Damage to other organs such as subserous colonic and small bowel haematomata are to be expected although they do not lead to clinical symptoms.

Key words: ESWL – Renal damage – Animal experiment

Introduction

Extracorporeal shock wave lithotripsy (ESWL) has rapidly become internationally established as a routine method for treatment of nephro- and ureterolithiasis since its introduction to clinical practice in 1982. Reports of therapeutic success have been presented from different centres involving large numbers of patients. These reports are in general agreement [8]. Within a short period of time, ESWL, together with other approaches (percutaneous litholapaxy, percutaneous ultrasound nephrostomy and ureteroscopy) has radically changed our thinking about the treatment of urolithiasis.

Although initial studies concluded that shock waves had no tissue damaging effect on renal tissue [10], phenomena have been observed during the clinical use of ESWL that suggest that damage in the renal parenchymal area might be induced by shock waves. There are also the rarely-observed but sometimes consisderable subcapsular renal haematomata [26]/(Fig. 1) as well as the temporary macrohaematuria that inevitably occurs during ESWL.

Various clinical and experimental studies of ESWL-related renal damage have been published. The clinical studies have used pre- and post-operative computer or MRI investigations to detect morphological changes [27, 22, 24, 16] or have employed laboratory tests of certain renal function parameters [7, 21, 23]. The experimental studies have used histological examinations on animal kidneys exposed to ESWL [20, 11, 21, 25, 4, 19, 1, 10].

The above-mentioned symptoms, which have been observed in other ESWL centres and reported many times, prompted us to consider the question of the possiblity of ESWL-related renal tissue damage by means of an animal experiment using canine kidneys. The object of the experiment was to try to explain the above-mentioned phenomena and to determine if they were associated with longterm renal damage.

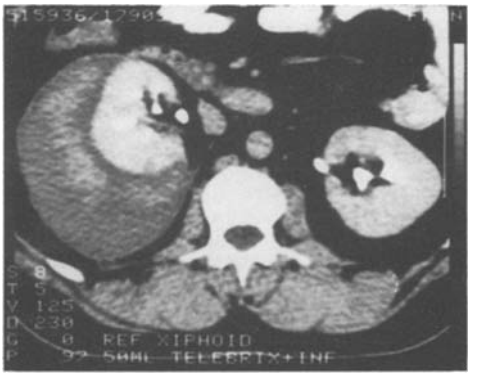
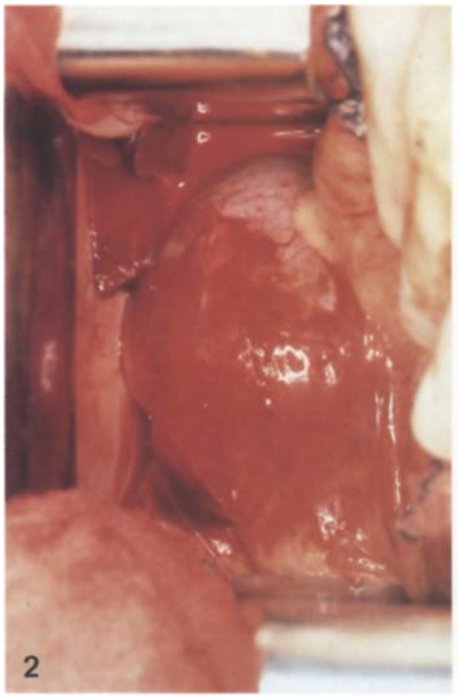
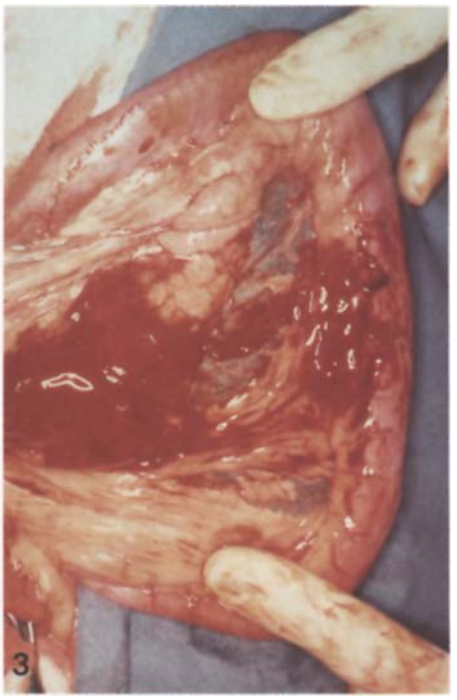


