ORIGINAL PAPER

UROLITHIASIS

# The histomorphological findings of kidneys after application of high dose and high-energy shock wave lithotripsy

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Citation: Demir A, Türker P, Bozkurt SU, İlker YN. The histomorphological findings of kidneys after application of high dose and high-energy shock wave lithotripsy. Cent European J Urol. 2015; 68: 72-78.

Article history
Submitted: Sept. 27, 2014
Accepted: Oct. 4, 2014
Published on-line: Jan. 23, 2015

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**Introduction** In this animal study, we reviewed the histomorphological findings in rabbit kidneys after a high number of high-energy shock wave applications and observed if there were any cumulative effects after repeated sessions.

**Material and methods** We formed 2 groups, each consisting of 8 rabbits. Group 1 received 1 session and group 2 received 3 sessions of ESWL with a 7 day interval between sessions, consisting of 3500 beats to the left kidney and 5500 beats to the right kidney per session. The specimens of kidneys were examined histomorphologically after bilateral nephrectomy was performed. For statistical analysis, 4 groups of specimens were formed. The first and second groups received 1 session, 3500 and 5500 beats, respectively. The third and fourth groups received 3 sessions, at 3500 and 5500 beats per each session, respectively. The sections were evaluated under a light microscope to determine subcapsular thickening; subcapsular, intratubular and parenchymal hemorrhage; subcapsular, intersititial, perivascular and proximal ureteral fibrosis; paranchymal necrosis; tubular epithelial vacuolization; tubular atrophy; glomerular destruction and calcification.

**Results** In histopathological examinations capsular thickening, subcapsular hematoma, tubuloepithelial vacuolisation, glomerular destruction, parenchymal hemorrhage, interstitial fibrosis, and perivascular fibrosis were observed in all groups. In statistical analysis, on the basis of perivascular fibrosis and tubular atrophy, there was a beats per session dependent increase of both.

**Conclusions** The detrimental effects from ESWL are dose dependent but not cumulative for up to 3 sessions. Histopathological experimental animal studies will aid in understanding local and maybe, by means of these local effects, systemic effects.

Key Words: ESWL (extracorporeal shock wave lithotripsy) ‹› high-energy shock waves ‹› histopathology ‹› kidney

## INTRODUCTION

Many medical centers are concerned about the adverse effects of extracorporeal shock wave lithotripsy (ESWL) on tissues [1]. Clinical and experimental studies revealed that this treatment might have severe acute and chronic effects on the kidney and its peripheral tissues [2, 3, 4]. The detrimental effects of ESWL include vascular trauma, perforation of abdominal organs, hepatic hematoma, pneumothorax, urinothorax, acute necrotizing pancreatitis, dissecting abdominal wall abscess, and iliac vein thrombosis, and are reported to occur in less than 1% or, in some studies, 3-7%, of patients [5, 6, 7].

New lithotripters appear to have increased the potential problems of shock wave (SW) application, as compared to first-generation devices [5], but their use is more effective, treatment is less painful, and


doi: 10.5173/ceju.2015.01.480

application is less complicated. Manufacturers have introduced new devices with significant modifications that, if used appropriately, may also be helpful to decrease adverse effects [8].
The aim of this study is to establish the histomorphological effects of ESWL using various SWs and to determine the maximum energy and dose that can be used without detrimental effects on kidneys after ESWL therapy.

## MATERIAL AND METHODS

This study was designed as an experimental animal study and was approved by the animal ethics committee of our instution and performed in accordance with the Helsinki Declaration of the World Medical Association. An electrohydraulic device (Spark Gap Technology, ELMED™ lithotripsy systems, Ankara, Turkey) was used.
White male New Zealand rabbits, 3-4 years old, weighing 3-4 kg, were divided into 2 groups, each consisting of 8 animals. The first study group received one session of ESWL, 3500 and 5500 SWs, in the left and right kidneys, respectively. The second study group received three sessions of ESWL with 3500 and 5500 SWs for the left and right kidney, respectively, with a period of 7 days between sessions. The ESWL protocols applied to both groups are detailed in Table 1. At the end of the sessions, bilateral nephroureterectomy was performed, and the obtained specimens were divided into four different specimen groups, which each underwent one of four different procedures These specimens were examined in terms of histomorphological changes, depending on number of sessions and SWs administered (Table 2). The results of the examination of the specimens were analysed among the four groups.

