


Smith's
Textbook of
ENDOUROLOGY



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Extracorporeal Shock Wave Lithotripsy: Complications

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Extracorporeal shock wave lithotripsy (ESWL) for the treatment of urinary stones was introduced to clinical practice in the early 1980s. Today, even with the refinement of endourologic methods for stone removal, such as ureteroscopy and percutaneous nephrolithotomy, ESWL remains an important treatment for uncomplicated upper urinary tract calculi.^{1,2} Although considered to be highly successful, lithotripsy is not a benign procedure, in that it is plagued by the occurrence of adverse effects and increased rates of significant injury linked to the use of high acoustic output machines. Clinical experience and studies with experimental animals treated with the first lithotripter (the Dornier HM3) have shown that a dose of shock waves sufficient to comminute a stone invariably causes trauma to the kidney.³⁻⁵ This injury can be severe and can lead to long-term complications such as new-onset hypertension,⁶⁻⁷ diabetes mellitus,⁷ and potentially brushite stone disease.^{7a} Moreover, morbidity may occur following a technically successful procedure as a result of the stone fragments produced. Complications following ESWL treatment result from stone-related problems, infection, effects of treatment on tissue and renal function, and a possible increased risk of stone recurrence.

In addition, recent studies now show that the present generation of "high-pressure" lithotriptors produce low stone-free rates, high re-treatment rates and an increased incidence of adverse effects.⁸⁻²⁴ Thus, a technology that should provide the best treatment option has become more problematic, and the lithotripter has become a risk factor itself.

ACUTE AND CHRONIC RENAL INJURY IN ESWL

ACUTE EXTRARENAL DAMAGE: CLINICAL OBSERVATIONS ESWL can induce acute injury to all extrarenal tissues that are within the boundaries of the focused shockwave front.^{3,25-27} Patients treated with an unmodified HM3 at 18 to 24 kV commonly complain of pain localized to the posterior body wall (flank) near the site of shock wave entry and renal colic.²⁸ Lithotripsy manufacturers have attempted to reduce the amount of flank pain by increasing the diameter of the entering shock front and have had some suc-

cess. ESWL has been associated with significant trauma to such organs as the liver and skeletal muscle as detected by elevated levels for total bilirubin, cholecystokinin, lactic dehydrogenase, serum glutamic transaminase and creatinine phosphokinase within 24 hours of treatment.²⁸⁻³¹ These parameters begin to fall within 3 to 7 days post-ESWL and are normal at 3 months. It should be noted that most of these findings were associated with the use of an unmodified HM3. This does not mean the unmodified HM3 is more prone to injury. The problem is that current clinical studies reporting on the use of second- and third-generation machines have inadequately reported side effects.

Gastric or duodenal erosion with hematoma formation are thought to represent one of the most common extrarenal complications of ESWL therapy³²⁻³⁶ with the potential of spillage of enteric contents³⁷⁻⁴¹ and hematochezia.³³ The incidence of bowel perforation is not known, but if one uses the data from the largest series ever reported (19,960 patients), only one small bowel perforation was noted.²³ Treatment in prone position might be an additional risk factor and should be used with caution.^{37,41}

ESWL-induced injury to other extrarenal organ systems has an incidence of 1% or less. The lung parenchyma is injured if exposed directly to shock waves.⁴² Acute pancreatitis associated with a marked rise in serum amylase and lipase levels has been observed or an increase in amylase levels in the absence of manifest pancreatitis^{28,29,43,44} as well as other forms of tissue injury.⁴⁵ Patients having a previous history of pancreatitis may be at a greater risk.⁴⁶ ESWL-induced splenic rupture may require a splenectomy.⁴⁷⁻⁵⁰ This complication may actually have a higher incidence for the third-generation machines characterized by tight focal zone and high-energy. Other ESWL-induced complications include, aortic aneurysms,⁵¹⁻⁵⁴ iliac vein thrombosis,⁵⁵ portal vein thrombosis,⁵⁶ scrotal bruising,⁵⁷⁻⁵⁹ and stimulation of the obturator nerve.^{60,61} In the early years of ESWL, it was recognized that shock waves could induce extrasystoles, thus, requiring electrocardiographic synchronization with R-wave triggering on the Dornier HM3 device.⁴² More recent clinical studies, however, have concluded that ungating was safe and effective in allowing patients with an

abnormal cardiac rhythm to be treated with the same shock time as gated cases (normal cardiac rhythm).^{62,63} This was probably a mistake, in that increasing the rate of ESWL delivery reduces the efficiency of stone breakage (see "Chapter 38, 'The Physics of Shock Wave Physics Lithotripsy'" and Chapter 40, "Treatment of Renal and Ureteral Calculi").

ACUTE RENAL INJURY: CLINICAL OBSERVATIONS

A clinical dose of shock waves induces a consistent and predictable pattern of acute structural changes in the treated kidney characterized primarily as a vascular insult with an acute inflammatory response. Gross hematuria always occurs (within the initial 200 to 300 shock waves, for the Dornier HM3), generally resolving within 12 hours^{42,64} and occurs regardless of the type of lithotripter employed. In fact, a lack of hematuria indicates a problem with shock wave delivery. The source of hematuria is direct injury to the renal parenchyma within the region of the focused shock wave.⁶⁵ Morphologic studies using both magnetic resonance imaging (MRI) and quantitative radionuclide renography or computed tomography (CT) have suggested that 63 to 85% of all ESWL patients exhibit one or more forms of renal injury within 24 hours of treatment,^{19,30,64,66-71} values much larger than that reported by Chaussy and Schmidt.²¹ These changes are not specific to any particular lithotripter, in that numerous reports have now documented identical renal bio-effects induced by the second- and third-generation lithotriptors.^{14-17,72,73}

Hemorrhage and edema within or around the kidney are the two most common renal side effects seen immediately after ESWL, causing the kidney to be enlarged (approximately 84%) and show a loss of corticomedullary demarcation (Figure 41-1).^{19,64,68,74-77} Clinically significant perirenal and subcapsular fluid (blood and/or urine) (Figure 41-2) accumulation was initially determined to occur in less than 1% of lithotripsy treatments¹⁹⁻²³ except for the report by Ueda and colleagues,¹⁷ where they detected a 4.1% hematoma rate. But these values rise to 32% of patients when screened by CT or MRI.^{19,64,68,73} In addition, the newer generation lithotriptors that have very small focal areas and extremely high peak positive pressures are reporting higher clinically significant hematoma rates of 3 to

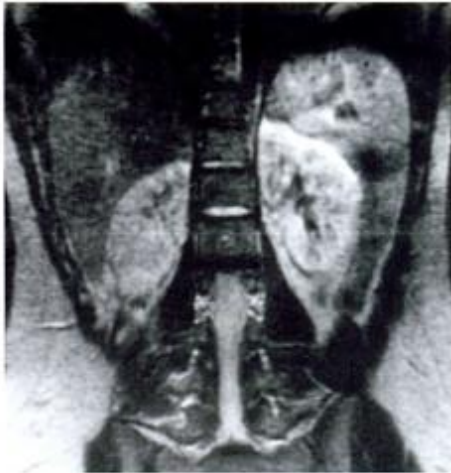


Figure 41-1 Magnetic resonance image of stone patient treated with extracorporeal shock wave lithotripsy demonstrating loss of corticomedullary junction demarcation in right kidney.

12%,^{14-17,24} a trend that is worrisome. Dhar and colleagues reported new clinical results with a Storz Modulith showing that the probability of developing a subcapsular hematoma increased 2.2 times for every 10-year increase in patient age.²⁴ All of these new data suggest that the lithotripter itself is now a risk factor for increased tissue injury. Hemorrhagic changes can range in severity from mild contusions localized within the renal parenchyma to large hematomas, which can be associated with severe bleeding requiring blood transfusions, arteriographic embolization, or percutaneous draining.⁵⁸ Such hemorrhage may produce a Page kidney with hypertension,⁷⁹⁻⁸¹ a state of acute renal failure,⁸²⁻⁸⁷ may require a partial or total nephrectomy,⁸⁸⁻⁹¹ and may result in death if the condition is not identified early.²³ Rubin and associates, using CT scans, noted changes in the perirenal soft tissues consisting of an increase in the number of septal strands and a thickening of Gerota's fascia suggesting focal regions of edema.⁶⁸ Usually, the perirenal fluid disappears within a few days, while



Figure 41-2 Computed tomography scan showing bilateral perinephric hematomas following bilateral simultaneous extracorporeal shock wave lithotripsy of a stone patient.

the subcapsular fluid or blood may take 6 weeks to 6 months (or more) to resolve (Figure 41-3).¹⁹

Acute histopathologic changes in the ESWL-treated kidney and surrounding tissues include dilation of veins with endothelial damage and thrombus formation, disruption of most renal corpuscles at F2, as well as milder degenerative changes in the nephron accompanied by hemosiderin granules and cast material.⁹² Seitz and colleagues studied the kidneys from four patients treated with a piezoelectric lithotripter and detected sites of intraparenchymal hemorrhage at the corticomedullary junction that increased in severity with increasing numbers of shocks (4,000 to 20,000).⁹³ They commented on how the gross and histologic appearance of these four ESWL-treated kidneys mirrored exactly the results published in animal studies. Human cadaver kidneys treated with a clinical dose always induced injury to nephrons and small to medium-sized blood vessels within F2.⁹⁴⁻⁹⁶ Again, as the number of shock waves was increased so was the amount of damage detected. In addition, Roessler and colleagues determined the size of lesion induced by an electromagnetic versus an electrohydraulic lithotripter and found a much larger lesion with the electrohydraulic machines.⁹⁶ This *ex vivo* model has numerous drawbacks, which prevents an investigator from drawing valid conclusions on the real extent of ESWL-induced damage and, therefore, should not be used.