Fig. 1. Subcapsular haematoma of the right kidney after ESWL





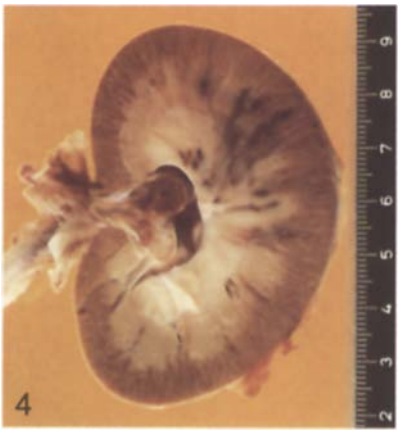


Fig. 2. Haemorrhage in the perirenal fatty tissue after ESWL (1 to 24 h)

Fig. 3. 1 to 24 h after treatment: Subserous bleeding foci in the small bowel loops and haemorrhage in the mesentry

Fig. 4. 1 to 2 h after treatment: Bleeding focus in a freshly removed kidney

Material and Methods

A total of nine dogs (mongrels, 20–28 kg) were e given an inhalation anaesthetic. An indwelling bladder catheter was introduced, and a percutaneous arterial catheter inserted with its tip in the region of the origin of the renal arteries. The animals were then placed in the HM3 Dornier spark gap lithotriptor. The renal poles were localised for treatment with the shock waves by injecting contrast medium through the arterial catheter and then centering with both monitors in two planes. Shock waves were regularly applied to the left superior pole and the right inferior pole. A count of 1,500 shock waves were given per kidney, the mean number used therapeutically for man. Following ESWL, nephrectomy was carried out at various time intervals: in one group one hour after the intervention; in a second group 24–36 h after the intervention; a third group 7–11 days after the procedure, and lastly three to six months following ESWL. Each grop therefore provided 4 kidneys. In order to make a comparison with results reported in the literature, a further kidney was treated with 4,000 shock waves, and two untreated control kidneys were examined.

The operation site was examined macroscopically, in particular by assessing those organs (small intestine, colon, ovaries) adjacent to the kidneys, the kidneys themselves, their position and the perirenal fatty tissue. Nephrectomy was then performed with immediate fixation of the organs. Assessment of the macroscopic appearance of the fixed preparation, cut in half longitudinally, followed later, along with removal of the tissue and the light microscopy examination. Further sections were prepared for scanning electron microscopy (SEM) and for transmission electron microscopy (TEM) examinations.

Furthermore, we performed aortography for each animal to visualise the renal vessles, in each case immediately before ESWL and immediately after the nephrectomy. Cytological examination of the urine during ESWL and comparison to the laboratory values before ESWL and before nephrectomy were also carried out. To allow a comparison with the histological findings, the kidneys of two untreated control animals were added and with one kidney that had received 4,000 shock waves were prepared and examined in the same way.

Results

Operation Site

As expected, the most marked changes were seen in those animals that had been operated shortly after ESWL, that is one hour later. In two cases, there were external signs of skin suffusions of about two centimeters in diameter. Haemorrhage into the back musculature was also noted in one case. Of special interest was a cellection of 200–300 ml of free blood in the peritoneal cavity. The perirenal fatty tissue, usually only sparsely represented, always showed a more or less marked infiltration with blood (Fig. 2). Subserous bleeding foci were also observed in the small bowel loops and in the mesentry (Fig. 3). The changes were more marked following the application of 4,000 shock waves to the kidney. In this case, we additionally found bleeding in the colonic wall and in the region of the ovary. With increasing time intervals between ESWL and the nephrectomy, the above-mentioned changes were no longer observed, and the operation site appeared practically normal.

