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ORIGINAL PAPER

The effects of shock waves on lung tissue in acute period: an in vivo study

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Abstract The acute effects of extracorporeal shock waves on lung morphology were studied by light microscopy in 30 New Zealand rabbits. The left kidneys of the ten animals were exposed to 2,000 shockwaves at 18 kV under anesthesia (ESWL group). Ten rabbits were in the control group; an intramuscular anesthetic agent (ketamine) and intravenous contrast media were administered to ten animals in the sham group. Localization of the left kidneys was achieved following contrast medium injection through an ear vein under fluoroscopic control. The animals were killed after the ESWL procedures and the lungs were removed. Edema, emphysema, hemorrhage, congestion, inflammation, loss of normal structure, and epithelial desquamation were determined and graded between 0 and 3 in all areas of both lungs. In order to determine whether proximity has any effect on the histopathological changes, left and right lungs were evaluated separately as well as upper and lower lobes. We found that ESWL exposed to kidney also affects all areas of the lungs in a rabbit model.

Keywords Shock wave lithotripsy · Lung · Histology

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Introduction

Since its introduction in 1980, shock wave (SW) has been commonly used for the treatment of renal and ureteral calculi [1]. Its rapid acceptance has been due to the simplicity of the treatment technique, its noninvasive nature, and the lower renal and perirenal complication rates. Currently, almost all stones in the upper urinary tract can be treated by SW with or without other endourological procedures [2]. However, the procedure is not completely free from side effects. Clinical studies and animal experiments demonstrated several renal morphological, glomerular, and tubular changes following SW exposure [3–6]. Injuries to the adjacent organs have been reported in less than 1% of patients [7]. These include pulmonary contusion [8–10], pancreatitis [11], bile duct injury [12], bowel perforation [13, 14], aortic aneurysm rupture [15], retroperitoneal hemorrhage [16], cardiac arrhythmias, and gastric erosions [17]. Since its introduction, clinical use of SW has been changing drastically. In the beginning, shock wave lithotripsy (SWL) treatment was rarely used in children. Since the first reports of pediatric SWL treatment in 1986, an increasing number of health centers have been reporting the efficacy of SW in treating children. Nowadays, SW has become the standard treatment for calculi in the upper urinary tract in children. Additionally, Shukla et al. [18] have shown the safety and efficacy of ESWL for low-birth-weight infants. Although case reports exist, there are not enough clinical or

experimental studies that determine the full impact of such treatment, particularly the lung complications of SW in pediatric population. Massive hemoptysis and death from pulmonary damage due to vascular and alveolar rupture has been reported in laboratory animals after a single exposure of the thoracic region to SWs [19]. This potential of SWs to cause pulmonary damage poses a real problem during lithotripsy in children because of the close proximity of the kidneys to the lungs [9].

In this study, we try to determine the acute effects of SW on lung tissue in a rabbit model, and the role of proximity on lung damage was also investigated. Rabbits may not be an adequate model to evaluate the effects of SW on adult lungs. However, it is hoped that the observations obtained from the application of SW to rabbits will provide insight into the impact and possible damage on children lungs because of the shorter distance between their kidneys and lungs compared with those of adults.

Materials and methods

Animals

Thirty adult male New Zealand white rabbits, each weighing 3–5 kg, were included in the study program. All animals underwent an adaptation period of 1 week in cages under normal conditions prior to the SW procedure and were fed with a standard rabbit chow and water. The animals were randomly assigned to one of three different groups, each containing 10 rabbits. The groups were named SW, control, and sham groups. Anesthesia was induced by intramuscular injection of a mixture of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg). After shaving the abdomen, the middle pole of the left kidney of the animals in the SW group was exposed to 2,000 shockwaves at 18 kV at a 90° angle. Localization of the kidneys was achieved following contrast medium (Iohexol 300 mgI/ml) injection through an ear vein, under fluoroscopic control. Only the sham group received the anesthetic agent (ketamine HCl, 50 mg/kg) and xylazine (5 mg/kg) and contrast medium (Iohexol 300 mgI/ml) without any shockwave application. All activities during the study period adhere to the "Guiding principles in the care and use of animals" published in the "Recommendations from the declaration of Helsinki."