ESWL-induced nephron injury has been assessed by detecting the spillage of tubular enzymes into the urine immediately after treatment.^{31,72,97-103} The list of tubular enzymes found elevated after ESWL includes: N-acetyl- β -D-glucosaminidase (NAG), alkaline phosphatase and β -galactosidase as proximal tubular lysosomal enzymes, γ -glutamyltransaminase (GGT) and angiotensin-converting enzymes for brush border of proximal tubular cells, calbindin-D for distal tubular cells and β_2 -microglobulin as a small circulating protein that is freely filtered but almost completely reabsorbed in the proximal tubules. There appears to be great variation in the levels of these markers in stone patients when pre- and post-ESWL levels were compared,¹⁰⁴ and no attempt has been made to document the presence or absence of bilateral stone disease. Significant proteinuria has been documented immediately after ESWL, which resolved 3 to 6 months post-treatment without detectable changes in whole kidney glomerular filtration rate.¹⁰⁵ Others have reported transient microalbuminuria.^{103,106} Transient increases in both prostaglandin E2 and thromboxane B2 levels have been noted in the urine and serum but they quickly return to baseline values.¹⁰⁷ Sarica and colleagues determined the plasma and urine levels of nitrite and adrenomedullin as markers of tubular and glomerular cell injury in stone formers and controls treated with lithotripsy.¹⁰⁸ Both markers were elevated in the plasma and urine of only the stone formers 24 hours post-ESWL and returned to normal at one week. Generally, in ESWL-treated adult patients, the enzyme

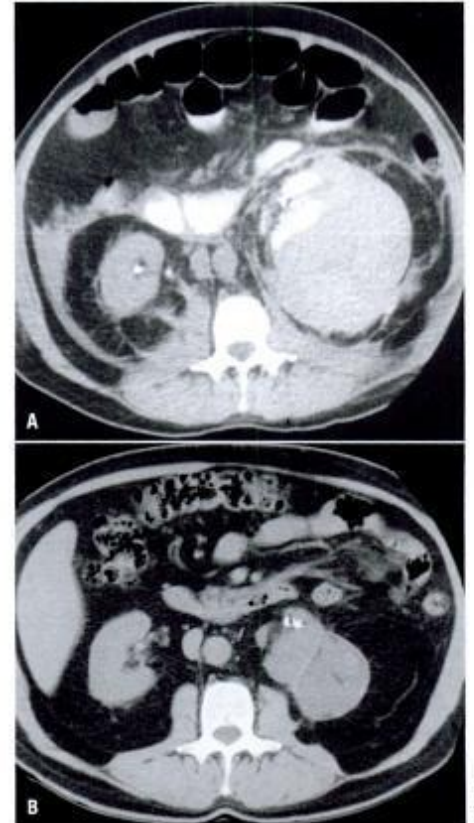


Figure 41-3 A, Computed tomography (CT) scan of a stone patient 48 hours after left extracorporeal shock wave lithotripsy (ESWL) for a 1 cm non-obstructive stone in the left renal pelvis. The patient received 1,000 shocks at 22 kV with an unmodified HM3 lithotripter. B, Abdominal CT 8 years after ESWL demonstrating persistence of a smaller hematoma around the left kidney.

changes return to baseline in a week; in children, however, the functional regeneration time increases to two weeks.¹⁰⁹ Clearly, there are conflicting reports on this topic that can be explained, in part, by the great variation in the parameters of ESWL delivery and the lack of appropriate control groups. Despite these issues, the majority of observations on human stone formers suggest that all portions of the kidney and surrounding tissues are vulnerable to shock waves, with the microvasculature being the most susceptible, and that the amount of injury increases with shock number.

Acute changes in renal function have also been found immediately after ESWL treatment, as documented by specialized imaging techniques such as radionuclide studies using orthoiodohippurate to measure effective renal plasma flow (ERPF), creatinine clearance for glomerular filtration rate (GFR) and color Doppler ultrasound for a measure of change in the vasoconstriction of intrarenal blood vessels. While these techniques are relatively imprecise, there are reports of a significant reduction in ERPF and GFR between 24 and 48 hours post-ESWL. Kaude and colleagues, the first group to report ESWL-induced changes in renal function, found an immediate decrease in

effective plasma flow, measured by renal scans, in 30% of kidneys treated with a clinical dose of ESWL (1,800 shock waves).⁶⁴ Several investigators have confirmed the decrease in ERPF¹¹⁰⁻¹¹² and/or a delay in—to complete loss of—contrast excretion in unobstructed ESWL-treated kidneys.^{64,74} These studies are supported by the observations that there is an apparent transient reduction of intrarenal blood flow at F2.¹¹³⁻¹¹⁶ While there are clearly studies that have not found functional changes,¹¹⁰ these different observations appear to be linked to the number of shocks administered. Thomas and associates found that a treatment regimen of approximately 1,500 shocks was safe, but higher levels induced a fall in renal plasma flow.¹¹⁷ Orestano and colleagues noted that fewer than 2,500 shocks produced changes in renal function that totally regressed by 30 days post-ESWL.¹¹⁸ However, a dose of greater than 2,500 shocks induced more extensive changes in renal function (reduction in clearance, prolonged 131 I-Hippuran transit) in the treated kidney as well as in the contralateral kidney. Other investigators have also detected functional changes in both the treated and untreated kidneys.^{111,119} Similar observations have been reported in the pig.^{120,121} As stated earlier, acute renal failure has been reported in a few ESWL patients; in most instances, however, this condition has been reversible. The majority of the studies just described indicate that renal function is acutely affected by a clinical dose of shock waves. There are reports that ESWL can result in a significant improvement in renal function in some patients.⁴² Many such patients, however, show evidence of ureteral obstruction prior to treatment, thereby biasing the functional changes (ie, increased clearance) in the direction of improvement.

In view of the adverse effects the ESWL treatment may have acutely on renal function, several investigators have attempted to protect the kidney from ESWL-induced injury. The protective effects of nifedipine and allopurinol on high-energy shock-wave-induced acute changes of renal function have been studied in 40 patients in a prospective randomized study, and the results indicated that nifedipine and/or allopurinol exhibits a protective effect on high-energy shock-wave-induced renal damage.¹²² In their original two studies Strohmaier and colleagues aimed to outline the limitation of shock-wave-induced renal tubular dysfunction by nifedipine and verapamil in 24 patients with renal pelvic or caliceal stones undergoing anesthesia-free ESWL.^{123,124} To assess renal tubular function, the urinary excretion of α_1 -microglobulin (AIM), N-acetyl- β -glucosaminidase (NAG) and Tamm-Horsfall protein (THP) were measured before, immediately, 12 hours and 24 hours after ESWL. Their results indicated that nifedipine and verapamil exhibit a protective effect on shock-wave-induced tubular damage similar to verapamil. Chan and colleagues and Benyi and colleagues have shown that pretreatment with aminophylline, nifedipine or allopurinol also blocks the fall in renal blood flow induced by ESWL.^{125,126}

The underlying mechanism(s) on how these drugs produce this effect is unclear; they may have a direct action on tubular cells or alter the effect that shockwaves have on the renal vasculature. A new study on pigs has shown that a pretreatment set of 100 to 500 shock waves administered at a low kilovolt level can greatly reduce a predicted lesion induced from a subsequent delivery of a clinical dose of shock waves.¹²⁷ These findings and the application to a clinical setting are discussed later in this chapter.