Macroscopic Changes in the Kidneys

We observed small subcapsular haematomata in some kidneys, although they had not all been freshly removed, i.e. one to 24 h after ESWL. Well-circumscribed wedge-shaped parenchymal bleeding foci were clearly seen on the cut fixed preparation (Fig. 4). These could be observed in all freshly removed kidneys and were always localised to the region of the pole treated with the shock waves. No pathological findings were present in those kidneys removed after a longer time interval following ESWL, either in the renal preparations or in the appearance of the operation site.

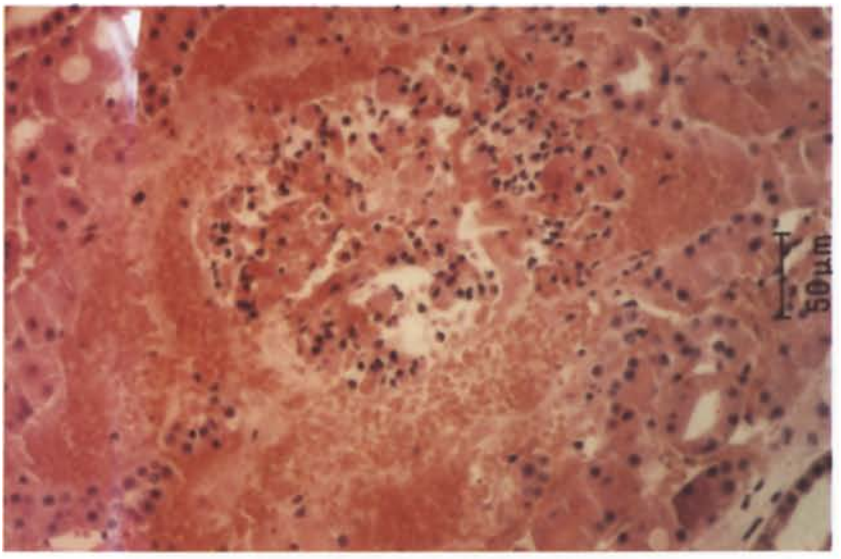


Fig. 5. 1 to 2 h after treatment: Rupture of the glomerular capsule, of veins and arteries with perivesicular haemorrhages. 1 h after ESWL

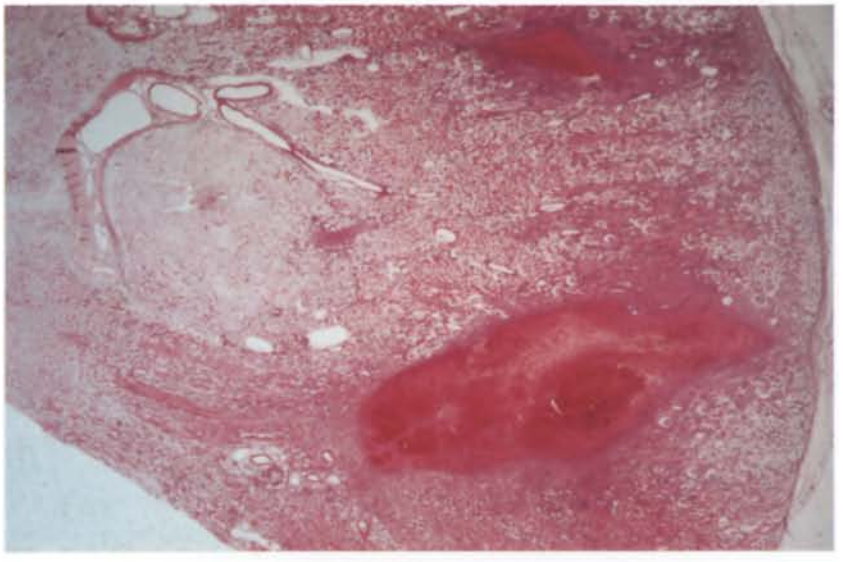


Fig. 6. One week after treatment: Haemorrhagic areas are engolfed by fibroblasts and collagenous fibres

