EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY OF GALLBLADDER STONES

EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY OF GALLBLADDER STONES

AN EXPERIMENTAL STUDY

EXTRACORPORELE SCHOKGOLF LITHOTRIPSIE
VAN GALBLAASSTENEN

EEN EXPERIMENTELE STUDIE

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Gutta cavat lapidem non vi sed saepe cadendo

Ovidius (43 BC - 17 AC)

CONTENTS

CHAPTER 1

Background and Aims of the Study

The prevalence of gallstone disease in the adult population of western societies is at least 10% and increases with age.[1-3] Only 10% to 20% of all persons carrying gallstones develop episodes of biliary pain or complications.[4-8] For asymptomatic (silent) gallbladder stones an expectant approach is recommended in most cases.[9-12]

For more than hundred years, cholecystectomy has been established as the standard therapy for patients with symptomatic gallbladder stones. It provides a permanent cure with a mortality rate of 0.1% to 0.3% and a morbidity rate of 5% to 10% in patients younger than 70 years. However, in patients older than 70 years the mortality and morbidity rates amount to 5% and 30%, respectively.[13]

To reduce the morbidity and mortality rates, especially of the elderly high-risk group, but also to restrain costs associated with hospitalization and sick leave from work, operative as well as nonoperative alternatives have been developed. One of these alternatives is extracorporeal shockwave lithotripsy (ESWL), which is the subject of this thesis.

ESWL was developed at the Department of Urology and the Institute for Surgical Research, Ludwig-Maximilians University, Munich, Germany, in collaboration with Dornier Medizintechnik GmbH, Friedrichshafen, Germany.[14-18] Shockwaves are characterized by high-pressure amplitudes which are built up within nanoseconds and respond to the physical laws of acoustics. In principle, shockwaves are generated extracorporeally and directed at the stone as the target. Because water is used as transmission medium, the focused shockwaves propagate through the body without causing severe tissue damage because the acoustical impedance of most body tissues is close to that of water. At the interface of body tissues or fluids and the stone surface, the shockwave energy is released because of the abrupt change of acoustic impedance. This causes shearing forces and the formation of cavitation bubbles on the surface of the stone, leading to progressive stone disintegration. In the first lithotriptor, made by Dornier, shockwaves were generated by an underwater electrostatic spark-gap discharge and focused by a parabolic reflector. The two other major methods of shockwave generation applied in second generation shockwave devices are based on the electromagnetic and piezoelectric principle, respectively.[19,20]

Since the clinical introduction of ESWL,[21,22] surgical treatment of urolithiasis is restricted to less than 5 percent of patients.[23] For obvious reasons this success of ESWL in urology led to investigation of the possibilities of ESWL in the treatment of other stones. Studies on ESWL of gallstones were initiated at first in laboratory animals in 1983,[24] and later in clinical studies.[25] With the original lithotriptor (Dornier HM3) patients had to undergo treatment under general or epidural anesthesia while immersed in a waterbath, making the procedure time-consuming and uncomfortable. With the advent of second generation extracorporeal shockwave lithotripsy devices, immersion in a waterbath is no longer necessary and patients can be treated under local anesthesia or even without any form of anesthesia.

From September 1987, a second generation electromagnetic shockwave lithotriptor (Lithostar, Siemens AG, Erlangen, Germany) has been successfully used in the University Hospital Dijkzigt Rotterdam, The Netherlands, for disintegrating urinary stones. In July 1989, the system was upgraded with an additional electromagnetic shockwave generator (overhead module) with an integrated in-line ultrasound scanner, especially ensuring easy targeting of gallbladder stones (Lithostar Plus).

At this time ESWL of gallbladder stones is combined with adjuvant dissolution therapy with oral bile acids, because - in contrast with urinary tract calculi - complete spontaneous discharge of residual fragments after ESWL cannot be expected due to anatomical barriers.[20,26] This adds considerable costs, which impairs the cost-effectiveness of this combined treatment modality.[19,27] Furthermore, adjuvant oral chemolitholysis restricts biliary lithotripsy to patients with a so-called "functioning gallbladder", i.e., a gallbladder that can be visualized by oral cholecystography which demonstrates cystic duct patency. The development of potent dissolving agents like methyl tert-butyl ether (MTBE) and d-limonene enables rapid dissolution of gallbladder stones after instillation of these solvents into the gallbladder by ultrasound-guided transhepatic puncture of the gallbladder,[28-30] a technique which has been safely employed in our institution.[31,32]

At the time of the production and the installation of the electromagnetic lithotriptor (Lithostar Plus), thorough data on the efficacy and safety of this shockwave device

with regard to ESWL of gallbladder stones was lacking. Therefore, it was mandatory to investigate the efficacy and potential adverse effects of shockwaves generated by the Siemens system before applying this new technology to patients.

The necessity of adjuvant therapy after ESWL of gallbladder stones to dissolve the residual fragments stimulated to evaluate the feasibility of topical dissolution therapy by MTBE following ESWL as an alternative for adjuvant oral bile acids.

The aims of the study were:

- assessment of the focal pressure distribution of the shockwaves generated by the Lithostar (Plus) *in vitro* (Chapter 3)
- assessment of the focal pressure distribution of the shockwaves generated by the Lithostar *in vivo* (Chapter 4)
- assessment of the efficacy and biological effects of shockwaves generated by the Lithostar, treating gallbladder stones in a pig model (Chapter 5)
- assessment of the efficacy of gallstone lithotripsy by the Lithostar Plus *in vitro* (Chapter 6)
- assessment of the *in vitro* gallstone dissolving capacity of various solvents for adjuvant contact dissolution after ESWL of gallbladder stones (Chapter 7)
- assessment of the efficacy and safety of treatment of gallbladder stones by ESWL alone compared with ESWL followed by MTBE contact dissolution, using the Lithostar Plus in a pig model (Chapter 8).

All experiments were carried out at the Laboratory for Experimental Surgery, Erasmus University Rotterdam, Rotterdam, The Netherlands, and at the Department of Medical Research and Development, Siemens AG, Erlangen, Germany.

The animal experiments were approved by the Committee on Animal Research of the Erasmus University Rotterdam.

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CHAPTER 2

Extracorporeal Shockwave Lithotripsy of Gallstones: Possibilities and Limitations

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Abstract

Recently extracorporeal shockwave lithotripsy (ESWL) has been introduced as a nonoperative treatment for gallstone disease. Except for lung damage, no significant adverse effects of ESWL of gallbladder stones have been observed in animals. In clinical use ESWL of gallbladder stones is now confined to 15% to 30% of symptomatic patients. To achieve complete stone clearance, ESWL of gallbladder stones must be supplemented by an adjuvant therapy. ESWL of bile duct stones is highly effective and can be considered in patients in whom primary endoscopic or surgical stone removal fails. Second generation lithotriptors allow anesthesia-free (outpatient) treatments, but the clinical experience with most of these ESWL devices is still limited. The likelihood of gallbladder stone recurrence is a major disadvantage of ESWL treatment, which raises the issue of cost-effectiveness. ESWL for cholelithiasis is a promising treatment modality with good short-term and unknown long-term results.

Introduction

Extracorporeal shockwave lithotripsy (ESWL) has revolutionized therapy of urolithiasis. Despite concern about the long-term effectiveness and possible inducement of hypertension,[1] this noninvasive treatment has gained worldwide acceptance. After the convincing success of ESWL in urology, it was tempting to extend this technology to the treatment of gallstones.

Gallstone disease represents an important health care problem in the western world. The estimated prevalence of gallstones is about 10% to 15% and increases with advancing age.[2] Although many gallstones do not cause symptoms and need not be treated,[3-5] gallstone disease is a major cause of hospitalization for surgical treatment. In the United States annually more than $ 1 billion is spent on treatment of gallstones, mainly for the 500 000 cholecystectomies performed each year.[6] Since Langenbuch performed the first cholecystectomy in Berlin in 1882,[7] operative removal of the gallbladder has become the standard therapy for patients with symptomatic gallbladder stones. Cholecystectomy has an overall mortality rate of 0.6% to 1.3%, increasing from 0.2% in patients younger than 70 years to 5% in patients older than 70 years.[8-11] A safe and effective treatment for many patients, the morbidity rate of cholecystectomy is 10% to 33%,[11,12] it is uncomfortable for the patient, it requires hospitalization, and usually causes invalidity for 1 month.[13] To reduce the morbidity and mortality rates, as well as the cost, several nonoperative therapeutic alternatives have become available for both cholecystolithiasis and choledocholithiasis. Although still in its infancy, ESWL of gallstones is one of the most promising noninvasive treatment modalities for cholelithiasis. In this review article we will discuss the possibilities and the limitations of ESWL for the management of gallstone disease.

Principle of Shockwave Application

The basic physical principles have been described in detail elsewhere,[14,15] and presently only the essential clinical facts have been compiled. Shockwaves cause high-pressure amplitudes to increase within nanoseconds and to respond to the known physical laws of acoustics. If water is used as a transmission medium, focused shockwaves spread

through the body evenly without severely damaging the tissues because the acoustical impedance of most body tissues is close to that of water. At its focus point, the wave impact against the stone liberates short-term high-energy mechanical stresses because of the abrupt change in acoustical impedance. This causes tear-and-shear forces, which, together with the formation of cavitation bubbles in the surrounding medium on the surface of the stone, eventually lead to the disintegration of the stone.[16,17]

Table 1. *Second generation extracorporeal lithotriptors (adapted from Ferrucci[18] and updated to October 1988).*

Manufacturer	Model	S G	Focusing	Target Imaging	Coupling	Suitability
Wolf (Germany)	Piezolith 2300	PE	spherical array	US	mini-tank	GB
Technomed International (France)	Sonolith 3000	SGE	ellipsoid	US	mini-tank	GB
EDAP (France)	LT 01	PE	spherical array	US	waterbag	GB
Siemens (Germany)	Lithostar	EM	acoustic lens	x-ray	waterbag	CBD
	Lithostar Plus	EM	acoustic lens	x-ray + US	waterbag	GB+CBD
Medstone International (USA)	1050 ST	SGE	ellipsoid	x-ray ± US	waterbag	CBD (+GB)
Nitech (Denmark)		SGE	ellipsoid	US	waterbag	GB
Dornier Medizin Technik (Germany)	HM 4	SGE	ellipsoid	x-ray	waterbag	CBD
	MPL 9000	SGE	ellipsoid	US	waterbag	GB
	MFL 5000[a]	SGE	ellipsoid	x-ray	waterbag	CBD
Direx (Israel)	Tripter X1	SGE	ellipsoid	x-ray + US	waterbag	GB+CBD
Northgate (USA)	SD 3	SGE	ellipsoid	US	waterbag	GB
Diasonics (USA)	Therasonic	PE	spherical array	x-ray + US	waterbag	GB+CBD
Storz Medical (Germany)	Modulith SL 10	EM	ellipsoid	US	waterbag	GB
	Modulith SL 20	EM	ellipsoid	x-ray + US	waterbag	GB+CBD

SG: shockwave generator; PE: piezoelectric; SGE: spark-gap electrode; EM: electromagnetic; US: ultrasound; GB: gallbladder stones; CBD: common bile duct stones.
[a] also marketed as Philips MFL 5000 (The Netherlands).