Shock waves

The present study was carried out with a Multimed 2001™ lithotripter (Elmed Co., Turkey) located at the Uromed Urology Center, Ankara, Turkey. This lithotripter has an 80-nF capacitor, 135 mm focal distance, and a focal zone (F2) of about 22 mm diameter × 7.5 mm length. Refurbished spark plugs were used for all experiments and were discharged after each set of 2,000 shots.

Pathological evaluation

Rabbits were killed using a high dose of intraperitoneal thiopental injection (100 mg/kg) on the first day after the SW procedures. The lungs were removed through thoracal incisions, fixed in 10% formalin for 24 h and embedded in paraffin. The lung tissues were fixed in buffered formalin. Samples were taken from upper and lower lobes in the right and left lungs in order to observe main bronchi and peripheral lung tissue. The tissue samples were processed through a graded mixture of alcohol and xylene and embedded in paraffin blocks. Tissues were cut in 6 μm sections and stained routinely with hematoxylin and eosin (H&E). The histopathological findings of lung tissues were scored by a single blinded observer. In order to determine the effect of proximity on the histopathological changes, left and right lungs were evaluated separately. The observer examined three different localizations of all sections according to these criteria:

A. Alveolar changes:
(−): No change
(+): Changes observed lower than 25% of alveoli
(++): Changes observed between 25 and 50% of alveoli
(+++): Changes observed higher than 50% of alveoli
Changes evaluated:
1. Loss of normal structure
2. Emphysematous areas
3. Interstitial congestion
4. Interstitial edema
5. Prominent alveolar septal vessels
6. Interstitial inflammation
7. Intra-alveolar hemorrhage

B. Changes in bronchioles:
(−): No change
(+): Changes observed lower than 25% in every bronchiole section
(++): Changes observed between 25 and 50% in every bronchiole section
(+++): Changes observed higher than 50% in every bronchiole section
Changes evaluated:
1. Intraluminal hemorrhage
2. Peribronchial edema
3. Peribronchial congestion
4. Inflammation in bronchial wall
5. Respiratory epithelial desquamation

Changes in main bronchi:
Changes were evaluated from distal to proximal bronchi.
(-): No change

(+): Changes observed in 1/3 distal main bronchi
(++): Changes observed in 2/3 distal main bronchi
(+++): Changes observed in entire main bronchi
Changes evaluated:
1. Intraluminal hemorrhage
2. Edema in main bronchial wall
3. Congestion in main bronchi wall
4. Inflammation in main bronchi wall
5. Respiratory epithelial desquamation

Statistical analysis

Data analysis was performed by using SPSS (Statistical Package for Social Science version 11.5). Data were shown as median values (min–max). For the comparisons within a group, a Friedman test was used. Kruskal–Wallis Variance Analysis was performed for between-group comparisons. When the differences between group and within-group comparisons were statistically significant, then Mann–Whitney and Wilcoxon Sign Rank tests were used in addition to the Bonferroni adjustment. A p value of less than 0.05 was considered statistically significant.

Results

The rates of emphysematous area (Fig. 1), intra-alveolar hemorrhage (Fig. 2), loss of normal structure, prominent alveolar septal defect and interstitial inflammation were significantly different in the SW group than compared with the sham and control groups (Table 1). Interstitial edema and congestion rates were similar in all groups.