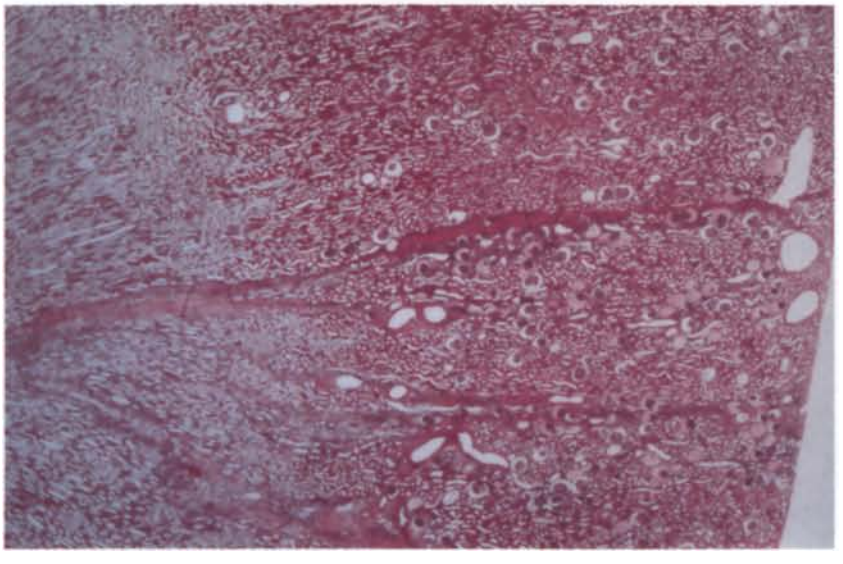


Fig. 7. 3 to 6 months after treatment: Focal, streaky interstitial and glomerular fibrosis at the site of the previous foci

Light Microscopy (Histological) Changes

Examination of the histological preparations confirms the appearance of changes that are very probably related to the shock waves, and that there is a relatively uniform and consistent pattern of change in all the experimental animals. This is typical for almost all time intervals following ESWL. The changes are found over a generally well-circumscribed area of the kidney, in keeping with the macroscopic findings.

Histological changes at nephrectomy one hour after ESWL: Bleeding foci were clearly seen, principally in the corticomedullary transitional area, but extending towards the medulla. These bleeding foci showed complete tissue destruction and the structures were no longer recognisable. Haemorrhages in the cortical region with subcapsular extension were also present. Ruptures of the glomerular capsule, veins and arteries, the juxtaglomerular apparatus an the peritubular vessels were observed, which led to perivascular haemorrhages in many areas (Fig. 5). Blood was also present intratubularly and intracapsularly in the glomeruli. The bleeding foci caused compression of the surrounding tissues in which compressed and flattened glomeruli and tubules were to be seen. A neutrophil granulocyte reaction provided evidence that these vessel ruptures were not artefacts. Furthermore, clusters of erythrocytes in the vessel wall itself were found due to bleeding into the ruptured arterial wall. There were, therefore, glomerular, periglomerular, tubular and interstitial haemorrhages. Subcapsular haemorrhages were also observed, although experimentally we did not see subcapsular haematomata of the size that are known to occur clinically.

Histological changes at nephrectomy 24–36 h after ESWL: Bleeding foci can be observed as before, but appear more sharply delineated. In particular, blood is to be seen intracapsularly and intratubularly. The most striking finding at this time, however, is the presence of vacuolated tubule cells at the edges of the haemorrhagic foci, apparently signifying the start of tubular necrosis. Fibrin was also observed in the region of the haemorrhagic foci signifying the start of encapsulation.

Histological findings seven to eleven days after ESWL: Encapsulation of the haemorrhagic foci due to migrated fibroblasts and collagen fibres is not evident (Fig. 6). The haemorrhagic foci are still present as before. In some cases, clumps of calcium deposits can be seen in the necrotic tubules near the foci. The first signs of a streaky fibrosis become apparent.