The original waterbath lithotriptor developed by Dornier generates shockwaves by an underwater electric spark discharge in the one focus of an elliptical reflecting cavity that are condensed in the second focus. Positioning of the stone in this second focus occurs with a fluoroscopic guidance system. Today a second generation of

ESWL devices is on the market, with the same concept of underwater generation of shockwaves (Table 1). They apply varying combinations of techniques for shockwave generation, focusing, and target imaging apparatus. Most manufacturers have replaced the water immersion tank with a compressible water bag that enables contact skin positioning of the shockwave applicator. Nearly all are more compact in design, operate at lower costs, require simpler patient positioning, and many have the potential capability for treating gallbladder stones.[18]

Experimental Application of ESWL

Abdominal shockwave exposition in rats, as well as exposure of eventrated isolated organs (liver, kidney, intestine), did not cause pathologic changes.[15,19,20] Shockwaves directed to kidneys or to implanted stones in the renal pelvis of pigs and dogs produced only slight and predominantly transient traumatization of the exposed kidneys. These dose-dependent alterations (small hematomas and/or diffuse intraparenchymal hemorrhages) are restricted to the high-pressure field of the shockwaves and do not affect renal function.[15,20-24] In acute experiments on dogs, shockwaves on the liver and gallbladder also caused slight changes: small ecchymoses on the liver surface and gallbladder wall. Petechial hemorrhages may also occur on the serosal surface of the pancreas and duodenum. These minor gross and histologic changes were not considered a contraindication to applying shockwaves for gallstone destruction in humans.[25-28] On the other hand, if shockwaves strike on a tissue-air interface, in the lung, for example, damage may occur due to release of energy caused by the large difference in acoustical impedance of air and tissue. When the rat thorax was exposed to shockwaves, fatal lung damage was found.[15,19,20] ESWL of surgically implanted gallbladder stones in dogs also resulted in pulmonary damage (alveolar hemorrhage) involving areas just above the diaphragm in one third of the animals;[29] no animal died, and no hemoptysis was noted after shockwave application (Delius, written personal communication, 1988). These serious side effects are dependent on the shockwave pressure field. They do not occur when the lungs are more than 4 cm removed from the shockwave axis.[30] Other investigators have observed no changes or lesions in the right lung only in dogs autopsied one day after ESWL; no changes were observed in

Table 2. *Results of ESWL of gallbladder stones.*

First Author and References	No. of Patients	Type of Lithotriptor	Fragmentation (% of pts)	Adjuvant Treatment	Mean Follow-up
Sackmann[40]	175-250	Dornier-HM 3 (modified) Dornier-MPL 9000	99	Urso + cheno[a]	6 mo
Heberer[41] (Munich)					
Greiner[42] (Wuppertal)	157	Dornier-HM 3 (modified)	94	Urso + cheno	8.5 wk
Ponchon[c] (Lyon)	91	Technomed Sonolith 2000/3000	71	Urso + cheno	6 mo
Pizzi[44] (Milano)	29	Siemens Lithostar	86	Urso	-
Hood[45] (London)	38	Wolf Piezolith 2200/2300	89	Urso + cheno	-
Manfredi[c] (Rome)	44	Technomed Sonolith 3000	80	Urso	4 mo
Bory[c] (Lyon)	20	Tripter Direx-X1	75	Urso + cheno	-
Darzi[46] (Dublin)	37	EDAP-LT 01	-	Bile acids (?)	-
Burhenne[c] (Vancouver)	48	Siemens Lithostar	90[f]	No adjuvant therapy	-
Peine[47] (Rochester)	8	Dornier-HM 3	50	MTBE[g]	-
Mosnier[48] (Suresnes)	57	EDAP-LT 01	98	Urso + cheno	-
Zuin[49] (Milano)	35	EDAP-LT 01	37 (fragm ≤5 mm) (max 3 sessions)	?	-
	35	Wolf Piezolith 2200/2300	43 (fragm ≤5 mm) (max 3 sessions)	?	-
Total	849		37 - 99		

[a] urso = ursodeoxycholic acid; cheno = chenodeoxycholic acid.
[b] expected to be stone free.
[c] Personal Communication,
Biliary Lithotripsy - First International Symposium, July 11-13, 1988, Boston, MA, USA.
[d] only in first 20 patients treated with old type of shockwave generator.[43]

Side effects (% of pts)						
Cutaneous Petechiae	Biliary Colic	Transient Gross Hematuria	Pancreatitis	Cystic Duct Occlusion	Others	Stone Free (% of pts)
14	35	3	2(n=5)	5	Incidental	80, 12 mo post-ESWL
-	25	5	3(n=5)	2(n=3)	Incidental	70-80, 12 mo post-ESWL[b]
-	11	2	1(n=1)	2(n=2)	22[d]/7	50, 9 mo post-ESWL
-	-	-	3(n=1)	-	-	-
11	-	-	3(n=1)	-	11	-
No significant complications						-
No complications						-
-	3(n=1)	-	-	-	-	14,[c] ? post-ESWL
-	-	-	2(n=1)	-	-	-
No significant complications						75, 8-26 hr post-ESWL
-	19	-	-	-	54	20, 1 mo post-ESWL
-	-	-	-	-	-	-
-	-	-	-	-	-	-

[c] 32% of patients >50% clearance.
[f] during first session.
[g] MTBE = methyl tert-butyl ether.

animals killed 14 days after treatment.[26,31] The differences in outcome of shockwave application can be explained by differences in shockwave pressure distribution in the acoustic fields generated by the various lithotriptors.

Differences in the physical characteristics of shockwave pulses generated by differing lithotriptors are also responsible for the variation in results of *in vitro* fragmentation studies of human gallstones.[32] Soft cholesterol stones with a low density, as assessed by computed tomography, required more discharges to fragment the stone than those with a high pigment and calcium content.[33,34] On the other hand, other studies revealed successful fragmentation regardless of the chemical composition or the calcium content of the stone and suggest that ESWL may be applied to all types of gallstones. The effectiveness of this therapy will then only be limited by the total stone burden and the time required to complete stone fragmentation. This corresponds well with the observation that the number of shockwaves required to bring about fragmentation of human gallstones *in vitro* correlated closely with the number, volume, weight, and diameter of the stones.[31,35-38]

Clinical Application of ESWL for Gallstones

Gallbladder Stones

The first successful ESWL treatment of patients with gallstones was reported by Sauerbruch and coworkers in 1986.[39] They treated nine patients with functioning gallbladders containing 1 to 3 symptomatic radiolucent stones that were not larger than 25 mm in diameter. All stones were disintegrated into sludge or fragments. At present more than 1000 patients with gallbladder stones, most of them in Germany, have undergone ESWL on different systems (Table 2). The selection of patients is usually determined according to the inclusion and exclusion criteria of the Munich group (Table 3).

Because only cholesterol stone fragments are susceptible to adjuvant dissolution therapy, patients with radiopaque, calcified stones have been excluded, with a few exceptions.[46-48]

Recently the results of the first 175 patients treated in Munich were published.[40] In this the best-documented series so far, 72% of patients with solitary stones 21 to 30

Table 3. *Inclusion and exclusion criteria for ESWL of gallbladder stones.*[40]

Inclusion Criteria	Exclusion Criteria
History of biliary pain	Acute cholecystitis / cholangitis / pancreatitis
Solitary radiolucent gallbladder stone ≤30 mm,	Biliary obstruction or known bile duct stone
or up to 3 stones with similar total volume	Gastroduodenal ulcers
Gallbladder visualization by oral cholecystography	Coagulopathy or anticoagulants or aspirin
Stone positioning possible in the shockwave focus	Aneurysms or cysts in shockwave path
Shockwave avoids lung and bone	Pregnancy

mm in diameter and 63% of those with two or three stones could be expected to be free of stones 1 year after lithotripsy and adjuvant oral dissolution therapy. Smaller stones disintegrated into smaller fragments than did larger stones. The success rate for single stones 20 mm or smaller in diameter was clearly higher than for larger and multiple stones. The disappointing results with multiple stones may be due to difficulties in sonographic identification of residual stones during ESWL treatment after disintegration of the first stone. The subsequent disintegration of the remaining stones may be less complete, resulting in larger residual fragments, the dissolution of which take a longer period. Although stones with a radiopaque rim could also be successfully disintegrated, more time was required for these stone fragments to disappear.

Complications have been few. Except asymptomatic petechiae at the entrance of shockwaves into the skin and incidental transient gross hematuria due to passage of shockwaves through the right kidney, no other adverse effects related to the administration of shockwaves were observed. Routine laboratory blood tests showed no significant changes, except a mild leucocytosis immediately after ESWL that normalized within 24 hours. Probably as a result of the passage of fragments, mild or moderate pancreatitis developed in two patients. Furthermore about one third of the patients suffered once or more frequently from mild biliary colicy pain, which was easily treated with spasmolytic agents. With the exception of diarrhea occurring in 4% of the patients, the adjuvant administration of oral bile acids did not cause adverse effects.

Biliary Duct Stones

The original clinical work done by Sauerbruch et al.[39] also suggested that common bile duct stones may be fragmented by ESWL without causing serious side effects. Subsequently their experience has been further extended and similar positive results of ESWL of common duct, intrahepatic, and retained cystic duct stones with both first and second generation lithotripsy devices have been accumulated in a number of patient series. ESWL of biliary duct stones in 346 patients resulted in an overall complete stone clearance rate of 63% to 100% (Table 4).

Most patients with bile duct stones that resist removal after endoscopic sphincterotomy can be treated by ESWL without general anesthesia; and ESWL may resolve life-threatening conditions, especially for high-risk and critically ill patients.[53,57,58] Significant adverse effects and alterations in laboratory tests, including liver and pancreas enzymes, usually do not occur. Transient hematuria is a common finding after ESWL of bile duct stones but is of little clinical significance.

