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ORIGINAL PAPER

Effect of SWL on renal hemodynamics: could a change in renal artery contraction–relaxation responses be the cause?

Erdal Yilmaz · Cagatay Mert · Zuhal Keskil · Devrim Tuglu · Ertan Batislam

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Abstract The aim of this study was to reveal the effect of shock wave lithotripsy (SWL) on renal artery contraction–relaxation responses and the relation of this effect with renal hemodynamics. Twenty-four rabbits are divided into six different groups. The first two groups evaluated as the control groups. After isolating the kidneys, we applied phenylephrine (Ph) and acetylcholine (Ach) in the first group and sodium nitroprusside (SNP) and histamine (H) in the second group. In the third, fourth, fifth and sixth groups, 14.5 kV shock wave (SW) was focused on the left kidneys. We adjusted the number of shocks to a total of 500, 1,500, and 3,000 SW, in the third, fourth and fifth groups, respectively. After isolating the kidneys, Ph, Ach was given in groups 3, 4 and 5. In the sixth group, to get the SNP and the H responses, 3,000 shocks modality was utilized. Marked contractile responses were obtained by phenylephrine in the control group. In kidneys that were exposed to 500 shocks SWL procedures, a decrease in contractile responses and hence, in perfusion pressures in different concentrations of phenylephrine was noted. However, a notable change in relaxation responses occurred after 3,000-shock applications. No difference in relaxation responses to nitroprusside, a direct vasodilating agent, was observed in any group, compared to the control group. Another cause of deterioration of renal hemodynamics after SWL can be attributed to the reduction in renal artery contraction–relaxation responses that result in the vascular smooth muscle and endothelial damage.

Keywords SWL · Renal artery · Contraction · Dilatation · Response · Renal damage

E. Yilmaz (✉) · C. Mert · D. Tuglu · E. Batislam
Department of Urology, Faculty of Medicine, University of Kirikkale, Tip Fakultesi, Uroloji AD, Saglik Sokak, 71100 Kirikkale, Turkey
e-mail: erdaly69@mynet.com

Z. Keskil
Department of Pharmacology, University of Kirikkale, Kirikkale, Turkey

Introduction

Shock wave lithotripsy (SWL) is a noninvasive treatment modality that is commonly used in urinary tract stone disease [1]. Although it is an effective treatment method in stone disease, it is well known that it can cause acute renal damage [2, 3]. This damage involves rupture of the medullary and cortical vessels, intraparenchymal hemorrhage, oxidative stress, inflammation and impairment of renal hemodynamics [4, 5]. Scar formation and loss of renal tissue function can develop due to acute renal damage [6, 7].

Acute changes in renal hemodynamics result in a temporary decrease both in the glomerular filtration rate (GFR) and renal plasma flow (RPF) [8, 9]. This decrease is very severe, particularly during the first 4 h, occurring with 2,000 shocks and 24 kV application [10, 11]. Many studies suggest that hemodynamics is subject to change not only in the treated side but also in the other kidney as well [5, 6]. While RPF decreases in the contralateral kidney, GFR is not affected [7, 8]. Corticomedullary and interstitial hemorrhage, dilatation in arcuate and interlobular veins and production of free radicals can occur, resulting in renal damage, as shown in animal studies [4–6, 12]. Free radicals exhibit toxic effects by initiating lipid peroxidation in the vascular membranes [13].

Changes in renal hemodynamics are detected mainly by resistive index in the previous studies [14–17]. It is shown

that renal hemodynamic changes are more apparent following SWL especially in elderly patients [18, 19].

One of the causes of renal hemodynamic changes can be alterations in the renal artery contraction–relaxation responses. As far as we know, contraction–relaxation responses have not been studied hitherto. We aimed to show the presence of vascular smooth muscle destruction or endothelial damage after SWL by evaluating contraction–relaxation responses. In our study, various concentrations of four agonists were used by isolated perfusion of kidneys in the rabbits in order to imitate endogenous mechanisms for contraction and relaxation responses.