**Table 1.** *Animal groups according to shock waves and sessions applied*

| Groups | The number of sessions | The groups according to the number of shock waves and sessions | | Nephrectomy day* |
|---|---|---|---|---|
| | | Left kidney | Right kidney | |
| 1 | 1 | Group 1: 3500 | Group 2: 5500 | 7 |
| 2 | 3** | Group 3: 3500 | Group 4: 5500 | 7 |

*Seven days later from the last session; **The interval between sessions is 7 days

### ESWL protocol

Before each session, Ketamine HCl (50 mg/kg) and Xylasine (5 mg/kg) were administered intramuscularly to each animal. Contrast material, Meglumine Amidotrizoate (10 ml of 0.65 mg/ml), was then given intravenously via the marginal vein of one ear. The rabbit was then placed on the lithotripter and the middle part of the kidney was targeted on F2 focus under fluoroscopic guidance and 3500 and 5500 SWs, at a frequency of 80 SWs/min at 7 days intervals, were administered at 23 kV power (without low energy applying) to the left and right side, respectively. All of these procedures were performed by two urologists, (AD, PT) both of whom hold a license for experimental animal studies.

### Abdominal exploration and nephroureterectomy

It has been reported that the acute changes associated with ESWL consisting of a low number of SWs of low energy disappear after the 7$^{th}$ day [9]. Therefore, we elected to perform abdominal exploration and nephroureterectomy on the 7$^{th}$ day, in order to determine whether the acute changes with the application of high numbers of SWs of high energy persist longer. Abdominal aorta dissection was used as the method of euthanasia whilst the animals were under anesthesia at the end of the bilateral nephroureterectomy. These procedures were performed by the same urologists (AD, PT).

**Table 2.** *The mean and standard error of the histological findings of specimens and their statistical analysis*

| GROUP | Capsular thickening | Subcapsular hemorrhage | Intraparenchymal hemorrhage | Perivascular fibrosis | Tubuloepithelial vacuolisation | Tubular atrophy | Glomerular destruction | Interstitial fibrosis | Ureteral fibrosis |
|---|---|---|---|---|---|---|---|---|---|
| 1 (3500 beats, 1 session) | 0.50 ±0.19 | 0.25 ±0.16 | 1.00 ±0.00 | 1.03 ±0.18$^{+}$ | 0.88 ±0.13 | 0.25 ±0.16 | 0.13 ±0.13 | 2.63 ±0.18 | 0.13 ±0.13 |
| 2 (5500 beats, 1 session) | 0.50 ±0.19 | 0.50 ±0.35 | 1.13 ±0.13 | 1.35 ±0.16 | 0.88 ±0.13 | 0.50 ±0.19 | 0.25 ±0.16 | 2.75 ±0.16 | 0.00 ±0.00 |
| 3 (3500 beats, 3 sessions) | 0.75 ±0.16 | 0.88 ±0.44 | 1.13 ±0.13 | 1.13 ±0.13* | 0.88 ±0.13 | 0.25 ±0.16 | 0.25 ±0.16 | 2.63 ±0.26 | 0.00 ±0.00 |
| 4 (5500 beats, 3 sessions) | 0.75 ±0.16 | 0.25 ±0.25 | 1.13 ±0.13 | 1.88 ±0.13*$^{+}$ | 1.00 ±0.00 | 0.63 ±0.18 | 0.13 ±0.13 | 2.50 ±0.33 | 0.13 ±0.13 |

0: None; 1: Mild; 2: Moderate; 3: Severe; +: Statistical difference between groups 1 and 4 ($p<0.05$); *Statistical difference between groups 3 and 4 ($p<0.05$)