Limitations of Biliary ESWL

Initially lithotripsy of gallstones was performed under general anesthesia, limiting ESWL to patients with a preoperative physical status compatible with class I or II of the American Society of Anesthesiologists.[39,59] Now intravenous analgosedation is sufficient for most patients, general or epidural anesthesia seldom being required. Treatments with piezoelectric lithotripsy devices are reported to be completely painless.[26,27,45] Nevertheless, depending on the type of lithotriptor, for certain patients intravenous opiate analgesia cannot replace adequate anesthetic techniques and the cooperation of an anesthesiologist (Schelling et al., unpublished data). Besides, unless triggered by the R-wave of ECG, the spark-gap systems especially can induce arrhythmias. Careful monitoring of the ECG is required, especially in patients with pre-existing cardiac rhythm disorders.

Anesthesia-free (outpatient) treatments have been made possible by lowering the total shockwave energy and by distributing the energy more diffusely at the skin surface. However the price for these technical adjustments is a lower initial stone fragmentation rate. For that reason more shockwaves are required, causing a longer

duration of the treatment session or resulting in a high retreatment rate because patient tolerance is limited.

In contrast to kidney stones most gallstones are radiolucent. Fluoroscopic targeting of a nonopaque gallbladder stone is not possible unless the stone has been visualized by contrast opacification of the gallbladder by oral or intravenous cholecystography. Therefore targeting of gallbladder stones can be best accomplished by ultrasound, but this can be difficult or impossible in obese patients.

Gallbladder Stones

Several distinctions immediately arise between lithotripsy of gallbladder stones and urinary tract calculi.[18] After ESWL at least 90% of fragments of renal calculi pass spontaneously through the ureter. Complete spontaneous discharge of residual fragments after ESWL of gallbladder stones cannot be expected because sufficient disintegration can rarely be obtained. This is crucial because experimental and clinical investigations indicate that only fragments smaller than 2 mm to 3 mm in diameter can pass into the intestine without causing local trauma.[60,61] Besides, both the spiral valves in the cystic duct and the choledochoduodenal sphincter are anatomical barriers presenting potential sites of relative obstruction. Furthermore the common bile duct has no peristalsis and there is a pre-existing relative dysmotility of the gallbladder that is not altered by ESWL treatment.[62,63] These factors imply that in addition to biliary colic, cholecystitis, cholangitis, and pancreatitis are possible serious complications.

Adjuvant therapy. The need for adjuvant treatment after ESWL of gallbladder stones has not been absolutely proved and is being investigated in the United States in a randomized clinical multicenter trial. For now it is likely that successful therapy of gallbladder stones will require a combination of ESWL and a subsequent adjuvant therapy to achieve complete stone clearance. This can be performed in three ways: (1) the use of oral dissolution therapy with bile acids (only cholesterol stones),[64] (2) percutaneous contact dissolution by direct transcatheter infusion into the gallbladder of solvents, the most promising of which is methyl tert-butyl ether (MTBE) (only cholesterol stones),[65,66] and (3) percutaneous drainage for evacuating the gallbladder (cholesterol and pigment stones).[67,68] Thus far bile acids have been used mainly as adjuvant management because they seem to offer the most simple and harmless treatment for remaining fragments of cholesterol stones. This implies that the nature

of the stone must be known.

Dissolution by oral (or local) agents is greatly enhanced by preceding stone fragmentation.[40,69-71] Despite this enhancement the expensive oral dissolution therapy still must be continued for at least 6 to 12 months after primary therapy by ESWL. Therefore, notwithstanding the more invasive character, adjuvant percutaneous dissolution therapy might afford a favorable alternative.[47,72-74] For patients with large or numerous stones currently being excluded for ESWL treatment, contact dissolution with MTBE may broaden the applicability of ESWL. Moreover MTBE also seems to be useful after ESWL of partially calcified cholesterol stones.[47]

With pigment stones a combination of ESWL and a percutaneous evacuation technique, with which stone fragments are removed mechanically or by aspiration, is possible.[67,68] Further development of solvents for contact dissolution of pigment stones may also be a future possibility.[75-77]

Tissue damage. On anatomical grounds the pulmonary damage found in dogs should present less of a problem in humans and such damage has not yet been observed in patients.[29,31,40] Nevertheless ESWL has the potential for causing significant soft-tissue damage in the high-pressure area of the shockwaves around the focus.[25,27,78] Patients subjected to ESWL immediately before elective cholecystectomy have shown gross evidence of acute tissue injury at laparotomy. Oedema of the gallbladder wall together with vascular dilatation, several petechial hemorrhages, and variable mucosal denudation were found (Johnson et al., unpublished data).[27,78] With the exception of the mucosal denudation, these changes were absent from gallbladders excised 24 to 48 hours and 5 days after ESWL, which indicates that these changes may be rapidly reversible.[45] The presence of intact epithelium in the mouths of the mucosal crypts, as visualized by scanning electron microscopy, may serve as a source of viable cells for re-epithelialization. Multiple small hematomas, which can be detected in the parts of the liver parenchyma which are transversed by the shockwaves, disappear within a few days to 4 weeks.[25] These changes, which are comparable to the small perirenal and intraparenchymal hematomas observed after ESWL of kidney stones, are of no clinical importance.[25,79-82] However this implies that patients with coagulation disorders should be excluded from ESWL treatment. Relying on the data presented in Table 2, the incidence of pancreatitis, which can be considered an adverse effect of the administration of shockwaves as well as a complication due to passage of fragments, is

small. This finding is rather surprising because the risk of acute pancreatitis is said to be increased in patients with microlithiasis of the gallbladder.[83] Thus far emergency cholecystectomy for acute cholecystitis has not been reported. Finally gas-filled intestines may cause ESWL-induced erosions in the upper gastrointestinal tract.[84]

Indications. Application of ESWL is limited to only 15% to 30% of patients with symptomatic gallbladder stones who are referred for therapy.[40,85] However the previously accepted selection criteria for ESWL of gallbladder stones (Table 3) seem to underestimate the number of suitable patients. Patients with stones larger than 30 mm in diameter, with more than three in number, and partially calcified stones have also been treated successfully,[40,46,47,51] but in light of the lower success rate other treatments may be more attractive. As to the mere histopathologic status, 60% of cholecystectomized patients who have no or very limited histologic changes in the gallbladder are potential candidates for ESWL.[86] In view of the diminishing need for anesthesia, it seems justified to extend this treatment to poor-surgical-risk patients, as recently reported.[53,57,58] Increasing experience and further improvement of lithotriptors may make ESWL of gallbladder stones possible for a larger population of patients. For now, however, it is unlikely that gallbladder lithotripsy will equal ESWL in urology, which is now the standard treatment for urolithiasis for almost all patients.

Stone characteristics. For lithotripsy of gallbladder stones it is not sufficient to know whether gallstones are present or absent. At least the number and size of the gallstones must be known and cystic duct patency must be assessed. Plain abdominal x-rays are of limited value in predicting gallstone type[87] because there is a 14% chance that radiolucent stones are pigment stones.[88] As the fragments of pigment stones cannot be dissolved with the agents in use so far, it is important to predict gallstone composition more precisely. Computed tomography seems to be of great value in discriminating between radiolucent cholesterol and pigment stones, and thus in the prediction of susceptibility to adjuvant dissolution therapy.[89-91] The exact role of this and other tests in differentiating between cholesterol and pigment stones has not yet been established.[92,93] Before ESWL of patients with gallbladder stones is performed, an extension of the diagnostic work-up is needed. Sonography should be combined with the almost-obsolete-but-now-reviving method of oral cholecystography to establish the functional status of the gallbladder.

Recurrence. A significant drawback of each alternative for cholecystectomy and

Table 4. *Results of ESWL of biliary duct stones.*

First Author and References	No. of Patients	Location of Stones	Type of Lithotriptor
Heberer[41] (Munich)	51	common bile duct	Dornier-HM 3
Sauerbruch[50] (multicenter trial)	113	(common) bile duct	Dornier-HM 3
Greiner[51] (Wuppertal)	36	(common) bile duct	Dornier-HM 3
Staritz[34,52] (Mainz)	30	intrahepatic (5) common bile duct (25)	Siemens Lithostar
Burhenne[53] (Vancouver)	8	common bile duct (4) cystic duct (remnant)(4)	Dornier-HM 3
Burhenne[b]	30	(common) bile duct	Siemens Lithostar
Terpstra[54] (Rotterdam)	13	common bile duct	Dornier-HM 3
Terpstra[b]	8	common bile duct	Siemens Lithostar
Faustini[55] (Milano)	14	(common) bile duct	Siemens Lithostar
Ginestal-Cruz[b] (Lisbon)	16	(common) bile duct	Siemens Lithostar
Bory[b] (Lyon)	11	common bile duct	Direx Tripter-X1
Fried[56] (Halifax)	16	(common) bile duct	Dornier-HM 3
Total	346		

[a] mortality = 30 day mortality.
[b] Personal Communication,
Biliary Lithotripsy - First International Symposium, July 11-13, 1988, Boston, MA, USA.

Complete Stone Fragmentation (% of pts)	Complete Stone Clearance (% of pts)	Side Effects	% of Patients
-	80	not documented	-
1 treatm: 86 ≥ 2 treatm: 91	86	mild severe mortality[a]	29 8 0.9
-	97	sepsis(n=1)	3
intrahepatic: 100 common bile duct: 70	-	cutaneous petechiae	-
75	75	short-term fever(n=3) mild hematuria(n=2) transient hemobilia(n=1)	38 25 13
-	±75	not documented	-
100	100	transient hematuria small subcapsular hematoma of right kidney(n=2)	77 15
63	63	sepsis(n=1) cutaneous petechiae(n=1)	13 13
100	100	none	-
69	69	cutaneous petechiae	69
91	91	not documented	-
94	88	transient hemobilia(n=2) short-term elevation of AST and LDH transient hematuria (n=1) cutaneous petechiae	12 most pts 6 81
63-100			

also of ESWL of gallbladder stones lies in the likelihood of stone recurrence. Although recurrence after ESWL has not been definitely assessed due to the relatively short follow-up period, experience with oral bile acid dissolution therapy suggests a 50% recurrence 5 to 7.5 years after complete disappearance of stone fragments.[94,95] This corresponds with the observed recurrence rate of 10% within 6 months after discontinuation of adjuvant dissolution therapy after preceding ESWL treatment.[41] The feasibility, effectiveness, and potential toxicity of long-term continuous low-dose or intermittent therapeutic-dose treatment with bile acids to prevent stone recurrence have not been conclusively investigated.[95,96] Oral administration of inhibitors of HMG-CoA-reductase, however, may be an interesting treatment to decrease the cholesterol excretion in the bile, thus reducing the chance of recurrence of gallstone disease. To prevent recurrent stone formation, the results of attempts of nonsurgical defunctionalization of the gallbladder by percutaneous occlusion of the cystic duct and ablation of the gallbladder by sclerosing agents are currently being evaluated in experimental models.[97-103] The results are promising and the first application in humans has recently been started (Becker, written personal communication, 1988).