Histological picture three months after ESWL: When kidneys are examined three or more months after ESWL has been performed, the histological changes are – as was to be expected from the macroscopic findings – minimal. The principle finding is a streaky interstitial fibrosis at the site of the previous foci (Fig. 7). This fibrosis contains some glomeruli and extends from the capsule through the cortex into the medulla. These findings represent healing by cicatrization of the renal tissue damage originally caused by the shock waves.

Discussion

Tissue damage due to the transmission of shock waves through tissues was not expected to occur following the development of shock waves generated by underwater spark discharge. This is because tissue and water have an almost identical acoustic profile. Naturally, however, particular attention was paid during the development of the lithotriptor to the possibility of shock wave induced renal tissue damage [10, 1, 4]. Whole human blood was used for the experiments on tissue's ability to resist shock waves, as they are directed at thighly vascular parenchymatous organs, and because the erythrocyte is a highly sensitive cellular structure. Blood samples were subjected to shock waved up to a frequency of 500. Only a mild degree of haemolysis occured, although increased haemoglobin concentration was measured in the samples and this bore a linear relationship to the number of shock waves [10]. A culture of human lymphocytes which had been subjected to sound waves twice was chosen to examine the effect on the proliferative activity of cells. No effect on the rate of stimulation was observed [10]. Indiscriminate bombardment of the abdominal area with shock waves, or the application of waves four times to resected small intenstine, resulted in no changes other than isolated petechial haemorrhages in the intestinal wall and at the mesenteric attachment [10]. There was also no evidence of damage histologically in the organs that were removed 14 days later. In the clinical use of ESWL, however, subcapsular renal haematomata are observed. Even if they occur rarely, they may have significant and even haemodynamic effects. Macrohaematuria, on the other hand, is a regularly observed symptom during ESWL. The usual explanation, that the macrohaematuria is due to a urothelial lesion caused by calculi particles being moved around in the renal pelvis, is not convicing for several reasons. Firstly, it is known from the early development work with the ESWL machine that the occurrence of stronlgy accelerated individual particles was not to be expected. Even after repeated exposure of renal calculi in an in vitro test, there was never any damage caused to a thin surrounding membrane, and it could be concluded from the position of the individual particles that the shock must cause minimal acceleration. It was therefore deduced that disintergration of the calculi occurs without significant traumatisation of the urotehlium [10]. These findings could be confirmed by our own in vitro observations of disintegrated aggregations. Macrohaematuria also occurred, however, after shock waves to stones that were wedged in calyces. Furthermore, macrohaematuria occured with ESWL in all cases of our series of canine kidneys that did not have renal calculi. Finally, we have observed massive micro- and sometimes macrohaematuria in all our patients who until now have been treated with ESWL for common bile duct calculi. This has also been observed by those who have used ESWL therapy for gallstones or biliary duct calculi. These observations argue against the view that the principle cause of macrohaematuria is urothelial damage caused

by the accelerated movement of calculi particles. The studies of Fischer et al. [11], however, show that this explanation cannot be completely discounted. The interior cavities of freshly removed and exsanguinated pig kidneys were filled with a suspension of graphite. The kidneys, with or without stones, were then exposed to shock waves. Histological examination of the organs showed displacement of the particles exclusively in the region of mucous membrane adherent to the stone, caused either by damage from high energy stone particles, or by cavitating cysts caused by fluid jets. In kidneys that did not have stones, however, there was no evidence of displacement of graphite particles caused by the shock wave or the rebound wave. Otherwise, the graphite particles were to be seen up to 1.5 mm deep in the tissue and therefore urothelial damage with bleeding cannot be excluded.

The question of ESWL induced renal damage has been approached from various angles. In contrast to the studies of Eisenberger, Chaussy et al. [10] who applied only a few shock waves [10], the newer studies have used considerably more, thus making them comparable to the numbers of shock waves used in clinical practice. Some workers even go very much higher than this number [19].