CHRONIC RENAL INJURY: CLINICAL OBSERVATIONS Although little information exists to date on the possible chronic renal changes after ESWL,^{3,7,25,26,128} potential long-term adverse effects are still emerging but include an accelerated rise in systemic blood pressure, a decrease in renal function, onset of hypertension, an increase in the rate of stone recurrence, diabetes mellitus and the development of brushite stone disease. All of these effects appear to be linked to the observation that the acute injury usually progresses to scar formation with time and is accompanied by a loss of functional tissue and blood vessels. Lechevallier and colleagues performed pre- and post-ESWL (30 days) single photon emission computed tomography (SPECT) studies in 12 patients treated with a piezoelectric lithotripter.¹²⁹ All ESWL-treated kidneys showed some loss of renal function, with 4 of the 12 kidneys showing a loss of local tracer uptake of greater than 4%. In addition, there were seven scars in the region of F2. Umekawa and colleagues examined a kidney of a patient in acute renal failure that occurred 90 days post-ESWL treatment and found evidence of anti-glomerular basement membrane production in glomeruli at F2.¹³⁰

The possibility that ESWL treatment might be associated with a long-term reduction in renal function has been suggested by several investigators. Williams and Thomas found a significant decrease in the percentage of effective renal plasma flow 17 to 21 months after ESWL for patients with two kidneys.¹³¹ Orestano and colleagues noted that patients receiving more than 2,500 shocks had a reduction in clearance and a prolongation of 131 I-Hippuran transit time at 30 days post-ESWL in the treated kidney and occasionally in the contralateral kidney.¹¹⁸ Brito and colleagues reported that patients with a solitary kidney showed elevated serum creatinine levels five years post-ESWL.¹³² These observations stand in contrast to the early reports by Chaussy, suggesting a significant increase in renal function three months to one year following ESWL.⁴² In addition, a longer-term follow-up study of patients treated in Munich failed to confirm this increase in renal function¹³³ as did other studies that looked at patients who received bilateral treatment¹³⁴ and those who received unilateral treatment.¹³⁵

There has been increasing concern and controversy over the association between ESWL and the development of hypertension. Peterson and Finlayson were the first investigators to suggest the possibility that ESWL might be associated

with significant changes in systemic blood pressure.¹³⁶ Subsequently, Lingeman and colleagues reported that 8.2% of 243 patients who were normotensive at the time of ESWL developed blood pressure changes requiring antihypertensive medication.¹³⁷ Mean follow-up in this group of patients was 1.5 years, giving an annualized incidence of hypertension of 5.5%. Similar data have been reported by Williams and Thomas.¹³¹

While this initial association between hypertension and ESWL may be alarming, not all data support the connection,^{133,138-141} and it has been suggested that stone patients have a higher incidence of hypertension to start with.^{142,143} Montgomery and associates retrospectively reviewed patients following ESWL on the HM3 and determined the rate of hypertension to be 8.1%; but the hypertension developed de novo in only 2.9%.¹³⁹ Yokoyama and associates retrospectively reviewed patients treated with the HM3 for either renal or ureteral calculi and determined an annualized incidence of new-onset hypertension to be 0.65%.¹⁴⁴ There was, however, a statistically significant annualized increase in diastolic blood pressure (DBP) (0.78 mm Hg). They suggested that a dose-response relationship might exist between blood pressure changes and shockwave energy administered. Claro and associates retrospectively reviewed blood pressure data from patients treated on a Lithostar lithotripter and found that DBP was statistically higher after treatment, but the incidence of hypertension was not significant.¹⁴⁰ All of these studies suffer from being retrospective in nature. Interestingly, in a small prospective study by Zanetti and colleagues following blood pressure changes in patients treated with an HM3, no significant increase in DBP was noted, although the incidence of new-onset hypertension was 6%.¹⁴¹

In an attempt to further elucidate the long-term association between ESWL and hypertension, Lingeman and associates retrospectively surveyed 961 stone patients treated at Methodist Hospital of Indiana for stone disease.¹⁴⁵ Eighty percent of the study group received therapy that exposed them to ESWL. The remainder of the patients were treated with percutaneous surgery or ureteroscopy and consequently were not exposed to shock waves and served as controls. Follow-up blood pressures were measured with random-zero devices at least one year following treatment. In patients treated with ESWL, the annualized incidence of hypertension (2.4%) did not differ significantly from that in control patients (4.0%). Moreover, in those patients exposed to ESWL, there was no correlation between the incidence of hypertension and the laterality of treatments, the number of shock waves administered, the voltage applied, or the power index. There was, however, a statistically significant rise in DBP after treatment with ESWL (0.78 mm Hg) that was not present in the control group (-0.88 mm Hg). These data were remarkably similar to findings reported by Yokoyama and colleagues.¹⁴⁴ As an extension of this survey, a second set of follow-up blood pressure measurements was conducted approxi-

mately 4 years after treatment in 749 patients (77.9%). The annualized incidence of new onset hypertension in ESWL patients was 2.1% compared to 1.6% in non-ESWL patients (not significant). A statistically significant difference in the annualized mean DBP was identified and was notably higher in the ESWL-treated patients compared to the non-ESWL patients at all time intervals following treatment. This change in blood pressure remains statistically significant even after controlling for other statistically significant risk factors such as pretreatment blood pressure, patient gender and patient age, as well as various treatment factors such as years since treatment, direct shock wave exposure to the kidney, and multiple shock wave sessions. Although exposure to shock waves was associated with a small but statistically significant rise in DBP up to 4 years following treatment, there was a trend of DBP back toward baseline during later follow-up.

A recent study from the Mayo Clinic reported on a retrospective chart review of 687 SWL treatments in 630 kidney stone patients over a 19-year period.⁷ The pthe SWL and control groups with the SWL groups more likely to have hypertension. The new-onset hypertension was not related to the total number of shock waves, average intensity or total intensity but with bilateral treatment.

A prospective study has addressed the issue of hypertension as a possible long-term complication of ESWL therapy.^{6,115,146} A group of investigators from the University of Innsbruck, Austria, calculated the intrarenal resistive index in 76 patients treated with a Dornier MFL 5000 lithotripter. In 15 of 20 patients over 60 years of age, the resistive index was higher than the upper limit of normal immediately following ESWL in the treated kidney but not in the untreated kidney. At 26 months of follow-up in these patients, the resistive index continued to increase in all nine patients who developed hypertension and a strong positive correlation (0.903) between the pathological resistive index levels and blood pressure was found. With one exception, an elevated resistive index and hypertension were observed exclusively in patients older than 60 years. No significant change in plasma rennin activity was observed in the four patients with new-onset arterial hypertension whose values were available because their blood pressures were not normalized with diuretics or angiotensin-converting enzyme inhibitors. Moreover, their rennin levels were not different from the values observed in five normotensive patients. Because in the condition of hypertension mediated by vascular disturbances originating in the kidney one would expect rennin values to be high, this result is surprising and raises speculations about the importance of local tissue activation of the rennin-angiotensin system or the release of another vasoactive peptide such as endothelin.

Therefore, age is probably a risk factor of new-onset hypertension due to ESWL. Resistive index has never been taken into account in previous studies, which may explain the lack of clear evidence that hypertension in elderly patients can

be a chronic complication of ESWL therapy. What is not known at this time is the future health risk for these patients or who is at risk. Clearly there are studies that have found no change in blood pressure after ESWL.^{26,138} The long-term effects of hypertension, if it is occurring, include an increased risk of stroke, myocardial infarction, and renal failure. Therefore, any therapy that might increase the incidence of hypertension should be rigorously examined.

Other groups have focused on determining if kidney stone patients have a greater risk for a loss of renal function, as detected by a change in creatinine clearance,¹⁴⁷ or GFR.¹⁴⁸ Such a change in renal function would suggest that stone patients have a kidney disease as the result of specific alterations in their kidneys. These data indicate that there is a significant interaction between the GFR value and the body mass index (BMI) level. In other words, if a stone patient had a BMI level greater than 27 kg/m², there was a significant association between a history of renal stones and a lower GFR value. If these data hold up, one must be concerned with any stone removal technique that would cause additional loss of renal mass in this subset of stone patients.

The recent Mayo Clinic study also detected the development of diabetes mellitus in 16.8% of the SWL-treated stone patients. The diabetes mellitus was related to the number of administered shock waves and treatment intensity. The authors suggested that the diabetes mellitus could be a result of damage to pancreatic islet cells, because a portion of the pancreas was probably located within the blast path of the HM3 machine.

An additional concern has been raised suggesting that stone recurrence rates may be higher following ESWL because of residual stone debris forced into the lining of the renal pelvis.¹⁴⁹ A recent study by Carr and colleagues documented all new stone formation in 298 consecutive patients who initially were determined to be stone-free after ESWL and compared those findings to 62 patients treated with percutaneous nephrolithotomy.¹⁵⁰ Their data showed a significant increase ($p = .004$) in the rate of new stone formation within one year of ESWL treatment compared to percutaneous nephrolithotomy. Furthermore, the location of the new stones changed from their original treatment site to the calices. The authors suggested that fine sand debris generated from ESWL treatment remained in the kidney, and gravity acted to position them as a nidus of the caliceal system.