Materials and methods

The experimental protocol in this study was carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committee of the Kirikkale University School of Medicine. Twenty-four 12-week-old male rabbits were used (New Zealand species, albino, young, mature). Rabbits, in which the kidneys did not perfuse completely, with anatomic anomaly or a general deteriorated mood before the experiment were excluded.

SWL was performed with an electrohydraulic Stone-Lithotripter (PCK^{TM}, Ankara, Turkey). The experimental studies were conducted with six randomized groups, each consisted of four participants.

Following were experiment groups:

Group 1: the control group, in which the kidneys were isolated without SWL application, and phenylephrine (PhE) and acetylcholine (Ach) responses were taken ($n = 4$).

Group 2: the control group, in which the kidneys were isolated without SWL application, and histamine (H) and sodium nitroprusside (SNP) responses were taken ($n = 4$).

Group 3: the group in which SWL was applied with a number of 500 shocks and a power of 14.5 kV; after 30 min, the kidneys were isolated, and PhE and Ach responses were taken ($n = 4$).

Group 4: the group in which SWL was applied with a number of 1,500 shocks and a power of 14.5 kV; after 30 min, the kidneys were isolated, and PhE and Ach responses were taken ($n = 4$).

Group 5: the group in which SWL was applied with a number of 3,000 shocks and a power of 14.5 kV; after 30 min, the kidneys were isolated, and PhE and Ach responses were taken ($n = 4$).

Group 6: the group in which SWL was applied with a number of 3,000 shocks and a power of 14.5 kV; after 30 min, the kidneys were isolated, and H and SNP responses were taken ($n = 4$).

The positions of the kidneys in the rabbits were marked by the renal ultrasound after the 2 ml intramuscular ketamine anesthesia in the department of SWL. Groups 1 and 2 were taken as control groups and no SWL was applied to these groups. In other groups, a standard power of 14.5 kV was given to the left kidneys of the animals in which SWL application was going to take place and shock waves of 500, 1,500, and 3,000 were applied according to their groups.

Pharmacological examinations of the kidneys of the rabbits were conducted 30 min after the SWL application. Anesthesia was given by injecting 30 mg/kg sodium pentobarbital from the ear veins of the rabbits. After an effective anesthesia was provided, abdomen was opened and kidneys were isolated.

The kidneys were cannulated from the renal artery, and after the perfusion with 10 cc Krebs solution containing heparin, the kidneys were suspended to isolated organ perfusion system with the objective of providing perfusion with constant volume. In the system of isolated organs, the rabbit kidneys were perfused in Krebs solution at 37 °C, with a rate of 6–7 ml/min. Perfusion pressure data of the kidneys were recorded using the Statham P 23 XL pressure transducer and Powerlab data recording, analysis system.

After the rabbit kidneys were suspended in the isolated organ perfusion system, perfusion pressure was maintained by perfusing with Krebs solution for nearly 45 min until equilibrium was reached. Agonist responses were obtained following this balancing period. Bolus injection was made before perfusion pump to hold different doses of each agonist at 0.1 ml. Phenylephrine (in the doses of 6.11, 20.4, 61.1 μg and 0.2 mg) and histamine (in the doses of 18.4, 55.2 μg and 0.18, 0.55 mg) were given with 0.1 ml bolus injection, and increases in the perfusion pressure were recorded distinctively for each dosage. When relaxation responses were being taken, phenylephrine was added into the Krebs solution to reach the submaximal concentration (10^{-5} M). Basal perfusion pressure was expected to increase by perfusing the kidneys with 10^{-5} M phenylephrine Krebs solution for a while. After increase in the perfusion, pressure reached an equilibrium state, Ach (0.18, 1.82, 18.2 μg and 0.18 mg) and SNP (2.98, 8. 94, 29.8, 89.4 mg) were given with 0.1 ml bolus injection and decreases in the perfusion pressure were recorded.

The chemical substances that were used during the experiment (phenylephrine, histamine, acetylcholine, nitroprusside) were purchased from the Sigma Company (Massachusetts, USA). The stock solutions of these substances were prepared with distilled water before starting to the experiment and they were preserved in the refrigerator. The

dilutions that were done in stock solutions were again prepared with distilled water, in the day that the experiment was going to be held.