### Histomorphological evaluation

Nephroureterectomy specimens were fixed in 10% formalin for 24 h. Tissue samples were dehydrated with graded alcohol baths, embedded in paraffin, and sectioned to a thickness of 5 $\mu$m. These sections were stained with hematoxylin-eosin (H&E), periodic acid Schiff (PAS) and Masson's Trichrome stain and examined under a light microscope (Olympus™, BX50). Masson's Trichrome stain was used to demonstrate the fibrosis and the PAS stain was used to demonstrate tubular epithelial vacuolization. Histomorphological evaluation was done according to the extensiveness of capsular thickening, ureteral, interstitial and perivascular fibrosis, subcapsular and intraparenchymal hemorrhage, tubular epithelial vacuolization and atrophy, and glomerular destruction. Histomorphological findings were scored as: none (0), no lesion was seen; mild (1), if the lesion was seen only in one microscopical field at ×200 magnification; moderate (2), if the lesion was seen in two microscopical fields at ×200 magnification; severe (3), if the lesion was seen in more than two microscopical fields at ×200 magnification.
The histopathological evaluation was performed by an experienced pathologist (SUB).

### Statistical analysis

Data was analyzed using SPSS-16.0 for Windows (SPSS, Inc., Chicago, IL USA) with one-way analysis of variance (ANOVA) method. Differences between the groups were determined with the Dunnett's multiple comparisons test and data was expressed as mean ±standard deviation (SD) of the mean. A probability level of $p < 0.05$ was considered significant.

## RESULTS

Petechiae of the skin was observed in 24/32 (75%) of the procedures (16 rabbits but 32 ESWL procedures, including both the right and left side of the same rabbit) immediately after ESWL. No macroscopical changes in the abdominal organs was noted during exploration.
The histopathological findings are summarized in Table 2. Capsular thickening, subcapsular hematoma (Figure 1), tubular atrophy, tubuloepithelial vacuolization, and glomerular destruction were detected at mild levels in all groups. Ureteral fibrosis was observed at mild levels in the 1st and 4th groups, but was not evident in the 2nd and 3rd groups. There was no statistical difference between the groups (Figure 2, 3, 4).

Parenchymal hemorrhage was mild, and interstitial fibrosis was severe in all groups. There were no statistically significant differences between the parenchymal hemorrhage and interstitial fibrosis findings of the four groups. Perivascular fibrosis was mild in the 3rd group, whereas it was moderate in the 4th group. When perivascular fibrosis was compared, we identified a statistically significant difference between the 1st and 4th, and between the 3rd and 4th group ($p < 0.05$) (Table 2).

## DISCUSSION

Eighty to 90% of all renal calculi are currently amenable to fragmentation by ESWL, however, complete