Mutscher et al. could not demonstrate any loss of function in treated kidneys using laboratory chemistry tests [2]. Ruiz-Marcellan et al. [23] measured N-acetyl glucosaminidase (NAG) and lactate dehydrogenase (LDH) in the blood and urine of 44 patients immediately before and after ESWL, to see if ESWL therapy caused the liberation of lysosomal enzymes as a consequence of renal tubular damage. NAG and LDH were regarded as good parameters of renal damage. The results showed a marked increase in NAG and LDH in the serum following ESWL, although this did not exceed the upper limit of normal. This data was interpreted as indicating renal micropathology, and the transitory macrohaematuria as the clinical symptom of this damage. No relationship was noted between the number of shock waves and the rise in enzymes. Chaussy et al. [4] were also unable to show any significant difference in laboratory values before and after the application of 500 shock waves. The creatinine clearance values following ESWL were also not significantly altered.

Even in the early developmental phase of ESWL attempts were made to find a change in renal function using scintigraphy before and after ESWL [4]. The activity concentration before and after ESWL, however, did not change, i.e. there was no lateralisation and therefore ESWL induced renal damage could not be demonstrated.

Since ESWL has been in clinical use, attempts have been made to get a true answer to the question of renal tissue damage particularly using imaging techniques, and above all radiological methods. Rubin et al. [22] performed CT on 50 patients before and after ESWL and, using this systematic methodology, found subcapsular haematomata (2 of which were large) in 15%; intrarenal haematomata in 4% and small subcapsular fluid collections of an uncertain nature in a further 6%. An increase in kidney size was observed in 9%. In a similar study using CT, Fischer et al. [12] found a delay in the appearance of contrast medium in the renal medulla and an increased junctional time. These changes were interpreted as indication on interstitial oedema of the medulla and were limited to the area of the kidney exposed to the shock waves. The severity of the change and the number of shock waves applied correlated with each other. Kaude et al. [16] examined the acute effect of ESWL on renal function and morphology using i/c-urography, quantitative radionuclide renography and MRI in 33 consecutive cases. They also found an enlargement of the kidney in 18%. With MRI, loss of corticomedullary differentiation was observed in one case; perirenal fluid collection in two cases; subcapsular haematoma in three cases; and bleeding into a cyst in four cases. A further five abnormalities could not be explained. The morphological and functional changes were interpreted as the result of renal contusion following the extravasation of blood and urine into the interstitial, subcapsular and perirenal tissues.

At the AUA Congress in 1986, Newman et al. also reported morphological changes following ESWL similar to those we found in the experiment described above, although these authors used very high numbers of shock waves from 4,500 to 8,000 [19]. Muschter et al. [21] have also reported on this subject and their findings agree with ours, the most important being marked parenchymal bleeding in the area of the cortical or corticomedullary junction. This can also be demonstrated in cast and maceration preparations. The haemorrhage has a uniform appearance and its extent is dependent on the number of shock waves applied. We can confirm this from our findings on the kidney exposed to 4,000 shock waves. This parenchymal bleeding is also very probably responsible for the macrohaematuria. It is of interest that after a relatively short period of time, that is 8–10 days, the haemorrhagic foci have largely disappeared to result in a cicatrising encapsulation. After a longer period of observation of 3–6 months only streaky scars can be seen at the sites of the original parenchymal bleeding.

On the basis of these studies it can be shown that the acute ESWL induced parenchymal damage is greater than was initially imagined, although this is strictly limited to the area that was exposed and focused upon, and heals relatively quickly by scar formation. No evidence of ESWL induced renal damage is reflected in elevation of the serum creatinine, or by a worsening of clearnace or of function using renal scintigraphy. Only the very sensitive indicators NAG and LDH reflect changes. There are also no changes observed using i/v-urography. The damage caused by ESWL is comparable in its extent to the loss of parenchyma caused by percutaneous renal litholapaxy or to the scar formed after a nephrotomy.

On the other hand, these results also show that a certain degree of damage to neighbouring organs is to be expected. This can be shown experimentally both morphologically and histologically, although is apparently not of any clinical signficance. In particular, we have never observed a post-ESWL induced paralytic ileus following perirenal retro-

peritoneal haematomata or as a consequence of a possible subserous haemorrhage in the small intestine or colon.

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