Statistical evaluation

The evaluations were done relying on the changes in the perfusion pressure of the isolated kidneys of the rabbits. Agonist responses that caused contraction in the vascular bed were evaluated depending on the increases that occurred in the basal perfusion pressure. The agonist responses that caused relaxation in the vascular bed were evaluated relying on the percent decrease causing the basal perfusion pressure which was increased by submaximal phenylephrine (10^{-5} M). Statistical significance among the different groups was evaluated by nonparametric variance analysis, Kruskal–Wallis and comparison of dual groups Dunn test. The cases when p was <0.05 were accepted as significant.

Results

Alpha-1 receptor agonist phenylephrine caused a more prominent increase in dose-dependent contraction accompanied by increased perfusion pressure in the kidneys belonging to the control group. In kidneys that received 500 shock SWL, phenylephrine in doses of 6.11 μg, 61.1 μg and 0.2 mg resulted in a statistically significant decrease in the contraction responses and hence, in the perfusion pressure ($p = 0.014$, 0.039 and 0.016, respectively). Although the perfusion pressures decreased in kidneys that were treated with 1,500 and 3,000 shocks, this decrease was not as much as those treated with 500 shocks (Fig. 1a). When contralateral kidneys are evaluated, the decrease in perfusion pressure in the treated kidney showed a similarity in terms of doses and number of shock waves (Fig. 1b).

Histamine, a second alpha agonist aimed at confirming the changes in contractile responses, was used. As expected, a dose-dependent increase in the perfusion pressure was detected in isolated rabbit kidneys. When dose-dependent responses were evaluated following the application of 3,000-shock SWL, contraction responses and hence, perfusion pressures were observed to be decreasing with the increased dosages. A statistically significant difference was observed especially when histamine was used at the dose of 0.18 mg ($p = 0.033$) (Fig. 2). Responses were found to be decreased in the contralateral kidney as well.

After attaining a submaximal increase in the perfusion pressures of the kidneys with phenylephrine (10^{-5} M), a decrease in perfusion pressure was recorded with bolus injections of acetylcholine in gradually increasing doses. Relaxation responses in kidneys receiving the 500 and

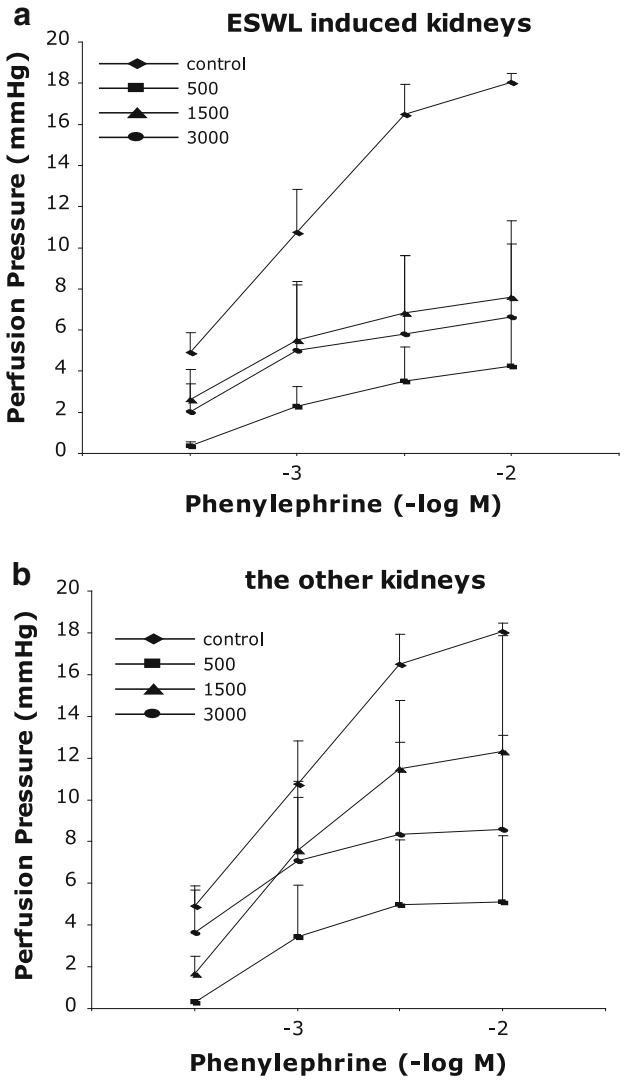

Fig. 1 Phenylephrine responses in isolated perfusion phase, in SWL applied (**a**) and contralateral (**b**) kidneys of rabbits