Lastly, our group has determined that there has been a significant rise in the number of calcium phosphate (CaP) stone formers over the last three decades,¹⁵¹ an observation supported by others.¹⁵² An intriguing finding (noted when all kidney stone formers were analyzed for the number of ESWL procedures) was that the CaP stone formers had received a significantly higher number of procedures than the idiopathic calcium oxalate stone formers when adjusted for number of stones and duration of stone disease. Furthermore, the brushite stone formers had received a

significantly higher number of ESWL treatments than the apatite stone formers. The histopathology of the brushite stone formers revealed advanced levels of tissue changes in the renal cortex and papilla that included interstitial fibrosis, tubular atrophy, glomerular obsolescence, and deposition of large amounts of hydroxyapatite in the lumens of inner medullary collection ducts.¹⁵³ While these data do not establish a cause-and-effect relationship, clearly there is an association between brushite stone disease and high levels of ESWL treatment sessions. Because we believe that apatite stone disease is primarily related to higher urinary pH levels in these patients, the animal studies showing the initial site of ESWL injury to be localized to the microvessels and collecting duct of the renal papilla might explain a loss of control over normal urinary fluid pH at this level.

RISK FACTORS Risk factors may predispose ESWL patients to increased acute renal injury. Knapp and associates found stone patients with existing hypertension to be at increased risk for the development of perinephric hematomas as a consequence of ESWL.¹⁹ In particular, those patients having unsatisfactory control of their hypertension at the time of ESWL had the highest incidence of hematomas. Dhar and colleagues reported new clinical results with a Storz Modulith showing that the probability of developing a subcapsular hematoma increased 2.2 times for every 10-year increase in patient age.²⁴ Additional risk factors included increased thromboplastin time and the use of aspirin¹⁵⁴ (even when discontinued up to two weeks prior to treatment), again not agreed on by all groups.¹⁵⁵ When the power setting and number of shock waves administered were evaluated as potential risk factors, no correlation was found with the occurrence of hematomas. Newman and Saltzman confirmed these observations.²² They noted that patients with coagulopathies and thrombocytopenia were at greater risk of developing a subcapsular hematoma. Additional risk factors identified for increased incidence of hemorrhage were diabetes mellitus, coronary artery disease, and obesity, all suggesting a link to a vascular disorder. In relation to risk factors, an interesting observation is that some patients with preexisting hypertension require higher doses of their blood pressure medication following ESWL therapy.⁶⁴ This suggests that preexisting hypertension is a potential risk factor for adverse acute effects of ESWL. In a study of solitary kidneys, Karlsen and Berg reported a significant reduction in GFR three months following ESWL.¹¹⁰

Age is a factor on both ends of the scale; children and the elderly appear to be at a greater risk for structural and functional changes following exposure to ESWL.^{6,156} The concern for children is that the smaller size of their growing kidneys to the fixed size of the focal area will always damage a greater proportion of their functional renal mass compared to the large adult kidney and the fixed size of the focal area. Although pediatric

ESWL is thought to be clinically well-tolerated and is reported to be associated with few adverse effects, there are only a few studies with a small number of patients that have addressed the issue of possible long-term complications.¹⁵⁷⁻¹⁶⁶ Adams and colleagues reported the results of ESWL in a group of 44 pediatric patients and noted normal renal growth in 14 treated renal units after a mean follow-up time of 23 months.¹⁵⁷ That initial study was followed up by a longer-term study (mean 9 years) on 29 patients where actual and predicted renal growth rates were compared.¹⁵⁶ The treated kidneys were stratified into normal and abnormal groups based on a history of renal surgery, evidence of recurrent infections and obvious anatomic abnormalities. Fifty-six upper urinary tract calculi were treated in 34 renal units. Twenty-two renal units were rendered stone-free and 65% of the patients continued to be stone-free. At follow-up, one patient was classified as having new-onset hypertension, and the mean serum creatinine was 0.93 ± 0.08 mg/dL. At treatment, the abnormal group of kidneys seemed to be smaller than expected (mean $Z -1.30 \pm 1.10$), whereas the group of normal kidneys was very close (mean $Z 0.18 \pm 0.54$) to the predicted mean. At follow-up, the deviations between actual and predicted renal length were significantly more negative. Although there was a trend toward the abnormal group having smaller kidneys than the normal group, both groups showed the same trend toward an age-adjusted reduction in renal growth at follow-up. The alterations in renal growth patterns observed in this population are unsettling and could be secondary to treatment effect (ie, ESWL) or, more likely, to some underlying pathology intrinsic to pediatric kidneys with urolithiasis. The results of this clinical study and the observations from several studies on immature and juvenile animals^{59,167,168} must still caution us about the potential for long-term complications in children treated by ESWL. Until further data are available, ESWL in the pediatric population should be applied with caution and at the lowest dosage sufficient to achieve stone breakage.

In addition to the list of risk factors described above that relate to conditions the patient brings to ESWL treatment, another set of factors is linked to the parameters of treatment. These factors include the discharge voltage, number of total shock waves administered, rate of shock wave delivery, and type of lithotripsy. Most of these data have been collected in animals so will be discussed below. The issues of increased side effects induced by the third-generation machines have already been cited above.

Acute renal injury may be an important consequence of ESWL, but a number of questions still need to be addressed that will require continual investigation. It is not known if renal function is altered in all ESWL patients, or if only a subset of patients is at risk. It is not known if patients with two kidneys tolerate ESWL therapy better than those with one kidney. Importantly, numerous data suggest that risk factors may predispose

the ESWL patient to acute renal injury, although such factors have yet to be fully defined.

ACUTE RENAL INJURY: EXPERIMENTAL STUDIES
In contrast to the early misperception within the medical/scientific community that ESWL does not produce injury⁴² subsequent animal studies have clearly demonstrated structural and functional changes in various organs,^{3,25,26,120,121,127,169-189} particularly the kidney, after shock wave administration, and that these changes correlate well with side effects observed in ESWL patients. Investigators have used a variety of animals that include the rat,^{42,188,189} the rabbit,¹⁸⁵⁻¹⁸⁷ the dog,^{169-171,173,175-178} and the pig.^{3,25,26,65,120,121,127,175,180-182,184} Clearly, the pig is the most appropriate animal model for these studies (Figure 41-4).^{3,26,65}

Macroscopically, the acute changes noted in dog and pig kidneys treated with a clinical dose of shock waves are strikingly similar to those described for ESWL patients. The lesion is predictable in size, focal in location, and unique in the types of injuries (primarily vascular insult) induced. These changes include hematuria, contusion-like lesions, subcapsular hematomas, hemorrhage, and kidney enlargement. Hemorrhage has been found in three general locations: perirenal, subcapsular, and intraparenchymal (but always at or near F2). The perirenal fat is a common site of extensive hemorrhage. Subcapsular hemorrhage is found to spread diffusely along the length of the capsule and/or form discrete hematomas (Figure 41-5). Sites of intraparenchymal hemorrhage are generally wedge-shaped being most severe at the corticomedullary junction, and extend from the papillary tip to the capsule. It has been our observation that the initial sites of damage always occur in the renal papilla involving injury to the wall of vasa recta and

nearby collecting ducts.¹⁸⁰ Hematomas localized within the renal parenchyma or subcapsular zone range in size, from very small to 0.5 cm in diameter,¹⁷¹⁻¹⁷⁷ and in number, from 1 to 10 per kidney. Our group has quantitated the hemorrhagic lesion and found it to be about 2% of the functional mass in an adult pig treated with an unmodified HM3, 2,000 shocks at 24 kV.^{120,121} Larger hematomas appear to compress the adjacent tissue. Interstitial edema is also common. The diffuse nature of this change would appear to account for enlargement of the kidney.

Histologic analysis has shown that the regions of hemorrhage are always near the site of F2 (Figure 41-6).^{3,26,65,167-170,180,187} These regions of damage reveal rupture of nearby thin-walled veins, walls of small arteries, glomerular and peritubular capillaries, which correlate with the vasoconstriction measured in both the treated and untreated kidneys.^{120,121} Venous thrombi are frequently associated with interlobular and arcuate veins located at the sites of hemorrhage. Evidence of extensive endothelial damage in these veins is noted by a loss of endothelial cells and the immediate attachment of numerous polymorphonuclear (PMN) cells and activated platelets to the luminal surface of these vessels depicting a vasculitis (Figure 41-7).^{3,180} Nephrons located near areas of massive hemorrhage show evidence of damage. These alterations consist of vacuolar changes in individual cells, tubular dilation, cast formation (hyaline-like, RBCs) and mild tubular necrosis.^{3,4,169,171,172,182} These observations show that both the microvasculature and nephron are susceptible to shock wave damage; the primary injury, however, appears to be a vascular insult.