Bile Duct Stones

Despite the potential of ESWL, the indications for ESWL treatment of bile duct stones will remain limited because there are other effective nonoperative treatment modalities such as endoscopic removal.[104,105] Therefore shockwave fragmentation should be considered only in patients in whom, after endoscopic sphincterotomy, stone extraction fails. This represents only 9% of all patients with bile duct stones referred for endoscopic removal.[50]

Unlike gallbladder stones, common bile duct stones are preferably localized by fluoroscopy rather than sonography.[106] To focus the shockwaves on the stone, bile duct stones have to be visualized, which is normally achieved by contrast injection through an endoscopically placed nasobiliary catheter.[41,50] This can also be performed by percutaneous transhepatic cholangiography.[53,54,56,107]

A treatment failure rate of 20% at the first session must be accepted (Sauerbruch, written personal communication, 1988). Failure of lithotripsy could not be predicted by analysis of the calculi before ESWL by computed tomography and did not depend on stone diameter. Interposition of bowel gas, which is likely to absorb

shockwave energy, is possibly responsible for failure of treatment.[52] In approximately 75% of patients additional interventional procedures, like endoscopic extraction of remaining fragments, are needed to achieve complete fragment clearance.[50]

Problems and Perspectives

A number of problems still must be solved. A major question is how to measure efficacy of ESWL treatment of gallstones. Most reports mention fragmentation rates and/or stone clearance rates, but much obscurity still exists about the effects on symptoms. Thus far only symptomatic gallbladder stones have been treated. For comparison of the long-term results it would be desirable to use a clear definition of "symptomatic gallstones," as was recently established by a working party at the Gastroenterology Meeting in Rome.[108] While for a silent (asymptomatic) stone in the gallbladder an expectant approach may be best, some form of active treatment has been recommended for asymptomatic choledocholithiasis.[108]

In the event of recurrence, retreatment with ESWL or dissolution therapy must be considered, although it is still uncertain if all recurrent stones will again cause symptoms. This raises the question whether ESWL as primary therapy for gallbladder stones is cost-effective, at least for young patients. Significant cost savings have been realized by hospital discharge 24 hours after cholecystectomy.[109,110] For most of the healthy and relatively young patients, cholecystectomy, which provides a permanent cure at a small risk, remains the most cost-effective option. For patients older than 70 years, ESWL will probably be of greater importance because of the higher morbidity and mortality rates of surgical management. The possibility of ESWL treatment on an outpatient basis should also be taken into account. Analysis of the cost-effectiveness of lithotripsy of gallbladder stones *versus* conventional cholecystectomy requires further observations of long-term results. This goal can be best achieved in prospective randomized studies, which are being conducted in Sheffield, England (Williams, written personal communication, 1988) and at our institution.

Although increasing steadily, experience with extracorporeal shockwave treatment of gallstones outside Germany is still limited, and the reports of results with second generation lithotriptors are based on small patient series. Most of these

preliminary studies have only a short follow-up and are not well documented. The (adapted) Dornier renal lithotriptor has proved to be a device to treat gallstones in the gallbladder and in the common bile duct successfully without serious short-term adverse effects in selected patients. Thorough data on the potential risk of harmful side effects and efficacy of most second generation lithotripsy devices, however, are still lacking. Caution in the clinical application of new ESWL systems for treatment of cholelithiasis is mandatory. Basic experimental work on the pressure distribution in the focal area as well as to safety and efficacy must be done for each new lithotripsy apparatus before human biliary application is justified.[13]

In conclusion ESWL for gallstone disease is a promising noninvasive treatment modality with acceptable short-time risks and efficacy. Long-term results and possible late complications still must be assessed.

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CHAPTER 3

Assessment of Shockwave Pressure Profiles in Vitro: Clinical Implications

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Abstract

Pressure profiles of shockwaves generated by different electromagnetic shockwave sources used in the Lithostar and in the overhead module of the Lithostar Plus (Siemens AG, Erlangen, Germany) were evaluated *in vitro*. Measurements were obtained using a polyvinylidene fluoride (PVDF) pressure probe placed in water at various positions in the respective acoustic fields. Maximum positive pressure (p^+) in the focus of the overhead module was twice as high as that of the Lithostar: 63.8 $\pm$ 0.1 MPa and 32.5 $\pm$ 0.2 MPa (mean $\pm$ SD), respectively. Both shockwave sources generated highly reproducible shockwaves with a low shot-to-shot variation. The -6 dB zone had a length of 95 mm and a width of 9 mm in the Lithostar at 18.1 kV. The equivalent values for the overhead module at generator power setting 9 were 40 mm and 3 mm, respectively. Interposition of fresh porcine tissue layers reduced p^+ by 15%. Placement of a human gallstone into the focus decreased p^+ by 85% (just distal to the stone). In clinical use, the narrow width of the focal area of shockwaves generated by the overhead module will minimize the chance of tissue damage in surrounding structures. In conclusion, the overhead module of the Lithostar Plus is a useful extension of the Lithostar, and is expected to be more effective and safer for the treatment of gallbladder stones than the Lithostar.

Introduction

Extracorporeal shockwave lithotripsy (ESWL) is currently the standard therapy for urinary stone disease. Recently, ESWL has also been used as a treatment for gallstones.[1] In spite of widespread clinical application, however, the underlying physical mechanisms of ESWL-induced stone fragmentation and effects on tissues are still not fully understood. Direct impact of shockwave pressure is supposed to cause tear-and-shear forces leading to stone fracturing.[2,3] Cavitation in the surrounding medium at the surface of the stone is also important.[4,5]

A shockwave is characterized by peak-positive and peak-negative amplitudes, pulse rise time, and pulse width.[6] Apart from the focal dimensions of the lithotriptor, these physical characteristics and the peak pressures in particular are of clinical importance as these parameters determine the efficacy of stone fragmentation as well as the biological effects in tissues.[6-8]

Most experience in ESWL treatment of urinary and biliary tract stones has been obtained by using the waterbath-type lithotriptor (Dornier HM3, Dornier Medizintechnik GmbH, Germering, Germany). In this system, electrohydraulic shockwaves are generated by an underwater electric spark discharge and focused by an ellipsoid reflector. Presently, second generation ESWL devices that apply alternative techniques of shockwave generation and focusing are commercially available. As the shockwave sources and focal geometry differ, it is mandatory to assess the physical characteristics of shockwaves as well as the dimensions of the focal area for any new type of lithotriptor to obtain a better understanding of the mechanism of operation. This article presents the results of *in vitro* pressure measurements of shockwaves generated by the Lithostar and by the overhead module of the Lithostar Plus (Siemens, Erlangen, Germany) and the effects of tissue and stone interposition.

Materials and Methods

Shockwave Device

The shockwave generators of the Lithostar and the Lithostar Plus are based on an electromagnetic principle.[9,10] The shockwave source consists of a slab coil, opposite to

and separated by a thin insulating layer from an adjacent metallic membrane (Fig. 1). An electric impulse applied to the coil induces opposite eddy currents in the membrane, resulting in a strong magnetic repulsion between coil and membrane. Due to the movement of the metallic membrane, a wave front is produced in a water-filled cylinder located behind it. During propagation this wave front steepens, leading to the formation of a shockwave, that is directed towards the focal point by a biconcave acoustic lens. A compressible waterbag is used for dry coupling to the patient.

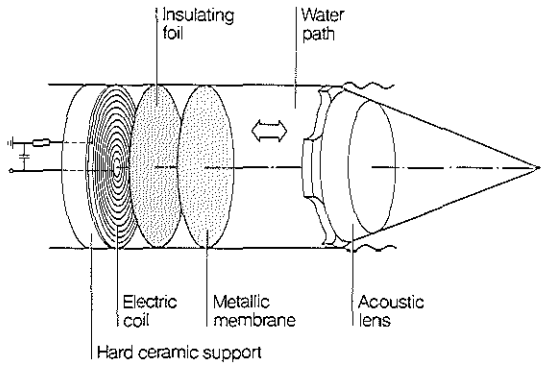

Figure 1. *Electromagnetic principle of shockwave generation.*

The Lithostar has a dual shockwave generator assembly and a two-axis intersecting x-ray system with image intensifier chain and television monitors for target imaging. Output of the shockwave generator is determined by the generator voltage (power) setting, which can be varied from 10 to 19 kV. The Lithostar Plus consists of a standard Lithostar supplemented by a movable overhead module containing a newly designed additional shockwave generator. The shockwave generator of this module is based on the same principle as the Lithostar, but has a larger diameter and contains an integrated ultrasound target imaging system. The output of the overhead module is determined by the generator power (energy) setting which can be varied from 1 to 9, setting 9 producing maximum output.

Pressure Measurements

The experimental set-up consisted of a water-filled test basin with a window in one side. The shockwave applicator was coupled by means of ultrasound coupling gel to a nonattenuating elastic membrane sealing off the window. Shockwaves generated at varying generator power settings were transmitted to the focal point in the test basin. Pressure measurements were obtained using a broad-band piezoelectric pressure probe (Imotec, Würselen, Germany) placed at various positions in the acoustic fields of the different shockwave sources. This probe, based on polyvinylidene fluoride (PVDF) with an outside diameter of 1.2 mm, and a sensitive element 0.5 mm in diameter, has a constant sensitivity up to 5 MHz. Measurements are possible up to the focal point with a measuring range from 0 to 200 MPa. Further details of the performance of this probe have been described.[11] Pressure waveforms were displayed as output voltage waveforms on a digital oscilloscope (Gould 4072, (Gould, Hainault, England) [frequency range 0-100 MHz] or Philips PM 3311 (Philips, Enschede, The Netherlands) [frequency range 0-60 MHz]). Single-shot voltage waveforms were plotted on the oscilloscope or photographed from the display screen. Absolute positive and negative pressures could be calculated from measurements of the corresponding positive and negative voltages as recorded on the oscilloscope. The respective calibra-

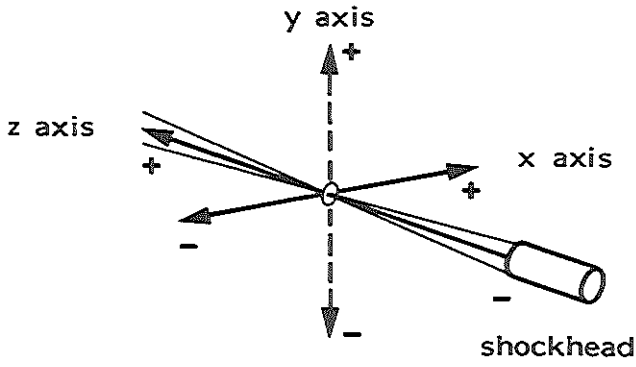

Figure 2. *Relation of X, Y, and Z axis to focus and position of shockwave generator. The Z axis resembles the shockwave transmission path (axial direction); and X axis (lateral direction), and Y axis are both perpendicular to the Z axis in the focal plane.*

tion factors for the probes used for measurements in the Lithostar and overhead module were 0.238 and 0.236 MPa/mV, respectively.