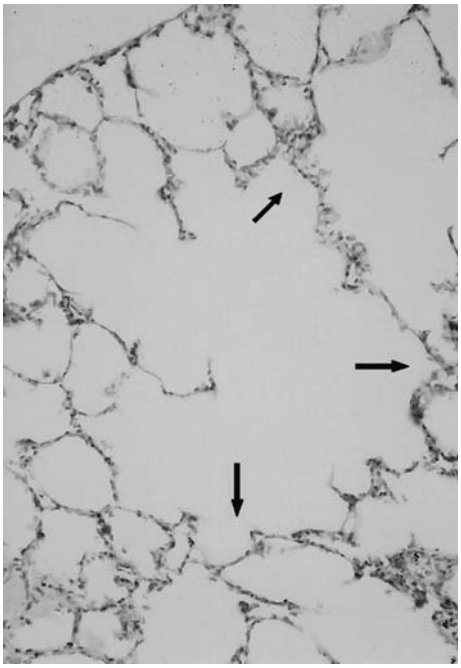

Fig. 1 Emphysematous areas (*arrow*) HE ×200

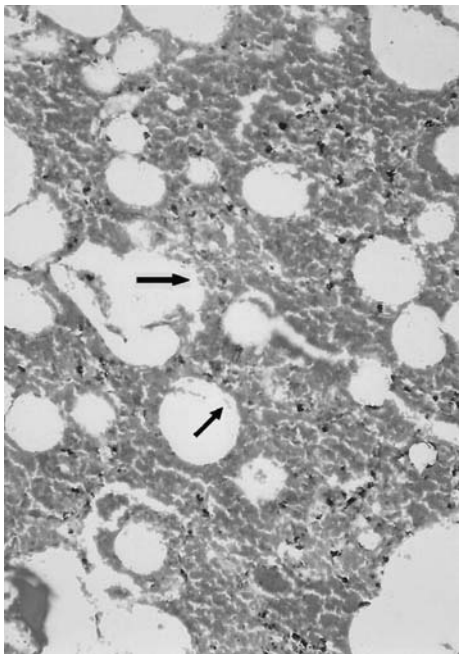

Fig. 2 Intra-alveolar hemorrhage (*arrow*) HE ×200

In order to determine whether proximity has any effect on lung pathologies, the right and left lung, as well as the upper and lower lobes of each lung were compared (Tables 2, 3). Intra-alveolar hemorrhage and interstitial edema rates were significantly higher in the left lung than in the right lung. There was no difference between the upper and lower lobes of the left lung, but intra-alveolar hemorrhage rates were significantly higher in the right lower lobe than those in the right upper lobe. According to bronchial evaluation; only peribronchial congestion rate was significantly higher in the SW group (Fig. 3). From these results, it can be concluded that proximity has a defining role in intra-alveolar hemorrhage.

Finally, when the main bronchi were evaluated, bronchial wall congestion and respiratory epithelial desquamation

Table 1 Comparison of SW & sham and control group on alveolar evaluation

	SW	Sham	Control	P
Loss of normal structure	1.7 (0–2)	0.5 (0–1)	0.0 (0–0)	$P < 0.05$
Emphysematous areas	1.7 (1–2)	0.5 (0–1)	0.0 (0–0)	$P < 0.05$
Interstitial congestion	1.7 (1–2)	1.5 (1–2)	1.0 (1–1)	$P > 0.05$
Interstitial edema	0.5 (0–1)	0.5 (0–1)	0.0 (0–0)	$P > 0.05$
Prominent alveolar septal vessels	1.8 (1–2)	1.1 (1–2)	0.6 (0–1)	$P < 0.05$
Interstitial inflammation	1.5 (1–2)	0.6 (0–1)	0.0 (0–0)	$P < 0.05$
Intraalveolar hemorrhage	1.0 (0–2)	0.3 (0–1)	0.0 (0–0)	$P < 0.05$

Table 2 Comparison of right and left lung on alveolar evaluation in SW group

	Right lung	Left lung	*P*
Loss of normal structure	1.2 (0–2)	1.7 (1–2)	$P > 0.05$
Emphysematous areas	1.2 (1–2)	1.5 (1–2)	$P > 0.05$
Interstitial congestion	1.5 (1–2)	2.6 (2–3)	$P > 0.05$
Interstitial edema	0.7 (0–1)	1.6 (1–2)	$P < 0.05$
Prominent alveolar septal vessels	1.6 (1–2)	1.5 (1–2)	$P > 0.05$
Interstitial inflammation	0.4 (0–1)	0.2 (0–1)	$P > 0.05$
Intraalveolar hemorrhage	0.7 (0–2)	2.3 (2–3)	$P < 0.05$

(Fig. 4) rates were high in the SW group and hemorrhage, inflammation, and edema rates in main bronchi wall were similar in all groups.

Discussion

Shock wave lithotripsy is currently considered the standard treatment for most renal and upper ureteral calculi; however, it is not a benign procedure [11]. Numerous clinical and experimental studies have shown that SW can cause acute adverse effects on the organs. Kidneys and the associated organs are the most commonly injured organs, but also the lungs, liver, pancreas, and gastrointestinal system can be affected by SW therapy. Clinical studies on lung contusion are very limited. A few animal study and case reports showed that SW could cause severe effects on the lungs.