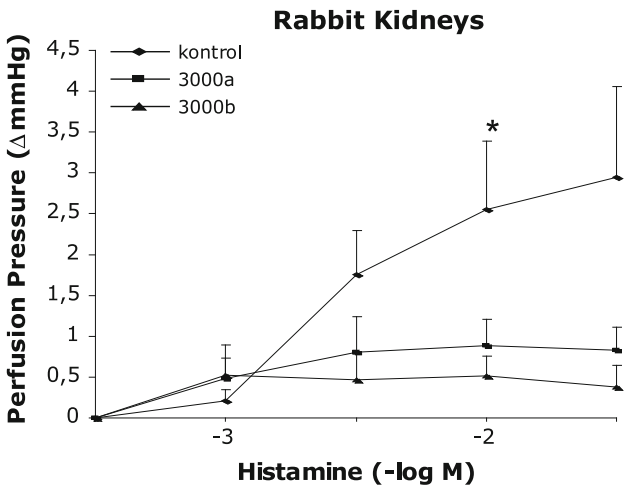

Fig. 2 Histamine responses in isolated perfusion phase, in SWL applied kidneys of rabbits

1,500 shocks did not change, while evaluations done following the 3,000-shock application revealed a decrease in relaxation responses in kidneys bilaterally. This decrease occurred mainly at the 0.18 μg and 0.18 mg doses in the shock-applied kidney ($p = 0.003$ and 0.019, respectively) (Fig. 3a). Meanwhile, a decrease was detected especially at the doses of 0.18 and 1.82 μg in the contralateral kidney ($p = 0.004$ and 0.046, respectively) (Fig. 3b).

In order to evaluate whether the changes related to relaxation responses were due to endothelium, SNP that causes direct vasodilatation was used. After a submaximal increase in perfusion pressure of the kidneys was obtained again with phenylephrine, the decrease in perfusion pressures was recorded via bolus injections of SNP in increasing doses. It was found that compared to the control group, no difference was present in responses and perfusion pressures following SWL applications (Fig. 4).