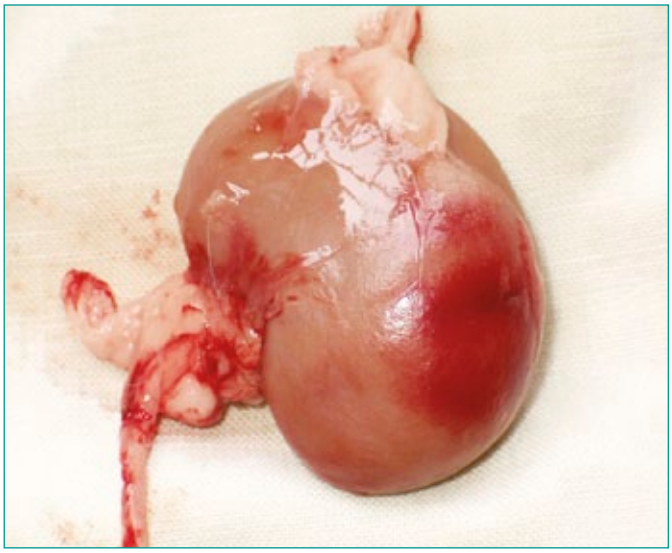

**Figure 1.** *Photograph of the nephrectomized kidney of group 1 (3500 beats, 1 session).*

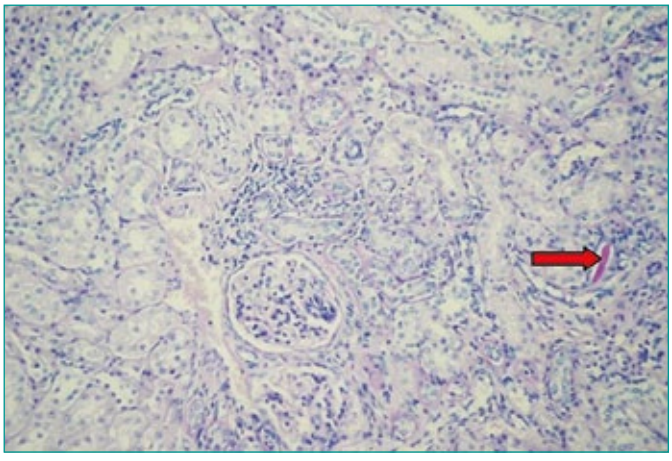

**Figure 2.** *Kidney section of group 4 (5500 SWs, 3 sessions) shows focal minimal tubular atrophy. One of them contains a PAS positive hyaline cast (arrow) (PAS, x200).*

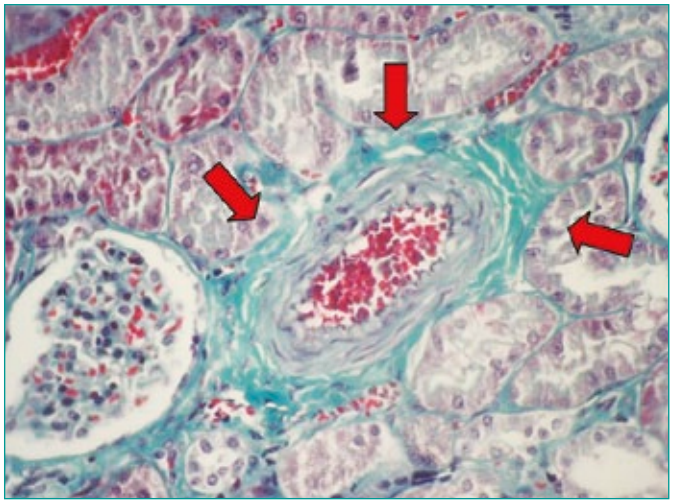

**Figure 3.** *Kidney section of group 4 (5500 SWs, 3 sessions) shows prominent fibrosis around vessels, appearing green in Masson's Trichrome stain. (Arrows) (Masson'sTrichrom, x400).*

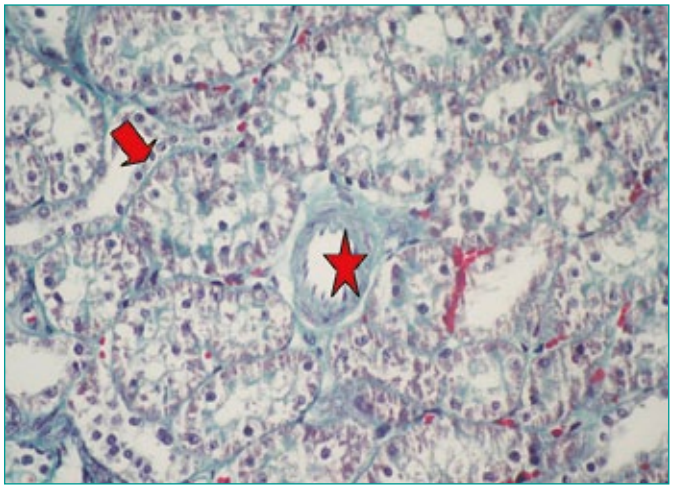

**Figure 4.** *Kidney section of group 1 (3500 SWs, 1 session) shows unremarkable histopathological findings. Here, tubular atrophy and perivascular fibrosis are not seen. (Asterisk shows blood vessel, arrow shows tubule) (Masson'sTrichrome, x400).*