Of great interest are those experimental animal studies that have determined factors of ESWL administration that appear to influence the degree of renal trauma induced by shock

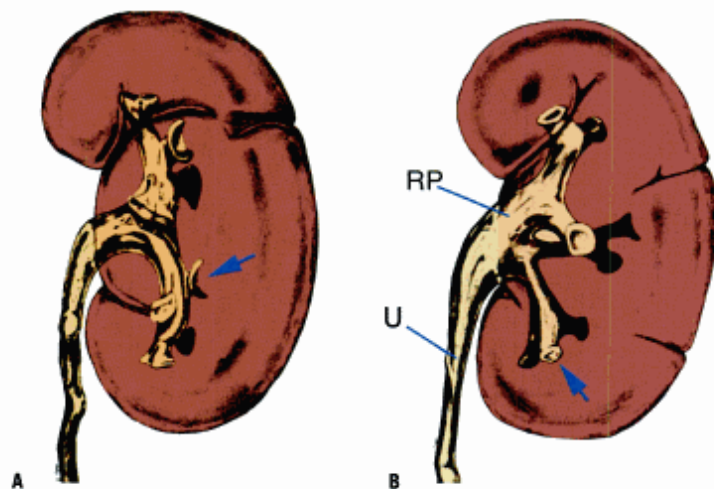


Figure 41-4 A, Drawing of the collection system of a human kidney. B, Drawing of the collection system of a pig kidney. Both the human and pig kidney are multi-papillary and may show considerable variability in the form of the collecting system. Generally, the human kidney has a greater number of minor calyces (arrows) than the pig, with longer calyceal stems and a larger renal pelvis (RP). U = ureter.



Figure 41-5 Magnetic resonance image of a pig kidney treated with 2,000 shocks at 24 kV with an unmodified HM3 lithotripter demonstrating a large subcapsular hematoma much like that seen in Figure 41-3A.



Figure 41-6 *A*, Histologic section of pig kidney treated with 2,000 shocks at 24 kV with unmodified HM3. This kidney shows sites of parenchymal hemorrhage extending from the renal papilla to the capsule. *B*, Digitized image of a pig kidney treated with 2,000 shocks at 24 kV or *C*, with 8,000 shocks at 24 kV and then processed, sectioned and captured by digital camera. The hemorrhagic lesion (colored light blue in *B* and *C*) seen in both the 2,000 and 8,000 shocked kidney was selectively segmented by a color range identifier for blood so that the area of the lesion could be determined for all serial sections. The site of F2 is signified by an open circle.

waves.^{120,121,171-174,180,181,185} Delius and colleagues¹⁷¹ and Willis and colleagues^{121,183} have noted that, as shock number is increased (1,000 to 8,000 shocks), a greater number of hematomas are formed, and lesion size increases, but not as a direct correlation with shock number (Figure 41-8). The higher shock number was also associated with larger hematomas. This is related to the fact that larger arteries are injured at high shock numbers.³ Delius and colleagues have also shown that more massive hemorrhage and tubular damage are induced by increasing the rate (1 shock/second to 100 shocks/second) at which the shocks are administered and by administering the shock waves in pairs.¹⁷¹⁻¹⁷⁴ Kidney size is clearly a risk factor for increased intraparenchymal hemorrhage, in that lesion size is 6% in a juvenile pig versus 2% in an adult pig (Figure 41-9).^{4,120,121,183,184} In addition, Evan and colleagues noted that the degree of injury induced by a clinical dose of ESWL is potentiated by a pre-existing condition like acute pyelonephritis.¹⁸¹ Under such conditions, a 2,000-shock dose acts as an 8,000-shock dose. Lastly, the degree of renal injury has been linked to the type of shock wave generator used.^{176,185} But these data are difficult to compare in that the parameters for shock wave delivery are so varied between instruments. Hypertension has been noted as a risk factor in animals treated with ESWL. A significant increase in post-ESWL arterial blood pressure was found in immature white rabbits.¹⁶⁷ Weber and colleagues tested the hypothesis that ESWL treatment induces hypertension.¹⁸⁸ They treated F1-hybrids of spontaneously hypertensive rats (rats with borderline hypertension) and normal Wistar rats with a clinical dose of shock wave and determined their blood pressure post-ESWL therapy. ESWL-induced hypertension in only the F1-hybrids indicated a potential risk factor for shock-wave-induced hypertension in genetically predisposed patients.

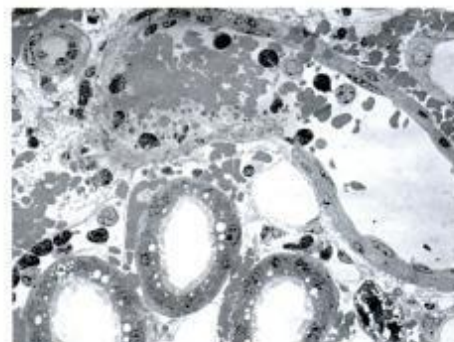


Figure 41-7 Transmission electron micrograph showing extracorporeal shock wave lithotripsy-induced vascular injury. This low-magnification image shows a damaged intermediate-sized artery from a pig kidney 1 hour after treatment with 2,000 shocks at 24 kV with an unmodified HM3 lithotripter. The left side of the vessel shows extensive injury to the endothelium and smooth muscle cells of the vessel wall permitting the extravasation of blood into the underlying interstitial space. Numerous polymorphonuclear neutrophils and other leukocytes have migrated to the site of injury.

Effect of Shock Number on SWL Lesion Size
(Six Week-old Pigs, 24kV)

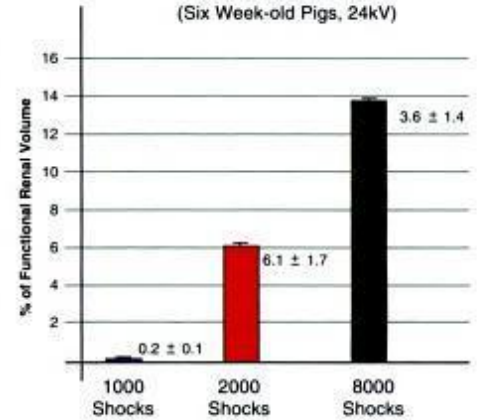


Figure 41-8 Effects of 1,000, 2,000 and 8,000 shocks at 24 kV with an unmodified HM3 lithotripter on lesion size. Data are expressed as mean ± SEM. *N* indicates the number of individual kidneys sectioned and quantified in each group. **p* < .05.

An obvious void in the experimental ESWL literature has been studies that documented changes in renal function after shock wave administration. Two early studies were done in dogs.^{190,191} Jaeger and Constantinides reported a significant decrease in creatinine clearance and an elevation of glucose excretion one-hour post-ESWL in dogs treated with 3,000 shocks (1,500 shocks per pole of kidney).¹⁹¹ Both values returned to normal by 24 hours post-ESWL. They also noted an increase in serum glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase levels at one-hour post-ESWL. The study by Karlson and colleagues found an increase in urinary osmolality and urine flow while renal plasma flow was reduced about one-third at 2 hours post-ESWL in dogs treated with 1,500 at 18 kV.¹⁹⁰ These authors found no change in glomerular filtration rate or urinary electrolyte excretion. A series of experiments by Willis and colleagues^{120,121,183,184} expanded these observations to include bilateral kidney function in the pig. These studies show that the application of 2,000 shocks at 24 kV with an unmodified Dornier HM3 lithotripter to one kidney consistently reduces renal blood flow (RBF) and GFR in that kidney (Figure 41-10). At 1 hour post-ESWL, the fall in RBF was 27% for the young adult animals and 50% in the juvenile pigs. By 4 hours post-ESWL, RBF returned to baseline in the young adult pigs but was still significantly reduced in the juvenile pigs. GFR followed a similar course but was reduced to a lesser extent than RBF measurements. In addition, these studies found a significant reduction in RBF in the untreated kidney at the 1-hour post-ESWL time point. These investigators also measured tubular function using *p*-aminohippurate extraction and found a significant reduction in the treated kidney but no fall in the untreated kidney. Again, the greatest reduction occurred in the juvenile pig