Our study showed that SW causes severe emphysema, hemorrhage, congestion, edema, inflammation, loss of normal structure, and epithelial desquamation in all areas of the lungs. A similar study evaluating SW-induced renal injury demonstrated visible pulmonary hemorrhage, in an animal model [20]. Chaussy et al. [19] noted hemorrhages and alveolar rupture in the lungs of rats directly exposed to SW. In clinical practice, generally SW therapy causes minimal lung contusion; however, hemoptysis and life-threatening hypoxemia due to SW have been reported [9, 10, 21].

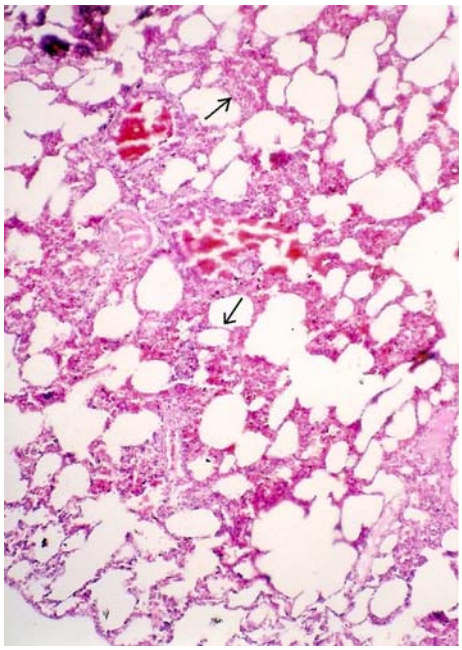

Fig. 3 Intra-alveolar hemorrhage and peribronchial congestion (*arrows*) HE ×200

During lithotripsy, the SWs pass through the water, the kidney, and the surrounding tissues without significant tissue injury because the acoustic impedance of water and the body tissues is similar [10]. However, when the shock wave approaches a medium with different acoustic impedance (e.g., renal calculus) there is significant dissipation of energy causing fragmentation of the stone [22]. Similarly, when SWs encounter a tissue–air interphase, the release of shock wave energy at the interphase will result in tissue injury. Lungs, being air-filled sacs, provide such an interphase. Making matters worse, children are more likely to sustain pulmonary injury as a result of the shorter distance between the lung base and kidney than adults [23]. The lung bases, especially in children, need to be protected from the SWs during lithotripsy. Animal experiments have demonstrated that a 3-mm-thick styrofoam sheet blocks the SWs completely [19]. Shukla et al. [18] suggested using gantry modification with a

Table 3 Comparison of right and left lung or upper and lower lobes of each lung on alveolar evaluation

	Right lung Upper lobe	Right lung Lower lobe	*P*	Left lung Upper	Left lung Lower	*P*
Loss of normal structure	1.2 (0–2)	1.2 (1–2)	$P > 0.05$	1.6 (1–2)	1.8 (1–2)	$P > 0.05$
Emphysematous areas	1.2 (1–2)	1.2 (1–2)	$P > 0.05$	1.5 (1–2)	1.5 (1–2)	$P > 0.05$
Interstitial congestion	1.7 (1–2)	1.3 (1–2)	$P > 0.05$	2.7 (2–3)	2.5 (2–3)	$P > 0.05$
Interstitial edema	0.6 (0–1)	0.8 (0–1)	$P > 0.05$	1.8 (1–2)	1.4 (1–2)	$P > 0.05$
Prominent alveolar septal vessels	1.8 (1–2)	1.4 (1–2)	$P > 0.05$	1.5 (1–2)	1.5 (1–2)	$P > 0.05$
Interstitial inflammation	0.6 (0–1)	0.2 (0–1)	$P > 0.05$	0.3 (0–1)	0.1 (0–1)	$P > 0.05$
Intraalveolar hemorrhage	0.4 (0–1)	1.0 (0–2)	$P < 0.05$	2.2 (2–3)	2.6 (2–3)	$P > 0.05$