All measurements were performed in room temperature water with the pressure probe placed in a plane exactly parallel to the major axis of the shockwave transmission path. To assess the spatial pressure distribution in the acoustic field, measurements were carried out on three axes through the focus: the Z axis, defined as the major longitudinal axis resembling the shockwave transmission path; and the X and Y axes, both perpendicular to the Z axis (Fig. 2). The attenuating effects of body tissue upon shockwave pressure were studied by interposing porcine tissue layers of increasing thickness up to approximately 8 cm between shockwave applicator and focus. These layers were obtained immediately after sacrifice and anatomically "rebuilt". Starting with skin only, subcutaneous tissue and an increasing number of abdominal wall muscles were subsequently added. On the Z axis, measurements were also carried out with a radiolucent human gallstone positioned in the focus.

The energy transported by a single shockwave front generated at maximum generator power setting was evaluated for the entire focal plane, as well as for two arbitrary focal areas 15 mm and 30 mm in diameter, respectively. The energy values were calculated from the pressure waveforms by measuring the wave pressure as a function of time at N different radii from the Z axis. The temporal integrals were evaluated at each radius by recording the pressure pulses on the oscilloscope. The acquired data were numerically integrated by computer. To yield the total temporal energy per pulse contained within the maximum radius r_N, the N measurements were summed according to the equation:

$$E=\frac{1}{\rho.c}\sum_{n=1}^{N}\left[\int_0^{\infty} p^2(r_n,t)dt\right].A_n,$$

where ρ=density of the medium (water, kg/m^3), c=speed of sound in water (m/sec), p=pressure (Pa), r=radius (mm), t=time (seconds), and $A_n=(r^2_{n+1}-r^2_n)\pi$=area (mm^2).

Results

Waveforms

The shape of the pressure waveforms, displayed as voltage waveforms on the oscilloscope, depends on generator power setting and position in the acoustic field. At maximum generator power setting focal waveforms of the Lithostar and the overhead module are nearly similar, differing mainly in absolute values of peak-positive voltage. This indicates a difference in maximum focal pressure (Fig. 3*a* and *b*). The focal waveforms are characterized by a peak-positive voltage (v^+) with a very short rise time (from 10% to 90% of v^+) and small pulse width (at 50% of v^+), falling to 0 in about 1 μsec and a peak-negative voltage (v^-) during approximately 2.5 μsec. The relation of focal waveform parameters to generator power setting is shown in Table 1.

A relatively slow initial rise of v^+ not occurring in focal waveforms at maximum generator power setting, arises when generator power decreases (Fig. 3*c*). This also occurs at positions outside the focus, irrespective of generator power setting. With increasing defocusing waveforms get a larger pulse width (Fig. 3*d*). Waveforms obtained on the X axis at symmetrical positions on either side of the focus and also at corresponding positions on the Y axis are identical (Fig. 3*e* and *f*).

Pressures

Table 2 gives the mean focal values of peak-positive and peak-negative pressure (p^+ and p^-) and the coefficients of variation, reflecting the shot-to-shot variation. Values of p^+, normalized to p^+ at maximum generator power setting of the overhead module, are illustrated in Figure 4. Decreasing the generator power voltage of the Lithostar from 19.0 to 18.1 kV reduced p^+ by only 1% . Therefore, to save the shockwave generator, the 18.1 kV setting was chosen for all further measurements in the Lithostar.

The shot-to-shot variation in p^+ in the focus was about 1% and ranged from 2% to 8% for p^- (Table 2). The shot-to-shot variation of p^+ and p^- at different positions outside the focus varied with a maximum of 5% for p^+ and 12% for p^-. The day-to-day variation in the mean focal pressures of the Lithostar as measured on three different days was maximally 4%. Variation of acoustic field position up to positions at which $<1/3$ of focal p^+ was present did not evidently change p^-: the weighted means of p^- were 3.6 MPa (range: 1.0-4.9) and 4.9 MPa (4.0-6.6), respectively, for the Lithostar and

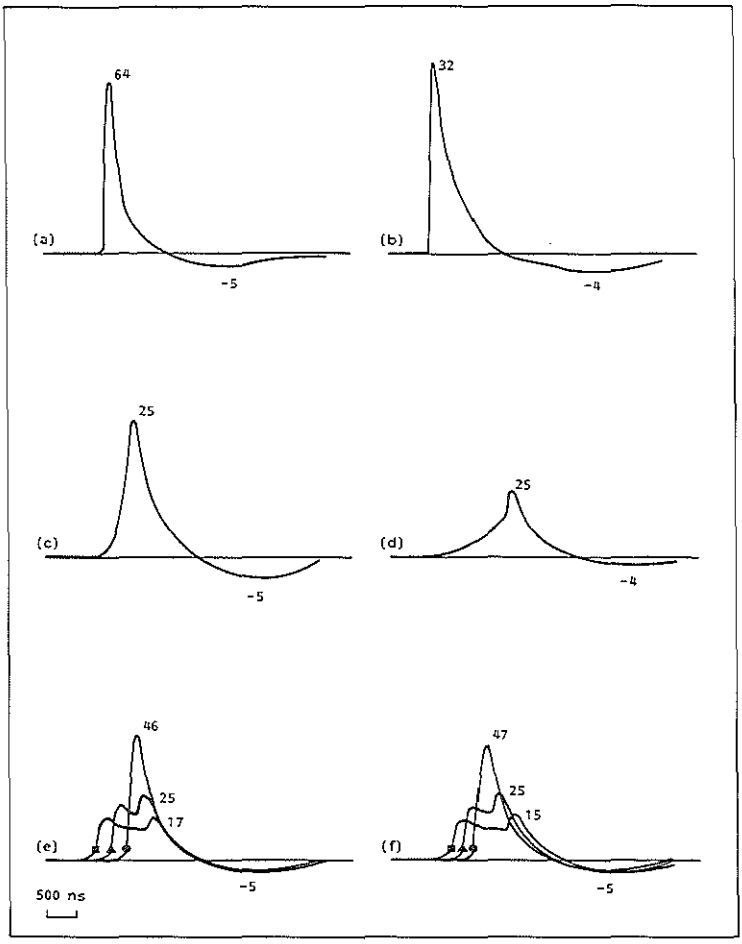

Figure 3. *Voltage waveforms at different generator power settings and acoustic field positions of the Lithostar and overhead module. Because voltages/division on the vertical scale differ, absolute peak-positive and peak-negative pressures are given in MPa. A horizontal scale division indicates 500 ns.*

a. overhead module, focus, setting 9 (max).

b. Lithostar, focus, 19 kV (max).

c. overhead module, focus, setting 1 (min).

d. overhead module, y = +30 mm, setting 9.

e. overhead module, ● x = -1 mm, ▲ x = -2 mm, ■ x = -3 mm, setting 9.

f. overhead module, ● y = +1 mm, ▲ y = +2 mm, ■ y = +3 mm, setting 9.

overhead module, irrespective of acoustic field position and generator power setting. Therefore, values of p^- have been omitted in the following figures. Increasing generator power setting of the overhead module from setting 1 to 9 caused a slight decrease of p^-. This relationship could not be established for the Lithostar because only three generator voltage settings (16.9, 18.1, and 19.0 kV) were investigated (Table 2).

Table 1. *Focal voltage waveform parameters at different generator power settings.*

Type of Lithotriptor	Generator Power Setting	Pulse Rise Time (ns)	Pulse Width (ns)
Lithostar	14.2 kV	150	290
	18.1 kV	50	400
Overhead module	1	300	430
	9	50	230

NOTE. Values based on single-shot recordings.

Figure 5 is a three-dimensional plot of the distribution of p^+ of the Lithostar, showing the typical property of any shockwave system. The pressure is distributed more widely in the axial direction (shockwave transmission path) than in the lateral direction (focal plane). This figure has been assessed by single-shot measurements in the X-Z plane. Negative and positive values on the Z axis (axial direction) correspond to positions in front of and behind the focus, respectively, which is recognizable as the position at which pressure is maximum at the intersection of the X and Z axis. Similarly, negative and positive values on the X axis (lateral direction) represent positions on either side of the focus in the focal plane. The pressure distributions on the single axes are shown as a longitudinal and a transverse section of the three-dimensional plot in Figures 6 and 7, respectively.

In Figure 6, the distributions of p^+ on the Z axis of the Lithostar and overhead module are combined. Maximum focal pressure of the overhead module is twice the value of the Lithostar, but relatively more sharply focused, indicated by the difference of -6 dB zone (i.e., the zone in which p^+ is at least 50% of maximum focal value), that had a length of 95 mm in the Lithostar compared to 40 mm in the overhead module.

Interpositioning of fresh tissue layers between shockwave applicator and focus reduced p^+ by 15% on average (Fig. 6). The attenuating effect of skin only appeared to be similar as that of a tissue layer composed of two full-thickness porcine abdominal walls.

Table 2. *Focal peak-positive and peak-negative pressures at various generator power settings.*

Type of Lithotriptor	Generator Power Setting	Peak-positive Pressure (MPa)	Peak-negative Pressure (MPa)
Lithostar	16.9 kV	29.1 ± 0.3 (1.0)	3.4 ± 0.2 (5.9)
	18.1 kV	32.1 ± 0.4 (1.2)	3.8 ± 0.3 (7.9)
	19.0 kV	32.5 ± 0.2 (0.6)	3.7 ± 0.3 (8.1)
Overhead module	1	25.5 ± 0.3 (1.2)	5.3 ± 0.1 (1.9)
	3	37.8 ± 0.3 (0.8)	5.2 ± 0.1 (1.9)
	5	50.6 ± 0.4 (0.8)	4.7 ± 0.1 (2.1)
	7	59.3 ± 0.2 (0.3)	4.7 ± 0.1 (2.1)
	9	63.8 ± 0.1 (0.2)	4.7 ± 0.1 (2.1)

NOTE. Values represent the means and standard deviations of 20 consecutive measurements with the coefficients of variation (shot-to-shot variation) given in parentheses.

The distribution of p^+ on X and Y axis of the Lithostar and the equivalent pressure distributions of the overhead module are superimposed in Figure 7. As could be deduced from the identical voltage waveforms (Fig. 3*e* and *f*), there was no significant difference in distribution of p^+ on X and Y axis. A rapid and symmetrical decrease of p^+ occurred on both sides of the focus, determining the small width of the -6 dB zone, which was about 3 mm in diameter for the overhead module compared to 9 mm for the Lithostar (Table 3).