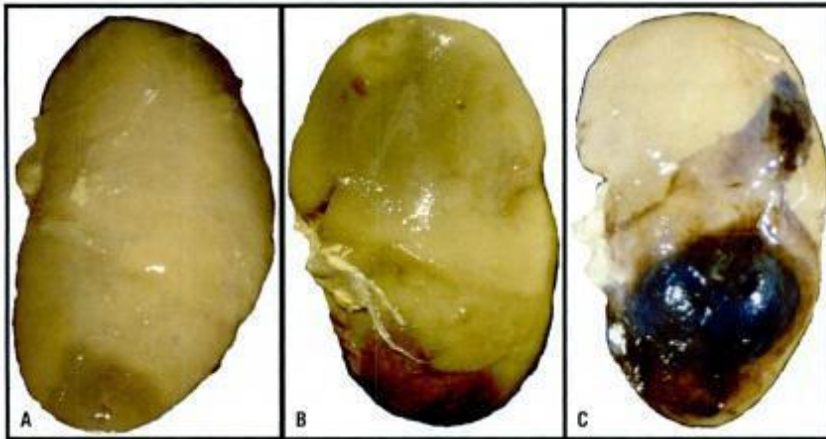


Figure 41-9 Gross appearance of pig kidneys treated with 2,000 shocks at 12 (A), 18 (B), and 24 (C) kV with an unmodified HM3. Note that the size of the subcapsular hematoma increases with increasing kV level.

compared to the young adult pig. These results show that the major change in renal function is vasoconstriction, and kidney size is indeed a risk factor for increased side effects. Willis and colleagues^{120,121,183} have found that high shock numbers (8,000 shocks) do not generate a greater decrease in RBF at 1 hour post-ESWL, but induce a sustained reduction noted at 24 hours post-treatment. Connors and colleagues evaluated the effect of kilovolt level of both RBF and lesion size and found lesion size to clearly increase as the kilovolt level was increased from 12 to 24 kV.¹⁸⁰ But the maximal vasoconstrictive response was already induced at the 12 kV level and remained there regardless of the kilovolt level used. These studies point out the sensitivity of the renal vasculature to shock wave lithotripsy. Elegant studies by Brendel and colleagues have shown, by video microscopy, that when shock waves are directed at a simple microvascular bed, acute spasms of arterioles and hemorrhage of venules are induced.¹⁶⁸ Vasoconstriction begins within and reaches its maximum after 20 to 30 seconds, lasting between 4 to 10 minutes. Dilation follows the constrictive event. Along with the sites of microhemorrhage in the small veins are areas showing leakage of macromolecules, and platelet aggregation. These authors also suggested that vasoconstriction was most pronounced in the region of peak pressure generated by the shock wave. Studies are needed that would directly correlate the physical characteristics of the shock wave with tissue damage.

Our group has uncovered a practical way to protect the treated kidney from the predicted lesion induced by a clinical dose of shock waves.¹²⁷ Prior to giving a clinical dose of 2,000 shocks at 2 kV with an unmodified HM3 to the lower pole of a kidney, a pre-treatment dose of 100 to 500 shock waves at 12 kV is administered, followed by the full clinical dose to the same site. Under those conditions, the normal lesion of about 6% is reduced to about 0.3%, a highly significant change (Figure 41-11). Our present thinking about the possible

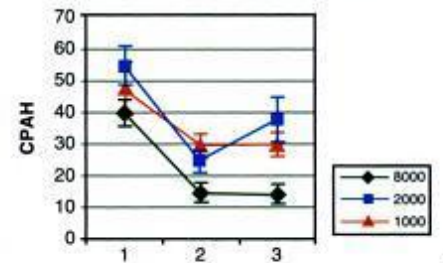
mechanism of this outcome is that the pre-dose of shock waves induces a significant vasoconstrictive event that could prevent an incoming stress from shearing the vessel wall or perhaps prevent/reduce the number of cavitation events. A reduction in cavitation would potentially protect the parenchyma from cavitation-induced injury. A clinical trial is needed to test this result in stone patients.

Investigators have suggested that the vascular injury might induce an ischemic injury to the already damaged tissue.^{3,26,182,187} Thus, Cohen and colleagues¹⁹² and Brown and colleagues¹⁹³ determined in the pig that a clinical dose of shock-waves induces lipid peroxidation and free radical formation in the treated kidney. The concern for ischemic changes is for both the treated and untreated kidney, in that ESWL induces a vasoconstrictive response in both kidneys.^{4,120,121} Delvecchio and colleagues recently determined a dose-related increase in conjugated diene ratio levels from the pole of the treated kidney¹⁹⁴ and, to a lesser degree, from the untreated kidney—a result consistent with the data from Willis and colleagues.¹²⁰ Animal models have also been used to investigate protective agents against shock-wave-induced renal injury. Verapamil^{184,195-197} and antioxidant vitamins (E plus C)⁵⁸ can significantly reduce shock-wave-induced renal injury.

CHRONIC RENAL INJURY: EXPERIMENTAL OBSERVATIONS Chronic changes in renal structure after shock wave treatment have received minimal investigation. At two weeks post-ESWL, Jaeger and Constantinides noted calcium deposits, streaky fibrosis, and encapsulation of sites of acute hemorrhage.¹⁹¹ Newman and coworkers identified permanent morphological changes in the dog kidney 30 days after ESWL treatment.¹⁷⁵ These alterations consisted of diffuse interstitial fibrosis, focal areas of calcification, nephron loss, dilated veins, and hyalinized to acellular scars running from the cortex to the medulla (Figure 41-12). Morris and colleagues

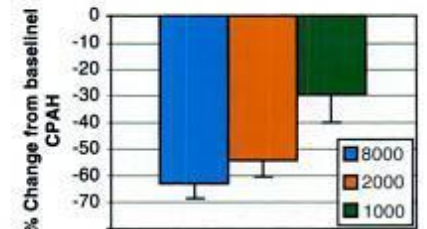
found a direct correlation between the number of shock waves and the size of the resulting scar.¹⁹⁸ As the number of shocks was increased from 1,000 to 2,000, the size of the scar increased from 1.37% to 12.76%. In addition, Banner and colleagues have noted mesangioproliferative glomerulopathy in pigs treated with either the HM3 or the EDAP lithotripter.¹⁹⁹ With time, deposits of complement C3 and traces of immunoglobulin G (IgG) were found to increase in amount in the mesangium. Interestingly, these changes were noted to occur in both the treated and the untreated (contralateral) kidney to about the same degree, suggesting the induction of a systemic factor or bilateral injury induced by ESWL. Delius and associates reported that most of these renal alterations were reversible in sev-

24 kV - Effect of Shock Number



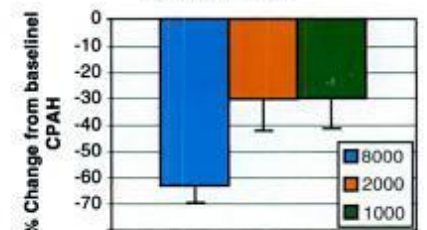
A

24 kV - Effect of Shock Number at One Hour



B

24 kV - Effect of Shock Number at Four Hour



C

Figure 41-10 *p*-Aminohippurate clearance in treated pig kidney after 1 and 4 hours post-extracorporeal shock wave lithotripsy (ESWL) treatment with 2,000 shocks at 24kV. **A**, All three dosage levels induce a significant fall in *p*-aminohippurate clearance at one hours post-ESWL. **B**, The 8,000 shock treatment induced a greater fall in *p*-aminohippurate clearance compared to the 1,000 shock dose. **C**, At four hours post-ESWL, the 1,000 and 2,000 shock dose show similar changes while the 8,000 shock dose shows a persistent reduction in *p*-aminohippurate clearance.

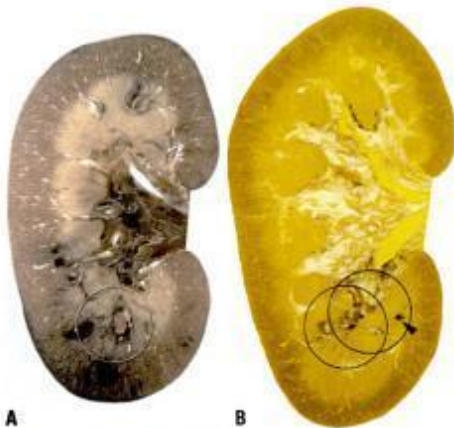


Figure 41-11 *A*, Digitized image of a pig kidney treated with 2,000 shocks at 24 kV. *B*, Digitized image of a pig kidney treated with 500 shocks at 12 kV followed immediately with 2,000 shocks at 24 kV to the same pole. This pre-treatment protocol protects the kidney from the predicted lesion induced by 2,000 shocks at 24 kV. Arrow-head shows the only site of hemorrhage in the kidney that received the pretreatment protocol. The sites of F2 are signified by an open circle.

eral weeks except for some of the large hematomas.¹⁷¹ These observations suggest that the acute changes induced in the kidney can be classified as either reversible or irreversible; but a clinical dose of ESWL always induces irreversible injury that ends as a region of scar. In contrast to these studies, Chaussy reported no