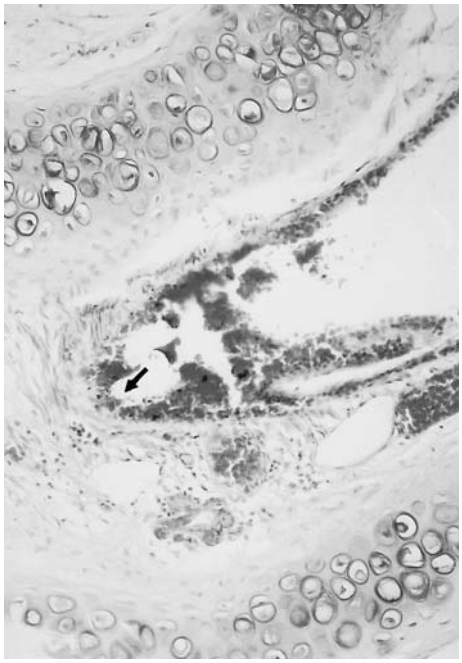

Fig. 4 Respiratory epithelial desquamation (*arrow*) HE ×200

wooden platform and polystyrene foam positioning for lung and visceral protection. Bergen and Zeitling [24, 25] have looked at the effect of differing modes of ventilation on lung and renal calculus excursion. High-frequency jet ventilation, low-volume conventional ventilation, and neuraxial anesthesia have been compared to conventional mechanical ventilation. However, no difference was shown between these methods, in terms of the effectiveness of SW. Additionally, these methods cause inadequate alveolar exchange necessitating conventional mechanical ventilation.

In the present study, rabbits were used as models. When these animals were put on the lithotripter, their lungs were within the area of SW focus. This situation may be duplicated in children during the treatment of renal calculi. In a child lying in a prone position during SW treatment, the distance between the kidney and lung is small, and so the lungs may lie directly in line with the SWs. Furthermore, this distance will even be smaller if the stone is located in the upper calyx of the kidney.

Although our study and the other animal studies show a severe pulmonary effect, in clinical practice we rarely encounter severe pulmonary complications. If SW caused similar effects on human lungs we would have encountered hemoptysis, hypoxemia, and cough very frequently. However, since its introduction, only a few cases with such side effects due to SW have been reported. Although the exact cause of this paradox is not clear to us, there are several possibilities. Based on the results of this study and observations about human application, we can now hypothesize six implications. First, it may be postulated that the voltage (18 kV) is too high for the animals. Second, animal lungs can be more prone to extensive damage than human lungs. Third, if the human F2 focus (focal point) of the machine is adjusted correctly, shocks are very rarely directed at the lungs. Fourth, only patients who have a vascular disease are vulnerable to pulmonary damage from SWs. Fifth, the diaphragm may absorb most of the misdirected SWs. Sixth, some unimportant defects may occur in most of the patients, but they are healing themselves without any clinical manifestation.

It is important to consider that factors related to the patient's breath, kidney position and movement posture may also impact the SW path. If patients breathe deeply, have a malrotated kidney or move, this may displace the stone, leading to unnecessary trauma to adjacent organs, as well as partial or no disintegration of the stone itself. These factors may also cause the SWs to pass across the lungs. Gantry chair position can also influence the SW path. If the patient is too upright in the gantry chair, the SWs can enter the flank at a more acute angle and exit more anteriorly, with the probability of passing through the lung base [10].

Despite the evidence that SW damages animal organs, it cannot be inferred that SW impacts humans in the same way. In contrast to animal studies, SW causes minimal pulmonary damage in humans which is rarely noticeable clinically. The animal studies seemingly imply that SW for renal calculi should not be applied to humans**.** However, in their 25 years of use, complications have very rarely been observed in clinical studies. Even so**,** caution must be taken to protect the lungs from SWs. Lung function tests, pathological and cytological evaluation must be done in clinical studies in order to determine the real effect of SW.

References

1. Chaussy CH, Brendel W, Schmiedt E (1980) Extracorporeally induced destruction of kidney stones by shock waves. Lancet 2:1265–1268
2. Benyi L, Weizheng Z, Puyun L (1995) Protective effects of nifedipine and allopurinol on high energy shock wave induced acute changes of renal function. J Urol 153:596–598
3. Karalezli G, Gogus O, Beduk Y, Kokuuslu C, Sarıca K, Kutsal O (1993) Histopathologic effects of extracorporeal shock wave lithotripsy on rabbit kidney. Urol Res 21:67–70
4. Kaji DM, Xie HW, Hardy BE, Sherrod A, Huffman JL (1991) The effects of extracorporeal shock wave lithotripsy on renal growth, function and arterial blood pressure in an animal model. J Urol 146:544–547
5. Serel TA, Ozguner F, Soyupek S (2004) Prevention of shock wave-induced renal oxidative stress by melatonin: an experimental study. Urol Res 32:69–71
6. Weber C, Moram ME, Braun EJ, Drach GW (1991) Injury of rat renal vessels following extracorporeal shock wave treatment. J Urol 147:476–481
7. Ilnyckyj A, Hosking DH, Pettigrew NM, Bernstein CN (1999) Extra-corporeal shock wave lithotripsy causing colonic injury. Dig Dis Sci 44:2485–2487