removal with ESWL monotherapy is difficult for stones larger than 2.5 cm or for hard stones, such as those composed of calcium monohydrate or cystine. These complex calculi may require multiple treatments and higher power settings to accomplish adequate fragmentation with ESWL [10]. In our study, the principal reason of choosing the 3500 and 5500 shock waves was to investigate whether the detrimental histopathological and cumulative effects of the SWs are increased at such a high dose and energy. For that reason, we did not apply low energy waves at the beginning of the procedure to minimize the risk of renal injury. If there are no substantial changes in terms of adverse effects, it might be advantageous to apply high dose and high energy SWs in the presence of suspected hard stones, thereby potentially achieving adequate fragmentation and reducing the number of ESWL sessions required. According to our results, the use of high dose and high energy SWs may be preferred in cases of hard stones because of the possibility of complete fragmentation within the first session, thus reducing the number of required sessions and thereby preventing a cumulative effect.

An average of 700 to 3000 shocks of variable voltage is preferred to disintegrate kidney and ureteral stones by ESWL [11]. However, the initial *in vivo* studies on the effects of these energy waves on physiologic functions and cellular structures were limited to much lower numbers of SWs and voltage [12]. The margin of safety for the kidney during SW application is as of yet largely unknown [13]. The appearance of detrimental effects after intense ESWL applications has been confirmed in many studies [13, 14]. In animal models, no pathological changes were observed after application of 500 SWs. However, the pathological changes began to appear at higher doses, and 8000 SWs were reported to be lethal for a rabbit in the Guneasekaran study [12, 15]. In addition, animal studies have demonstrated that acute changes following ESWL are similar to those seen in human subjects [15, 16]. Moreover, the chronic renal changes noted in animal studies include diffuse interstitial fibrosis, loss of nephrons, focal calcification, and perinephric scarring [17].

In our histomorphological evaluations, subcapsular hemorrhage, tubuloepithelial vacuolization, tubular atrophy, glomerular destruction and ureteral fibrosis were detected at low levels in every group. Intraparenchymal hemorrhage and perivascular fibrosis were also mild. There was no statistical difference between the groups in terms of histomorphological parameters, except for perivascular fibrosis. Although, there was a significant difference for perivascular fibrosis between the 3$^{rd}$ and 4$^{th}$ group ($p < 0.05$), no significant difference could be established between the 1$^{st}$ and 2$^{nd}$ groups, in which one session of ESWL was applied. This finding might indicate a possible cumulative effect of ESWL. In the literature, the cumulative effects of ESWL after repeated sessions were similarly observed in a study by Koga et al. [17]. We observed severe interstitial fibrosis in all groups. In contrast to other studies, we did not demonstrate any local renal contusions or focal calcifications [17, 18, 19].

In the present study, interstitial hemorrhage, subcapsular hemorrhage, capsular tension and perirenal hemorrhage, were evident after ESWL, in ac-

cordance with the findings of studies by Newman et al. and Karalezli et al. [13, 14], however, intratubular hemorrhage, subcapsuler fibrosis, and parenchymal necrosis were not observed. These findings may be interpreted as acute effects of ESWL. Furthermore, evidence of permanent changes (e.g., fibrosis, tubular and glomerular damage, chronic inflammatory alterations) was also observed in our study, which is in accordance with other studies [13, 14]. Therefore, we recommend that in such studies, additional histomorphological evaluation should be performed at the 3rd month post-therapy in order to determine whether such chronic changes are permanent.

Early experimental animal studies using ESWL were performed with a dog model, but subclinical levels of SW treatments were used. Only 500 SWs were given to each kidney and none of these kidneys demonstrated any pathological changes [12]. Although the histomorphological effects of ESWL treatment have been studied previously, our aim was to investigate the side effects of ESWL at high number of SWs (3500–5500 SWs) of high energy (23kV power). Here we assessed the dose-dependent effects of ESWL doses of 3500 and 5500 SWs and the cumulative effects of up to three sessions. We detected no statistical difference between the 1st and 3rd session with respect to histomorphological findings, except for perivascular fibrosis. Our perivascular fibrosis findings also showed a significant difference between the 1st and 4th group and between 3rd and 4th group. Koga et al. also reported cumulative destructive effects with repetitive ESWL applications [18].