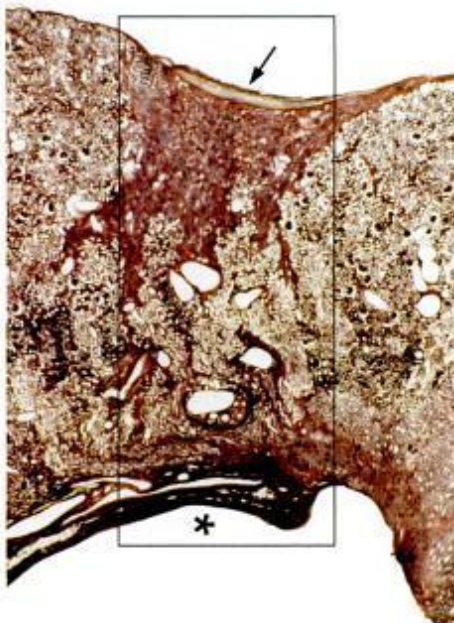


Figure 41-12 Histologic section from a pig kidney treated with 2,000 shocks at 24 kV in an unmodified HM3. The acute injury induced at the site of F2 (seen within rectangle) resulted in a scar that extends from the renal capsule (arrow) to the renal medulla. The renal papilla is no longer present, being reduced to scar tissue (asterisk).

histologic abnormalities in the dog kidney up to 1 year post-ESWL.⁴²

Only a few studies have attempted to determine the chronic changes in renal function induced by ESWL. Neal and colleagues treated infant adult rhesus monkeys with 1,500 shocks at 15 kV or 2,000 shocks at 18 kV to each kidney, while adult animals were treated with 2,000 shocks at 18 kV to each kidney.¹⁶⁸ A highly significant decrease in effective renal plasma flow was noted in the infant group 6 months post-treatment when those values were indexed to body surface area. In another study, immature rabbits receiving 1,000 to 2,000 shocks developed a significant rise in mean arterial blood pressure at 4 and 8 weeks post-ESWL compared to controls.²⁰⁰ Pre-treatment of these animals with either allopurinol or mannitol prevented the development of hypertension. Both of these studies suggest strongly that there can be long-term functional consequences to a clinical dose of ESWL and that the young or immature are a great risk for such complications.

The mechanism for the traumatic effects of ESWL is not known; Delius and colleagues, however, have speculated that cavitation bubbles generated by the shock waves are primarily responsible for the cellular changes.¹⁷¹ This idea is based on data showing the presence of cavitation bubbles in the liver during shock wave application, and that lithotripter shock wave can cavitate water and blood in vitro.^{201,202} Crum²⁰³ documented that ESWL does produce acoustic cavitation, possibly as the result of the high intensity of the shock wave amplitude. He noted that cavitation microjets are sufficiently forceful to pit or deform metal test foils. But acoustic cavitation has only been detected in the parenchyma of the treated kidney after 1,000 shock waves and at a time when pooling of fluid within the tissue or at the capsule was noted.²⁰⁴ Of interest are the animal studies that employed a Styrofoam insert into the brass reflector of an unmodified HM3 lithotripter.²⁰⁵ Neither lesion nor renal functional changes were seen in these kidneys, compared to our usual result with a clinical dose using the unmodified HM3.¹²⁰ This insert had been shown to reverse the normal pressure wave so that the negative tail precedes the positive portion of the wave.²⁰⁶ Cavitation activity is greatly reduced and so is the renal parenchymal lesion. It is tempting to link the reduction in cavitation activity with the smaller lesion. But there is still another potential mechanism for tissue injury: shear stress. Lokhandwalla and Sturtevant showed by computation that shock waves are capable of causing cell rupture by inducing unsteady flows (shear waves) in the surrounding media.²⁰⁷ Subsequent experimental studies using overpressure to eliminate cavitation and a parabolic reflector to refocus the wave field within the sample vial showed that, even in the absence of cavitation, shock waves could deform foils, and that cell lysis was significantly enhanced by shear as a damage mechanism.²⁰⁸ This gives validation to

PROBLEMS RELATED TO STONE FRAGMENTS

Much of the morbidity associated with ESWL results when stone fragments fail to pass out of the ureter after lithotripsy. This may be caused by poor fragmentation, so that larger stone pieces pass and obstruct the ureter, or a stone that is finely disintegrated may pass down the ureter, resulting in a column of sand—Steinstrasse (“street of stone”)—that may obstruct the kidney (Figure 41-13). This occurs in less than 10% of patients.²⁰⁹ Several factors are responsible for the degree of fragmentation after lithotripsy. The nature of the stone burden treated may affect how successfully a stone is fragmented by ESWL. The risk of Steinstrasse increases with larger stone burdens—in one study of 885 patients, it occurred in 0.3% of stones less than 10 mm, 7% of stones between 10 and 20 mm, and 11.5% of stones between 20 and 30 mm.²¹⁰ In a series of 4,634 patients, multivariable analysis showed stone size > 20 mm to be an independent predictor of Steinstrasse, with a 3.7-fold increase in risk compared to smaller stones.²¹¹ Larger calculi fracture less completely, and more often require additional treatment. The stone composition will also affect the degree of fragmentation. Struvite, uric acid, and calcium oxalate dihydrate calculi fracture into small particles that can pass relatively easily. On the other hand, calculi of calcium phosphate dihydrate (brushite) and calcium oxalate monohydrate tend to break up into larger pieces that are more difficult to pass.²¹² Cystine calculi are especially difficult to treat with lithotripsy since, as an organic compound, cystine has acoustic properties that do not differ greatly from those of the surrounding tissues.²¹³ Recognition that stone size and composition can affect the degree of fragmentation, and, therefore, treatment outcome can help urologists determine which modality is best. Other important factors



Figure 41-13 Complex Steinstrasse following treatment of a large staghorn calculus by extracorporeal shock wave lithotripsy.

include stone location, the type of lithotripter used, and the power index (number of shocks and generator voltage). Lingeman noted that multiple ESWL treatments are more likely to be required when stones are located in the lower pole.²¹⁴

Most Steinstrasse are short and will pass with only mild discomfort. Longer Steinstrasse are more troublesome (see Figure 41-13). Steinstrasse can produce a variety of symptoms or a patient may be completely asymptomatic. Renal colic will occur in almost a third of patients treated with the Dornier HM-3 lithotripter²⁸ and occurs in almost all patients with Steinstrasse.²¹⁵ To identify silent obstruction, the urologist must follow up with plain abdominal films, ultrasound, and/or an intravenous pyelogram 4 to 6 weeks after ESWL.²¹⁶

Steinstrasse is best managed by averting the problem if possible before ESWL is performed. Placement of an indwelling ureteral stent in kidneys with moderate stone burden (aggregate stone diameter 0.25 mm) before ESWL can significantly reduce the incidence of symptomatic Steinstrasse.²¹⁷ The theoretic advantage of using ureteral stents with ESWL is that they may allow continued passage of urine and gravel. Initially, small particles pass around the stent. With time, the ureter dilates, and after stent removal, larger fragments pass through the distended ureter.²¹⁸ Fine and colleagues noted that, during fluoroscopic examinations, ureteral stents allowed urine reflux from the bladder to the kidney.²¹⁹ They proposed that this initiates ureteral peristalsis, propelling urine and gravel into the bladder.

The use of ureteral stents is not without problems, however. Bregg and Riehle found that a third of lithotripsy patients with indwelling stents had moderate discomfort that was not associated with stent material, size, or location.²²⁰ Of their patients, nearly half complained of severe to intolerable pain that was relieved after stent removal. They also noted obstruction caused by the stent itself. In another study of ureteral stents and ESWL, symptoms from the stents often led to the necessity for early stent removal.²²¹

In general, stones 0.3 cm are best managed percutaneously; if ESWL is performed, however, the incidence of Steinstrasse is lowered if ureters are stented prior to treatment.²²² Overall, morbidity is reduced when stents are placed prior to ESWL therapy of larger stones.²¹⁷ Smaller calculi less frequently result in significant Steinstrasse.²²³ Moreover, stents do not decrease the incidence of Steinstrasse following lithotripsy of small to moderately sized stones.²²⁴ Consequently, small calculi rarely require ureteral stenting.

One must weigh the benefits, risks, and costs associated with ureteral stents that are placed before ESWL. The routine use of ureteral stents is generally not indicated because fragments from smaller stones will pass spontaneously with minimal discomfort and with little risk of obstruction. In general, stents should be reserved for a large stone burden (0.25 mm or 300 mm²), for patients with a solitary kidney, or to assist in stone localization.