A human gallstone (15x12 mm) placed in focus of the overhead module decreased p^+ and p^- just distal to the stone to 15% and 40%, respectively, of the pressure measured without stone. However, after application of 40 shockwaves leading to fragmentation of the stone, the reduction of p^+ became less, since 30% of pressure measured without stone remained (Fig. 8). Similar results were obtained with the Lithostar.

In Table 4, the calculated values of energy are given for the entire focal plane (total energy) and the two defined focal areas.

Discussion

Until now, little data on shockwave pressure measurements had been available. Recently, measurements of pressure waveforms in the acoustic field of the Dornier HM3 lithotriptor have been reported.[12] In this article, the results of comparative measurements of pressures generated by two different electromagnetic shockwave sources are presented.

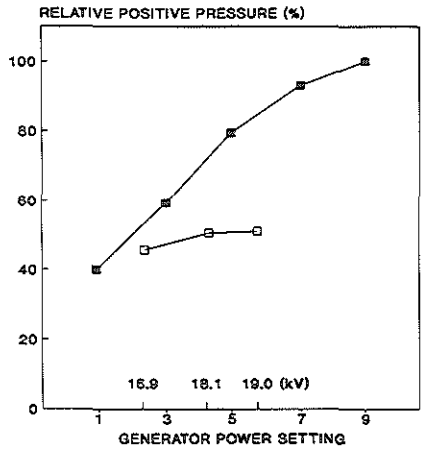

Figure 4. *Relative focal peak-positive pressures of the Lithostar and overhead module at different generator power settings. Values are normalized to the maximum value of the overhead module. Generator power of the Lithostar is indicated by voltage settings, 19 kV being maximum. For the overhead module generator power varied from setting 1 (min) to 9 (max).*
□ *Lithostar;* ■ *overhead module.*

Accurate measurements in the focal zone, which is characterized by the occurrence of shockwaves with high pressures and frequencies, are technically difficult. A durable and sensitive pressure probe is needed, with a sufficiently rapid response time to record the fast rising peak pressures. Previous measurements of shockwave pressures have been performed using probes with a narrow bandwidth and are therefore, considered to be less accurate.[13,14] More reliable data can be obtained by use of a broad-band polyvinylidene fluoride needle probe, because of the wider frequency response.[10] This type of probe is able to withstand the high shockwave pressures without losing sensitivity over a period of time. Linearity between pressure and electrical output signal of this probe has been verified up to 30 MPa.[11] However, a constant sensitivity of the piezoelectric material has been proved up to 80 MPa,[15] sufficiently exceeding maximum pressures measured in this study. For various reasons, assessment of absolute values of pressures still entails appreciable uncertainties.[16] Actual pressures may be overestimated or even be higher than those measured. Nevertheless, the reported pressure data of the Lithostar and the overhead module are comparable

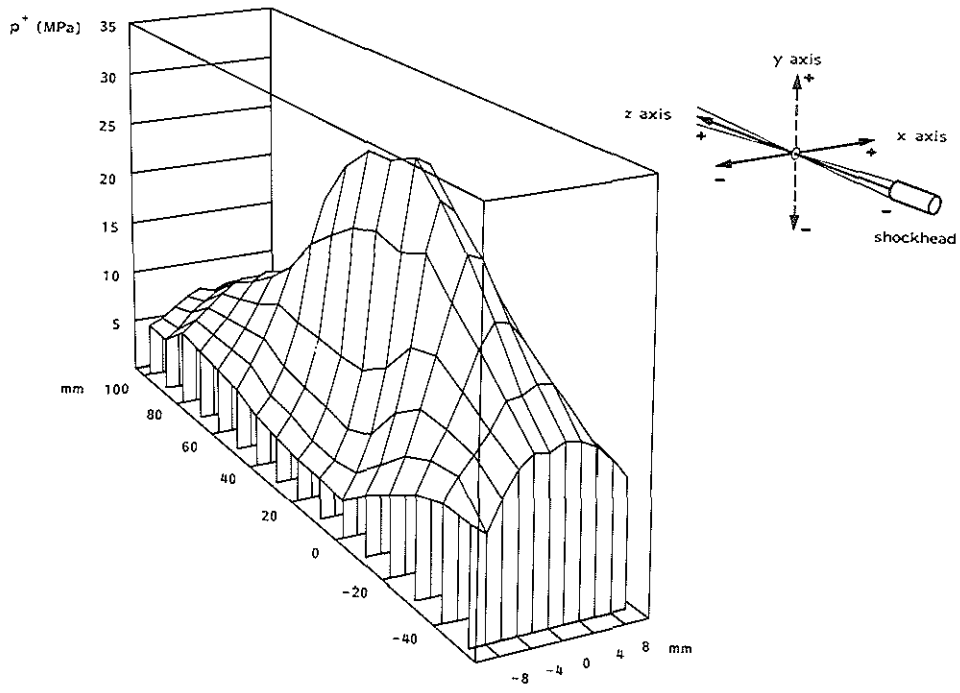

Figure 5. *Positive pressure distribution of the Lithostar along X and Z axis at 18.1 kV. The X axis (lateral direction) is perpendicular to the Z axis (axial direction). In the focus being located at the intersection of the axes pressure is maximum.*

because identical pressure probes have been used. Comparisons with pressure measurements of other machines are only possible as far as measurements have been performed with probes of at least approximately similar sensitivity.

Apart from peak voltages, further waveform parameters as pulse rise time and pulse width certainly play a role, although their significance has not been clarified in detail. Both parameters are assumed to be important in determining fragment size. The best fragmentation grade is achieved by shockwaves with minimal pulse rise time and width,[6,10] occurring in the focus at maximum generator power setting.

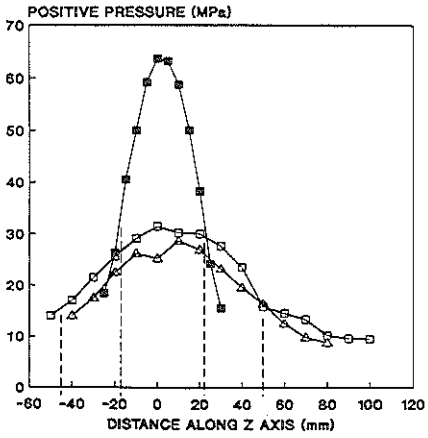

Figure 6. *Positive pressure distribution with indication of -6 dB zone (i.e., the zone in which p^+ is more than half of that of the focus) along Z axis (shockwave transmission path) of the Lithostar (18.1 kV) and overhead module (setting 9). Negative and positive values on the horizontal axis correspond to positions in front of and behind the focus (z = 0), respectively.*

■ *overhead module;* □ *Lithostar;* △ *Lithostar with interposition of a 4-cm thick porcine tissue layer between shockwave source and focus.*

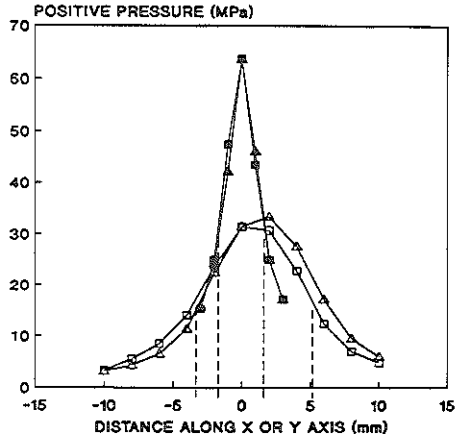

Figure 7. *Positive pressure distribution along X and Y axes (focal plane) of the Lithostar (18.1 kV) and overhead module (setting 9). Negative and positive values on the horizontal axis correspond to positions on either side of the focus (x,y = 0). The -6 dB zones are indicated only for the X axes.*

□ *X axis, Lithostar;* △ *Y axis, Lithostar;* ■ *X axis, overhead module;* ▲ *Y axis, overhead module.*

Maximum focal value of p^- of the overhead module was only 20% higher than that of the Lithostar. Unlike the pattern of p^- in other lithotriptors,[16] p^- did not change significantly with varying generator power settings (Table 2). A focusing effect on p^- did not occur as values of p^- did not seem to vary with acoustic field position. Furthermore, both shockwave generators produce relatively low negative pressures in comparison with maximum values found in several other ESWL units.[16] This feature is of clinical importance, as possible tissue damage and pain perception during ESWL are associated with negative pressure induced cavitation.[5-8,10] On the other hand, a complete absence of negative pressure components of the shockwaves is not desirable since cavitation phenomena contribute to stone fragmentation.[4-6,13]

Table 3. *Dimensions of -6 dB zone (i.e., the zone within which more than 50% of maximum focal pressure occur) on X, Y, and Z axis.*

Type of Lithotriptor	Generator Power Setting	Width		Length
		X axis (mm)	Y axis (mm)	Z axis (mm)
Lithostar	18.1 kV	9.1	9.7	95
Overhead module	1	3.8	4.4	38
	5	3.1	3.2	35
	9	3.4	3.5	40

Table 4. *Energies delivered by a single shockwave front at maximum generator power setting into the entire focal plane and into focal areas 15 mm and 30 mm in diameter, respectively.*

Type of Lithotriptor	Generator Power Setting	Energy (mJ)		
		Focal Plane (Total Energy)	ϕ 15 mm	ϕ 30 mm
Lithostar	19.0 kV	90	21(23%)	44(49%)
Overhead module	9	70	28(40%)	48(69%)

NOTE. Data are given as absolute values and expressed as a percentage (in parentheses) of the total energy in the focal plane.

Shockwaves generated by electromagnetic sources are highly reproducible,[9,10] as corroborated by the 1% shot-to-shot variation in p^+ measured in the focus resulting in stable focuses. This finding justifies assessment of pressure profiles by single-shot measurements as reported in this article. This is an advantage of electromagnetic shockwave sources over spark-gap lithotripsy systems. In the Dornier HM3 lithotriptor, values of positive pressure were found to fluctuate by approximately 25% to 45%, attributable to the inherent variability of the electrical discharge.[12,14] Variations in mean focal pressures on different days may be caused by a variation of sensitivity of the pressure probe by temperature.