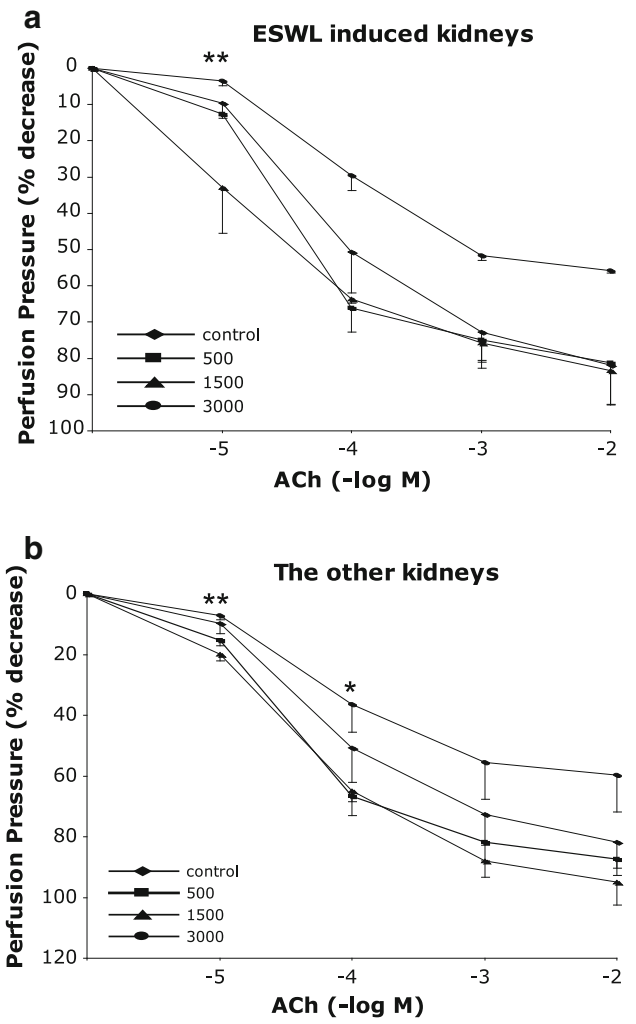

Fig. 3 Relaxation responses with acetylcholine after submaximal contraction with phenylephrine responses in isolated perfusion phase, in SWL applied (**a**) and contralateral (**b**) kidneys of rabbits

Discussion

Although SWL is a treatment method very commonly used in urinary system stone disease, it has some potential complications [1, 11]. There are numerous studies concerning that SWL can cause acute renal damage [2–4]. This damage also involves impairment of renal hemodynamics. This impairment in renal hemodynamics is reported in many studies [5–10].

Using dynamic gadolinium-DTPA enhanced magnetic resonance imaging, Mostavafi et al. [20] have reported a decrease in cortical flow and an increase in medullary flow in six out of seven patients. A decrease in renal perfusion in the kidney that was treated and in the contralateral kidney was also shown. Beduk et al. [21] have reported that no changes occurred in resistive index (RI) before and after SWL. Juan et al. [22] have underlined that right after SWL, intrarenal blood flow did not show any change in hydronephrotic kidneys compared to the untreated kidneys. On the contrary, Katakoa et al. [23] have identified a marked increase in RI immediately after SWL. Similarly, Knapp et al. [24] have shown positive linear correlation after SWL between patient's age and RI. Mitterberger et al. [19] have also reported that RI increased in elderly patients after SWL. Aoki et al. [25] have suggested that there was more renal tissue damage after the SWL in elderly patients.

Renal damage can be shown by biochemical parameters as well [26, 27]. Increases in urinary and blood renin, creatinine, *N*-acetyl-β-D-glucosaminidase, β_2-microglobuline and proteinuria get back to normal in few days. Endothelin-1 (ET-1) is a peptide originating from endothelium and it has a strong vasoconstrictor activity. Ferenz et al. [26] have reported that ET-1 in the serum and urine of children increases right after SWL and 3 months afterwards. Strohmaier et al. [27] did not

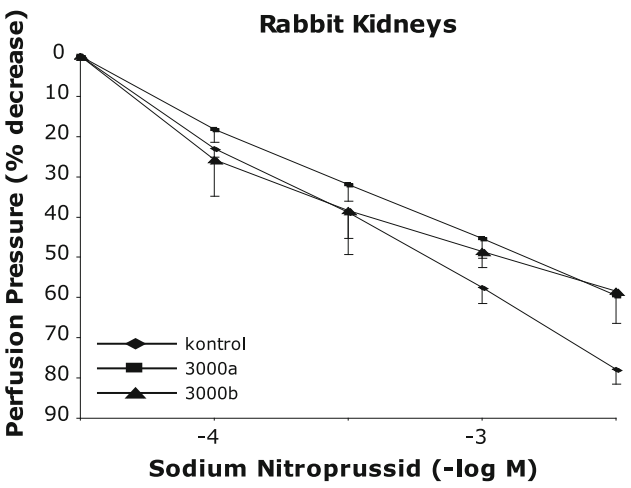

Fig. 4 Relaxation responses with sodium nitroprusside after submaximal contraction with phenylephrine responses in isolated perfusion phase, in SWL applied kidneys of rabbits

find similar results in adults; however, they recorded elevated ET-1 levels in elderly patients who have high RI.