Steinstrasse that is asymptomatic or minimally symptomatic can be followed conservatively as long as function of the affected kidney is not impaired. Management of symptomatic Steinstrasse is based on the symptoms and the degree of ureteral involvement. In one study, for symptomatic Steinstrasse with an average length of 2.6 cm, observation and symptomatic treatment resolved the obstruction in 64% of patients.²¹⁵ In the same study, one-third of patients were treated with ESWL in situ, and Steinstrasse resolved completely in 90% of patients. Similar results have been reported by Miller and Hautmann.²²⁵ Sigman and colleagues managed distal Steinstrasse by performing a ureteral meatotomy.²²⁶ Although one-third had a great reduction in the length of Steinstrasse, more than half demonstrated vesicoureteral reflux on cystograms 2 months later. Ureterscopy and basket extraction are useful, especially if a large lead fragment is present. Several authors have described a variety of techniques to irrigate the sand from the ureter.^{227,228} If retrograde methods are not successful, percutaneous nephrostomy will decompress the kidney and often allow gravel to pass spontaneously.⁴²

At the Methodist Hospital of Indiana, management of Steinstrasse depends on the degree of ureteral involvement. Simple Steinstrasse are defined as columns of gravel 0.5 cm in length in a patient who has no evidence of urosepsis. If symptoms require intervention, simple Steinstrasse can be effectively managed by ureteroscopy if a guidewire can be passed beyond the obstruction. Bypassing the Steinstrasse is often facilitated with the use of hydrophilic guidewires. If a guidewire cannot be passed, ureteroscopic manipulation should be abandoned because the risk of ureteral perforation during manipulation is greatly increased. Alternatively, ESWL in situ to the obstructed region of the ureter can relieve the obstruction in many cases, especially if a large lead fragment can be identified. Complex Steinstrasse, in which columns of stone fragments 5 cm are present or there are signs of urosepsis, is a more serious problem. In this situation, the risk of ureteral injury with ureteroscopy increases significantly. In addition, the sequelae of urosepsis demand rapid resolution of the obstruction. Consequently, complicated Steinstrasse is best managed with a percutaneous nephrostomy to allow decompression of the kidney and alleviate symptoms. Ureteral peristalsis will aid spontaneous stone passage even without urine flow. A guidewire can be placed in an antegrade manner to facilitate future ureteroscopic manipulation if necessary.

INFECTION

Overall, the reported incidence of sepsis following ESWL is less than 1%,² although for staghorn calculi, the rate is 2.7%.²²⁹ The risk of sepsis increases if a urine culture yields positive results before ESWL.²³⁰ The renal trauma and vascular disruption associated with ESWL may allow bac-

teria in urine to enter the bloodstream. Moreover, with the destruction of infected calculi, bacteria are released from the stone into the urine and may be absorbed systemically. In the presence of urinary obstruction, the risk of urosepsis increases dramatically. The rate of bacteremia following ESWL has been reported to be as high as 14%.²³¹ Infectious complications of ESWL include perinephric^{232,233} and psoas abscess,²³⁴ miliary tuberculosis,²³⁵ and endophthalmitis.²³⁶⁻²³⁸ Although rare, death from sepsis following ESWL can occur.²³⁹ In general, while routine administration of prophylactic antibiotics for ESWL is not necessary,²⁴⁰⁻²⁴² certain clinical and radiographic factors may indicate the need for antibiotic therapy. Prophylactic antibiotics do not prevent infectious complications²³⁸ but should be considered in patients at high risk for them. Therefore, ESWL should be performed only in the presence of sterile urine and in the absence of distal obstruction.

SUMMARY: CAN LITHOTRIPSY BE IMPROVED?

We see at least two logical paths that can lead to significant improvements in ESWL: (1) reinvention of the lithotripter, and (2) rediscovery of how to use it. Our look at the evolution of lithotripsy shows that patient outcomes were never better than during the era of the first-generation lithotripter, the unmodified Dornier HM3. Subsequent technological advances did not produce a better instrument and did not yield better results. Instead, lithotriptors have progressively become too powerful. With the widespread adoption of these machines, stone-free rates have dropped, re-treatment rates are up, and reports of adverse effects are on the rise.

There is an important lesson to be learned from the history of lithotripsy. We cannot expect to solve the problems associated with shock wave therapy solely from what we have learned about the physics of lithotriptors. We need to pay attention to the clinical findings as well. When manufacturers saw that their second-generation machines did not perform to expectations, they found a solution based on laboratory results. Boosting the power of the lithotripter broke stones better in vitro. For example, the Storz Modulith breaks stationary artificial stones better than the Dornier HM3.²⁴³ This result does not take into account that, in a living breathing patient, it is more difficult to keep the third-generation machine on target, and that excessively powerful shock waves lead to increased trauma to the kidney.

There is recent evidence for a move back to the basics. As mentioned above, a new lithotripter has been introduced that, like the first-generation Dornier HM3, produces low-to-moderate acoustic pressures focused to a relatively broad focal zone. Initial clinical findings with the Xi Xin-Eisenmenger machine are encouraging.²⁴⁴ This lithotripter may not prove to be a solution to the problems that currently face ESWL— independent assessment of the device is needed—but

it appears to be a step in the right direction. To be sure, this machine is a departure from the trend in ESWL toward high-acoustic-pressure devices. If this machine continues to deliver good results, it may set a new trend. We may see the development of other low- to moderate-power devices—a reinvention of the first-generation lithotripter.

On the other hand, how lithotripsy is performed may be more important than which lithotripter is used. Our endorsement of the HM3 is a matter of siding with the "lesser of two evils." We are well aware that adverse effects occur with the HM3. It is safe to say that any lithotripter can be used to overtreat a patient. Likewise, it seems reasonable to suggest that, with the proper treatment protocol, most any lithotripter can be used more effectively and with improved safety.

There are several basic conditions of shock wave treatment that will give better outcomes. All physicians should: (1) use lower power, (2) treat at a slow shock-wave rate, (3) sedate the patient and (4) keep the dose (number of shock waves) low.

As for power, there are no good published studies to show the effect of power setting on stone comminution. In our experience using the Dornier HM3 (at the Methodist Hospital) we have found that most classes of stones respond well to treatment at 12 to 15 kV. Use of low power has been recognized to be effective in the treatment of pediatric patients. Also, initial results with the Xi Xin-Eisenmenger lithotripter report using this machine at very low power. We recommend starting treatment at low power and increasing the power only if the stone does not break up.

As for shock wave rate, there are several reports to show that slowing the rate of shock wave administration improves the effectiveness of treatment.^{245,246} This concept was first tested in vitro and then demonstrated using model stones implanted in pig kidneys.²⁴⁵ Preliminary results from the first prospective randomized clinical trial of shock wave rate show that treatment at 1 SW/sec is more effective than treatment at 2 SW/sec.²⁴⁶ Also, the initial report of favorable results with the Xi Xin-Eisenmenger lithotripter describes treatment at a very slow rate (0.3 Hz, 20 SW/min).

The issue of sedation is controversial. Many patients would rather not be sedated. Many urologists would rather not sedate their patients. Many lithotripters are intended to be used as "anesthesia-free" machines. Still, there is very good evidence to show that outcomes are much better when the patient is under sedation.¹¹ This may be simply a matter of targeting the lithotripter. When the patient moves around, it is more difficult to hit the stone.

The severity of collateral damage to the kidney increases with the dose of shock waves. The fewer the number of shock waves delivered, the better. Some urologists take the position that it is better to overtreat than to re-treat. We contend that it is best to monitor treatment closely and to stop as early as possible. We realize that a major part of this issue is the poor quality of our present imaging equipment. What is needed is better imaging tools to help the physician know more precisely when

complete stone comminution has been achieved. Ongoing refinements in diagnostic ultrasound and radiologic imaging should lead to advancements that will improve this aspect of ESWL.

There may be other factors, other features of treatment that can and should be improved in ESWL. Shock wave coupling is one. In "dry table" lithotripsy, transmission of shock wave energy into the body is dependent on the gel interface between the shock head and the skin. This interface can be a site for attenuation of the shock wave and possibly scattering or refocusing of the pulse. We know of no systematic study that has assessed the quality of coupling on stone comminution or on tissue injury.

In some respects, lithotripsy has been an ongoing experiment. A lot of observations have been made but few improvements have been realized. We think there is reason to expect that lithotripsy is about to change for the better. For one, awareness has never been higher that ESWL can cause adverse effects. As a result, urologists are more keenly aware of the potential for collateral damage and are more likely to treat conservatively. We now know that some lithotripters are more dangerous than others. We expect that urologists will begin to demand better instruments, and that this will lead to the development of safer, more effective lithotripters. We are beginning to learn that how shock waves are delivered (how the urologist controls the parameters of shock wave delivery) can have a significant effect on the outcome of treatment. This is a positive development and will improve how ESWL is performed regardless of the lithotripter that is used.

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