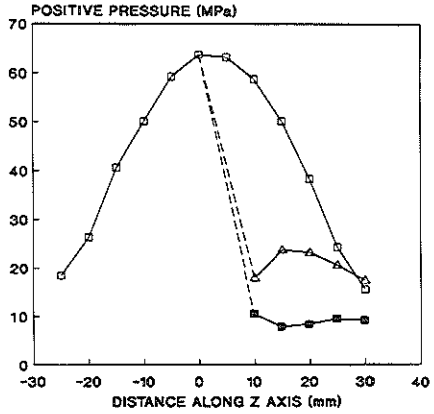

Figure 8. *Positive pressure distribution along Z axis (shockwave transmission path) of the overhead module with/without placement of a human gallstone in focus (setting 9). Negative and positive values on the horizontal axis correspond to positions in front of and behind the focus (z = 0), respectively.* □ *without stone in focus;* ■ *with stone (15 x 12 mm) in focus;* △ *with stone in focus after application of 40 shockwaves.*

Although it seems reasonable to compare different shockwave sources on the basis of -6 dB focal dimensions, it becomes apparent that direct comparison of the -6 dB zones has a limited significance, since both types of shockwave sources generate shockwaves with different maximum pressures. The -6 dB level of the overhead module, for instance, corresponds to 90% of maximum pressure of the Lithostar. Therefore, quantitative comparisons based on isobar zones, i.e., zones with the same pressure levels, are certainly more significant.[17] On the other hand, specification of the -6 dB zones is still meaningful since they are indicative for the focusing capability of the system. As demonstrated for the overhead module the focusing properties did not significantly depend on generator power setting (Table 3).

As potential tissue damage should not be restricted to -6 dB focal zones, success of fragmentation cannot be exclusively related to maximum focal pressure amplitudes. Both focal geometry and peak pressures have to be taken into account. This can be accomplished by calculating the energy transported into a pre-determined focal area, expressed as a percentage of the total energy delivered in the focal plane. Despite high peak pressures, a successful stone fragmentation cannot always be achieved when shockwaves are too sharply focused, possibly leading to bore effects. On the contrary, with a wide shockwave front large parts of the delivered shockwaves will not be utilized and give rise to needless tissue exposure.[6] Instead of comparing different lithotriptors by -6 dB or isobar zones, a more sophisticated method of comparison consists of the calculation of the energy within prescribed areas around the focal point. We choose areas with diameters of 15 mm and 30 mm in view of the prevailing criteria

for selection of patients with gallbladder stones for ESWL (only stones with a diameter of up to 30 mm).[1] Comparing both Siemens shockwave generators in this way, it becomes clear that in spite of a lower total energy the overhead module has more disintegrative power, because more energy is condensed in a correctly focused stone (e.g., ϕ 30 mm) as a result of sharper focusing. This contributes to lower exposure of surrounding tissues to shockwave energy, as verified by low pressures measured behind the stone.

We could not confirm that in tissues at a depth of 8 cm pressures would be decreased by 50%.[12] Interposition of porcine tissue with a thickness up to 8 cm decreased p^+ measured in the axial direction by an average of 15%, in accordance with other investigators.[3] The attenuation was not influenced by increasing the thickness of the tissue layers, which may be explained by the absence of acoustic interfaces in muscle and subcutaneous layers. The major part of the attenuation was caused by the skin, which may be attributed to the presence of air-containing crypts around the hair follicles, sunken in the dermis.

Our findings are of clinical interest as the focus of both electromagnetic shockwave sources have proved to be stable. However, because of the narrow width of the pressure distribution in the lateral direction a relatively small misalignment out of focus may lead to insufficient stone fragmentation and potential tissue damage, underlining the accuracy of the employed focusing technique. On the other hand, as long as focusing is correct, only an insignificant amount of energy will pass along the stone.

ESWL of gallbladder stones requires higher energy compared to urinary stones,[6] and is preferably performed using sonographic targeting.[18] The overhead module equipped with ultrasound imaging technique, has more disintegrative power than the Lithostar, which has been proven effective and safe in urology.[19] As lung damage is a possible complication of ESWL of gallbladder stones,[7] the small width of the lateral, together with the short length of the axial pressure distribution of the overhead module contributes to a low chance of tissue damage. Therefore, the overhead module seems to be especially suitable for treatment of gallbladder stones.

In conclusion, the overhead module of the Lithostar Plus is a useful extension of the Lithostar, and is expected to be more effective and safer for treatment of gallbladder stones than the Lithostar.

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CHAPTER 4

In Vivo Assessment of Shockwave Pressures: Implication for Biliary Lithotripsy

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Abstract

During extracorporeal shockwave lithotripsy, the pressure profile, which is generated by the lithotriptor, determines the risk of tissue damage. In the present study, the pressure distribution of a lithotriptor (Lithostar; Siemens AG, Erlangen, Germany) was investigated in 10 pigs, five of which had gallstones surgically implanted into the gallbladder. The *in vivo* values were compared with *in vitro* data. Measurements were carried out along the shockwave transmission path at the focus within the gallbladder, the adjacent liver, the diaphragmatic surface of the right lung, and the shockwave exit site from the skin. Interposition of ribs did not cause a significant decrease in focal positive pressure. However, a gallstone positioned in the focus caused a 30%-65% reduction in pressure, recorded immediately behind the stone. Pressures obtained *in vivo* were always 15%-25% lower than those measured *in vitro*. The spatial distributions of the positive pressure *in vivo* and *in vitro* were almost identical. There was a high correlation between the pressures *in vitro* and *in vivo* ($r=0.88$; $p \leq 0.01$). This justifies assessment of shockwave energies generated during biliary lithotripsy by extrapolation of *in vitro* data. It is concluded that it is possible to characterize different lithotriptors by *in vitro* pressure profile measurements.

Introduction

Extracorporeal shockwave lithotripsy (ESWL) is a promising treatment modality for the management of gallstones in selected patients.[1-3] To date, the underlying biophysics have not been extensively studied. Furthermore, a physical basis for quantitative analysis of tissue damage after shockwave exposure has not been established.

Shockwaves exert a direct and an indirect effect on the tissue; the latter effect is mediated by cavitation phenomena. A shockwave is characterized by peak-positive and peak-negative pressure amplitudes, pulse rise time, and pulse width.[4] The exact significance of each of these parameters in inducing possible tissue damage has not been clarified in detail. The negative pressure component is associated with the formation of cavitation bubbles. These bubbles may collapse when they are struck by the positive pressure component of a shockwave that follows; this is considered a probable mechanism of acute tissue injury.[5]

During ESWL, considerable acoustic energy is dissipated in and adjacent to the focal area. It is likely that the severity and extent of tissue damage is directly related to the level of this energy, which is determined by the positive pressure amplitudes and the focal geometry of the lithotriptor. Although some manufacturers of biliary lithotriptors specify the *in vitro* pressure profile of their machines, little is known of the spatial pressure distribution of shockwaves *in vivo*. Before a study on the biological effects of shockwaves on tissues can be undertaken, the correlation between *in vitro* and *in vivo* pressure measurements as well as the effect that a gallstone has on the pressure distribution when correctly focused must be investigated.

In this article, the results of *in vivo* pressure measurements of shockwaves generated by the Lithostar (Siemens AG, Erlangen, Germany) in a pig model, the correlation with *in vitro* values, and its clinical implication for biliary lithotripsy are discussed.

Materials and Methods

Shockwave Device

The shockwave source of the Lithostar is based on the electromagnetic principle.[4,6,7] Wave fronts are produced in a water-filled cylinder by movement of a metallic

membrane when electrical impulses are applied to an adjacent coil. The wave front travels through water and is focused by means of an acoustic lens.

The Lithostar has a dual shockwave generator assembly and a biplanar intersecting x-ray system with image intensifier chain and television monitors for target imaging. Output of the shockwave generator is determined by the generator voltage (power) setting, which can be varied from 10-19 kV, with the highest kilovolt setting producing maximum output.

Procedures Before Pressure Measurements

Pressure measurements were carried out in 10 Yorkshire pigs (weighing 27.7 $\pm$ 1.8 kg, mean $\pm$ SD) under general anesthesia. Immediately before the measurements, human radiolucent gallstones were implanted at laparotomy in the gallbladders of five pigs. Imaging and subsequent focusing of the radiolucent stones was achieved by injection of contrast (Conray; Byk Nederland BV, Zwanenburg, The Netherlands) into the gallbladders. To prevent premature contrast leakage into the common bile duct, the cystic ducts were occluded by a ligature. In the remaining five pigs without stones, opacification of the gallbladder was achieved by ultrasound-guided, percutaneous instillation of contrast into the gallbladder.

Pressure Measurements

To enable comparative evaluation of the shockwave pressures it was essential to position all pigs in a consistent fashion. The difficulties created by anatomical variations in porcine gallbladder sites and the fixed focal distance of the Lithostar were overcome by placing the pigs in a waterbath, thus enabling variation in the length of the shockwave transmission path. The waterbath had a window in the left side, and the temperature of the water was maintained at 37°C. The left shockwave applicator was coupled by means of ultrasound coupling gel to a nonattenuating elastic membrane sealing off the window. All pigs were placed in a prone/right-oblique position on a support system in the bath so that the gallbladder was in focus.

Pressure measurements were obtained using a broadband piezoelectric pressure probe (Imotec, Würselen, Germany) based on polyvinylidene fluoride (PVDF) with an outside diameter of 1.2 mm and a sensitive element 0.5 mm in diameter. Further details of the performance of this probe have been reported previously.[4,8] The probe

was mounted on a rigid sound that could be moved in a very precise way in all directions by a steering mechanism. Pressure waveforms were displayed as output voltage waveforms on a digital oscilloscope with a frequency range of 0-100 MHz (Gould 4072; Gould, Hainault, England) and plotted as single-shot recordings. Absolute positive and negative pressures were calculated from measurements of the corresponding positive and negative voltages as recorded on the oscilloscope, using a calibration factor for the probe of 0.204 MPa/mV. Measurements were performed at varying generator voltages with the pressure probe always placed in a plane parallel to the major axis of the shockwave transmission path. Before and after animal measurements, focal pressures were measured in water (37°C).

To assess the spatial pressure distribution in the acoustic field, measurements were carried out on two axes through the focus: the Z axis, defined as the major longitudinal axis, resembling the shockwave transmission path (axial direction), and the X axis (lateral direction), perpendicular to the Z axis in the focal plane (Fig. 1). At each position on the Z axis, pressures were also measured at distances of 5 and 10 mm, respectively, from the Z axis parallel to the X axis.