The difference of results among studies investigating the bioeffects of ESWL arises due to the fact that there still has not been a consensus on the multiple mechanisms acting on stone fragmentation and tissue damage. Growing concerns over the acute and long-term adverse effects associated with ESWL requires treatment strategies to reduce renal injury and improve the efficiency of stone disintegration [20]. The kind of lithotripter used in these studies may also affect the results. Recent studies concerning the mechanism of stone disintegration, SW focusing, coupling, and application may address some of these problems [8]. Four generating principles are used in clinical lithotripters. In electrohydraulic lithotripters (EHLs), a spark discharge between two electrodes produces the SW. EHLs have a high shot-to-shot variability, since the spark location varies as the electrodes wear down. The significance of this "jitter effect" is under debate [21], with some suggesting that it might be less relevant in large-focus sources [22]. The electroconductive system (EDAP TMS, Vaulx-en-Velin, France) employs electrodes surrounded by a highly conductive solution, resulting in repeatable spark location because of shorter inter-electrode distance and reduced electrode wear [23]. Electrode lifetime exceeds 40.000 impulses. Electromagnetic and piezoelectric sources provide stable SW release lasting for more than a million shocks; however, acoustic output instability may occur [24].

Reducing the pulse rate frequency (PRF) from 120 to 30 SWs/min resulted in a pronounced decrease in particle size and an increase in particle surface [25]. Slowing the delivery rate from 60 to 30 SWs/min also provided a dramatic protective effect on the integrity of renal vasculature in a porcine model [26]. These findings support potential strategies of reduced PRF to improve safety and efficacy in ESWL [20]. However, in clinical practice, low PRF prolongs treatment time significantly and may be inconvenient for patients who are unable to maintain a stable position. The analysis of seven randomized controlled trials (n = 1235) suggests a better outcome at 60-80 SWs/min compared with 120 SWs/min, mostly in stones >10 mm in diameter [27, 28].

In addition, experimental studies in the pig model show that lithotripter settings for power and SW rate, and the sequence of SW delivery can be used to reduce the trauma to the kidney. Stepwise power ramping used to acclimate the patient to SWs causes less tissue trauma when the initial dose is followed by a brief (3-4 min) pause in SW delivery. Slowing the firing rate of the lithotripter to 60 SWs/min or less is also effective in reducing renal injury and has the added benefit of improving stone breakage outcomes [29]. Neither strategy to reduce renal injury – power ramping with 'pause-protection' or delivering SWs at reduced SW rate – have been tested in clinical trials [20].

Besides renal injury, ESWL is not completely free from other serious complications, such as gastrointestinal injury (in approximately 1.8% of cases), including colonic perforation or duodenal erosions [30]. Findings of our study showed no macroscopical changes in the intra-abdominal organs during exploration. Nevertheless, these complications may have been underestimated due to the low number of animals in our study.

Multisequential ESWL treatments and high-energy shock waves are required to treat large and resistant calculi. Our knowledge until now demonstrates that SWL results in short-term temporary histopathological changes. Although no pathological findings were observed in small doses, the detrimental effects on different parameters began to appear in varying intensities with increasing doses of ESWL.

To date, no study has been performed that can fully show the long-term effects of ESWL on the kidney. Newman et al. reported dose-dependent renal parenchymal fibrosis in dogs, and this was also proven in rabbits by Morris et al. [31]. These findings are similar to ours.

### Study limitations

Although there were statistical differences between the assessed parameters, these significances are not very strong due to the low number of subjects. In addition, the rabbits did not have renal stones, which limits projecting these results to everyday clinical practice, since stones targeted during ESWL treatment also absorb energy from SWs.

## CONCLUSIONS

Our findings in terms of perivascular fibrosis suggest that a cumulative effect may occur with the application of sequential high doses. Future studies should include histopathological evaluation of the kidneys at a later time point (ie. at 3 months), which may illustrate better the long-term effects of ESWL.

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