8. Tiede JM, Lumpkin EN, Wass CT, Long TR (2003) Hemoptysis following extracorporeal shock wave lithotripsy: a case of lithotripsy-induced pulmonary contusion in a pediatric patient. J Clin Anesth 15:530–533
9. Malhotra V, Gomillion MC, Artusio JF (1989) Hemoptysis in a child during extracorporeal shock wave lithotripsy. Anesth Analg 69:526–528
10. Malhotra V, Rosen RJ, Slepian RL (1991) Life-threatening hypoxemia after lithotripsy in an adult due to shock-wave-induced pulmonary contusion. Anesthesiology 75:529–531
11. Hassan I, Zietlow SP (2002) Acute pancreatitis after extracorporeal shock wave lithotripsy for a renal calculus. Urology 60:1111–1113
12. Hung SY, Chen HM, Jan YY, Chen MF (2000) Common bile duct and pancreatic injury after extracorporeal shock wave lithotripsy for renal stone. Hepatogastroenterology 47:1162–1163
13. Geh JL, Curley P, Mayfield MP, Price JJ (1997) Small bowel perforation after extracorporeal shock wave lithotripsy. Br J Urol 79:648–649
14. Castillon I, Frievro O, Gonzales-Enguita C, Vela-Navarrete R (1999) Colonic perforation after extracorporeal shock wave lithotripsy. BJU Int 83:720–721
15. Gugulakis Ag, Matsagas MI, Liapis CD, Vasdekis SN, Sechas MN (1998) Rupture of the abdominal aorta following extracorporeal shock-wave lithotripsy. Eur J Surg 164:233–235
16. Bex A, Goepel M, Mollhoff S (1992) Extensive retroperitoneal hematoma following extracorporeal shock wave lithotripsy with second generation lithotripter. Urol Int 48:111–114
17. Newmark JR, Wong MYC and Lingeman JE (1996) Complications. In: Smith AD (ed) Smith's Textbook of Endourology. Quality Medical Publishing, St. Louis, pp 681–693
18. Shukla AR, Hoover DL, Homsy YL, Perlman S, Schurman S, Reisman EM (2001) Urolithiasis in the low birth weight infant: the role and the efficacy of extracorporeal shock wave lithotripsy. J Urol 165:2320–2323
19. Chaussy CG (1982) Extracorporeal shock wave lithotripsy: new aspects in the treatment of kidney stone disease. Karger, Munich, pp 24–35
20. Delius M, Enders G, Heine G, Stark J, Remberger K, brendel W (1987) Biological effects of shock waves: lung hemorrhage by shock waves in dogs-pressure dependence. Ultrasound Med Biol 13:61–67
21. Chaussy C, Schmiedt E, Jocham D et al (1982) Extracorporeal shock wave lithotripsy. Karger, Basel, pp 1–112
22. Sigman M, Laudone VP, Jenkins AD, Howards SS, Riehle R Jr, Keating MA, Walker RD (1987) Initial experience with extracorporeal shock wave lithotripsy in children. J Urol 138:839–841
23. Sturtevant B (1996) Shock wave physics of lithotripters. In: Smith AD, Badlani GH, Bagley DH et al eds) Smith's textbook of endourology. Quality Medical Publishing, St Louis, pp 529–552
24. Berger JJ, Boysen PG, Gravenstein JS, Banner MJ, Carlson CA (1987) Failure of high frequency jet ventilation to ventilate patients adequately during extracorporeal shock-wave lithotripsy. Anesth Analg 66:262–263
25. Zeitling GL, Roth RA (1988) Effect of three anesthetic techniques on the success of extracorporeal shock wave lithotripsy in nephrolithiasis. Anesthesiology 68:272–276