In previous studies, GFR and RPF have been shown to decrease following SWL [28, 29]. In some studies, however, this decrease was noted only in elderly patients [19, 20]. SWL causes parenchymal damage resulting in the impairment of renal perfusion, especially in patients older than 60. A marked ET-1 and RPF changes have been noted in this age group. Decreases in renal perfusion have been detected both in the treated kidney and in the contralateral kidney using magnetic resonance perfusion imaging [20].

Many patients may need repeated SWL sessions. Koga et al. [10] have reported that cumulative renal damage occurred in dogs and repeated sessions intensified the damage. Lingeman et al. [11] underlined that 2,000–3,000 shocks caused damage in pig kidneys.

There can be several reasons for the deterioration of renal hemodynamics after SWL. One of them is edema formation that develops in the renal interstitium. It has been shown in short-term follow-ups after SWL that edema formation disturbs renal parenchymal perfusion [28]. This finding suggests that vascular changes alone do not cause hemodynamic changes. Apart from this, mediator hormones and/or other substances can also result in hemodynamic changes [16, 18]. Vascular endothelial cells synthesize many mediators such as prostacyclin, nitric oxide and endothelin that control vascular tone. It is reported that an endothelial-derived hyperpolarizing factor may be responsible for some part of endothelium-dependent relaxation responses [29]. Another cause of deterioration of renal hemodynamics after SWL could be attributed to the reduction in renal artery contraction–relaxation responses that result in the vascular smooth muscle and endothelial damage. Therefore, in order to show the effects of SWL on renal hemodynamics, contraction and perfusion responses were evaluated by isolated perfusion of the kidney in our study. Endogenous mechanisms were simulated by adjusting the severity of the stimulus using various concentrations of agonists that are used for contraction and relaxation.

Phenylephrine and histamine were used for contraction responses. A decrease in contraction responses by acetylcholine has been shown in our study and this finding was verified by another agonist, histamine. It was noted that the decrease in contraction responses started at 500 shocks. This suggested us that SWL causes some damage in vessel smooth muscle. The responding ability of the vessel decreases after shock wave. Another finding that could be considered important was that the contraction responses in the kidneys were decreased after SWL.

To obtain relaxation responses, acetylcholine that has an effect dependent on nitric oxide released from the endothelial layer and SNP, which causes vasodilatation, were used. It was noted that relaxation responses decreased at 3,000 shocks. That there was no change in the responses with SNP suggests that the decrease in the relaxation responses originates from the endothelium. Eventually, this finding can be considered as SWL decreases relaxation responses by causing endothelial damage as well.

These decreases in contraction and relaxation responses can effect renal perfusion [30]. Renal blood flow and GFR may decrease, which results in an increase in renin secretion [31]. Renin converts angiotensinogen produced in the liver to angiotensin [32]. Angiotensin causes blood pressure to rise by three mechanisms of action. First of these is achieved by providing contraction of smooth muscles located on the walls of blood vessels. Blood vessels constrict as these smooth muscles contract, thus blood pressure rises [32]. Angiotensin causes some nerve hormones, which lead to more contraction of the vessels, to join into blood. Its third mechanism of action is on the surrenal cortex. Angiotensin stimulates aldosterone secretion. Aldosterone increases blood volume and blood pressure by causing salt and water to join into blood plasma [32]. This damage occurred by SWL can result in newly emerging hypertension or worsening of existing hypertension. Thereby, renal damage can be reduced using angiotensin receptor blockers during and after SWL.

While this damage is temporary in the normally functioning kidneys, a permanent damage can occur in kidneys that suffer from dysfunction [10, 11]. It is obvious that extra care must be taken in children, in multiple SWL applications, in patients with single kidney, in patients who have venous insufficiency and glomerulosclerosis or glomerulonephritis.

Conclusion

Another cause of deterioration of renal hemodynamics after SWL could be attributed to the reduction in renal artery contraction–relaxation responses that result in the vascular smooth muscle and endothelial damage. Alteration of contraction responses following SWL occurred in less numerous shock waves, while that of relaxation responses occurred in numerous shock waves. This, in turn, suggests that both smooth muscle and endothelium damage are evident immediately after SWL. In order to understand whether the changes in these responses are temporary or permanent, it would be useful to evaluate late responses as well.

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