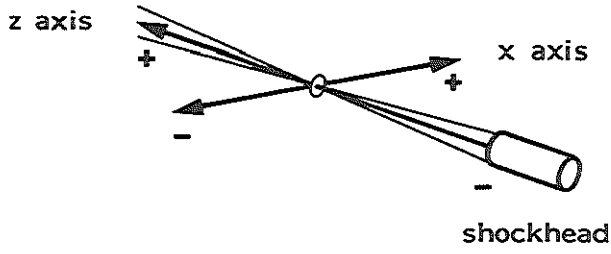

Figure 1. *Relation of X and Z axes to the focus and the position of the shockwave generator. The Z axis resembles the shockwave transmission path (axial direction). The X axis (lateral direction) is perpendicular to the Z axis in the focal plane.*

Along the Z axis measurements were performed only distal to the focus, starting with the pressure probe placed in a water-filled tube pressed against the skin at the shockwave exit site (Fig. 2). Then, a right-sided thoracotomy was performed, creating a square window of about 10 cm^2, for further measurements adjacent to the parietal

pleura at the base of the right lung. The distances between the focus and the skin and the focus and the parietal pleura were measured in all animals. To ensure immersion of the tip of the pressure probe, the thoracic cavity was partially filled with water. Thereafter, the diaphragm was opened and subsequent measurements were carried out by inserting the probe into the liver and recording pressures at 20 and 40 mm distal to the focus. Finally, focal pressures were measured inside the gallbladder by piercing the posterior wall of the gallbladder with the pressure probe. The attenuating effect of ribs was studied by turning the animals in such a way that the lower ribs became interposed between the shockwave applicator and focus, without interference of lung tissue with the shockwave path as was checked by fluoroscopy. All the pigs were killed immediately after the experiment.

Energies generated in the focal area *in vitro* were calculated previously from pressure waveforms by measuring the wave pressure as a function of time at N different radii from the Z axis.[4] The total energy per pulse (E) was calculated according to the equation:

$$E=\frac{1}{\rho.c}\sum_{n=1}^{N}\left[\int_{0}^{\infty}p^2(r_n,t)dt\right].A_n,$$

where ρ=density of the medium (water, kg/m^3), c=speed of sound in water (m/sec), p=pressure (Pa), r=radius (mm), t=time (seconds), and $A_n=(r^2_{n+1} - r^2_n)\pi$=area (mm^2). Under the assumption that the focal dimensions and the pulse width *in vitro* and *in vivo*, respectively, are nearly identical, this equation may also be used for calculation of energies *in vivo*. Since $E \sim p^2$, we deduced *in vivo* energies from *in vitro* values using a multiplication factor:

$$(f) = \left(\frac{\text{focal } p^+ \textit{ in vivo}}{\text{focal } p^+ \textit{ in vitro}}\right)^2 .$$

The study protocol was approved by the Committee on Animal Research of the Erasmus University Rotterdam.

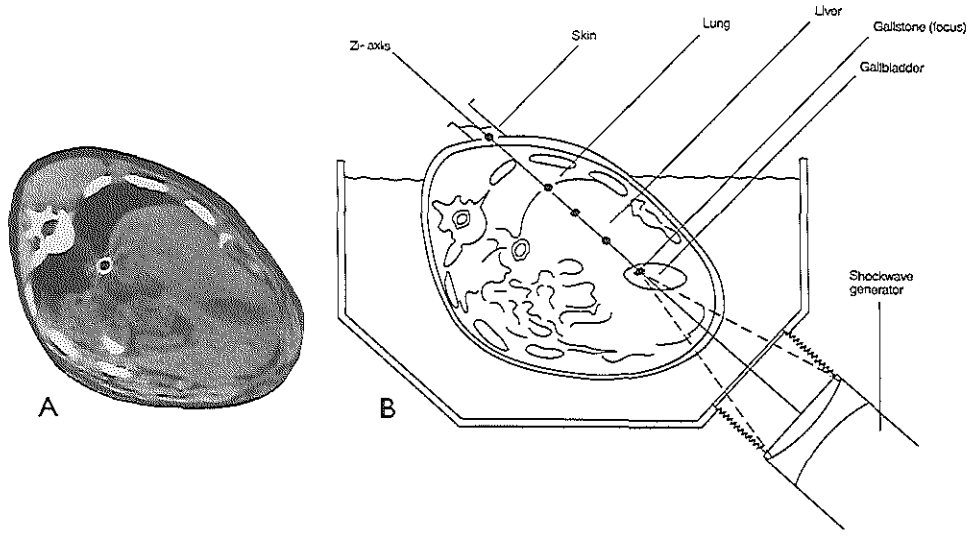

Figure 2. *Cross-sectional computerized tomography (CT) scan of a pig as positioned during pressure measurements (A) and schematic representation of the experimental set-up (B). For pressure measurements at the indicated positions along the shockwave transmission path (Z axis), the pigs were partially immmersed in a waterbath.*

Results

Waveforms

A shockwave pressure waveform, displayed as a voltage waveform on the oscilloscope, is characterized by peak-positive and peak-negative amplitudes (v^+ and v^-, respectively), pulse rise time (from 10%-90% of v^+) and pulse width (at 50% of v^+). The shape of the waveforms depends on their position in the acoustic field and on the generator voltage setting.

At 19 kV (maximum), focal waveforms obtained in the gallbladder of pigs, with and without stones, as well as focal waveforms in water have a similar shape and differ only with respect to v^+. Interposition of the lower ribs between focus and shockwave

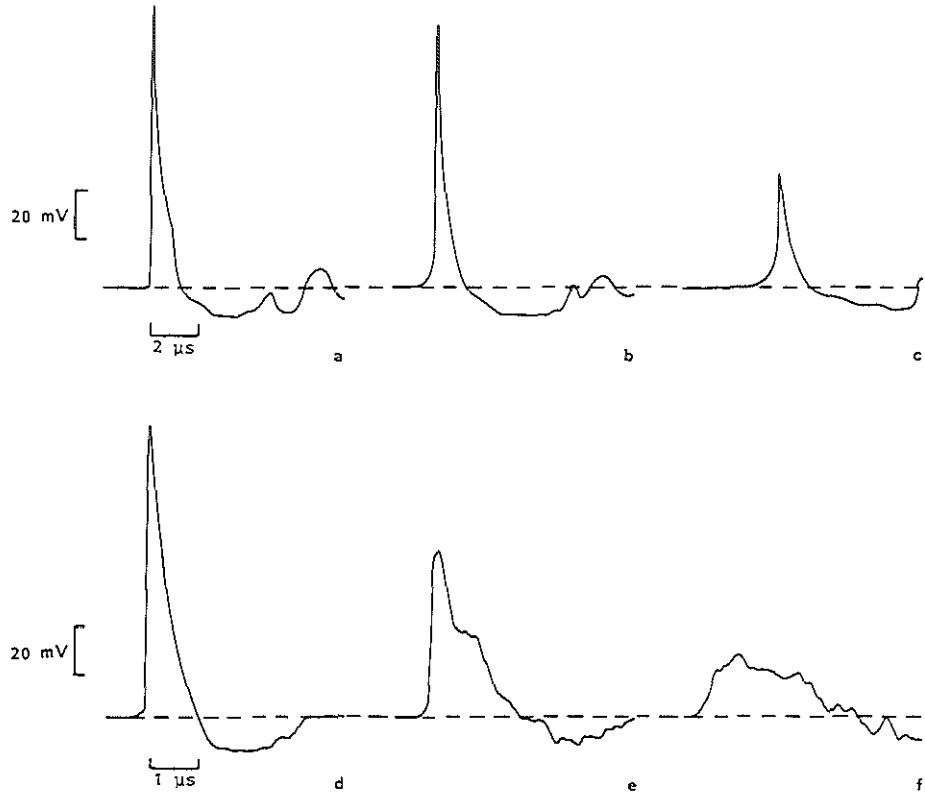

Figure 3. *Voltage waveforms at 19 kV for different acoustic field positions of the Lithostar in pigs without stones (a-c) and pigs with stones (d-f). The effect of moving outside the focus on the Z axis is represented in a-c; the corresponding effect on the X axis is illustrated in d-f.*
a. x = 0 mm, z = 0 mm (focal point inside gallbladder, with interposition of ribs).
b. x = 0 mm, z = 40 mm (liver).
c. x = 0 mm, z = 70 mm (parietal pleura).
d. x = 0 mm, z = 0 mm (focal point inside gallbladder, without interposition of ribs).
e. x = 5 mm, z = 0 mm.
f. x = 10 mm, z = 0 mm.

applicator did not result in altered waveforms (Fig. 3*a* and *d*). The focal waveforms have a steep front caused by the very short increase time. V^+ falls to 0 in about 1 μs and is followed by v^- during approximately 2.5 μs. (Fig. 3*a* and *d*). A relatively slow initial rise of v^+ occurs at positions outside the focus on either the Z or X axis.

Furthermore, with increasing distance from the focus v^+ decreases, which is equivalent to a decrease of pressure, and waveforms exhibit a larger pulse width (Fig. 3*b,c,e*, and *f*).

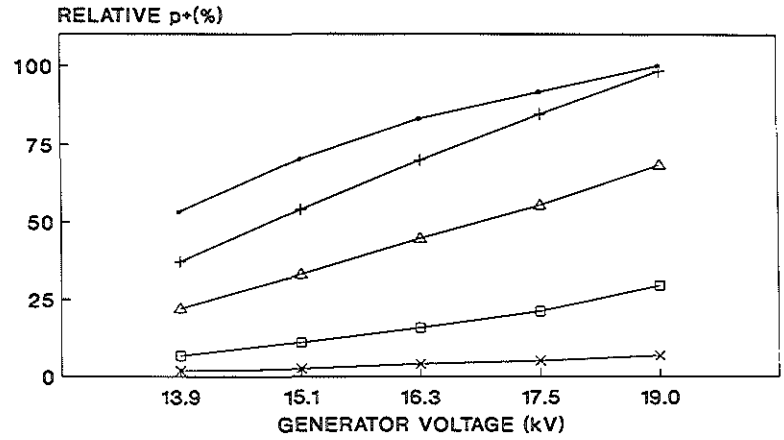

Figure 4. *Relative mean peak-positive pressures of the Lithostar at different generator voltages in pigs without stones. Values are normalized to maximum focal value at 19 kV.*
▩ *gallbladder (focus);* + *liver (z=20 mm);* △ *liver (z=40 mm);*
□ *parietal pleura (z=73 mm, on average);* × *skin (z=105 mm, on average).*

Pressures

The mean shot-to-shot variation of focal peak-positive and peak-negative pressures (p^+ and p^-) was assessed by calculating the coefficients of variation (cv) from consecutive measurements in the gallbladder of single pigs. At 19 kV, this variation was 2% and 5% for p^+ and p^-, respectively, irrespective of interposition of those lower ribs forming part of the abdominal wall.

For pigs without stones, Figure 4 illustrates the mean values of p^+ for different generator voltages. All values were normalized to maximum focal p^+ (gallbladder) at 19 kV. Increasing the generator voltage from 13.9 kV to 19 kV doubled focal p^+. The corresponding increase of focal p^- was only slight with a maximum of 3.3 MPa at 19 kV. Because even smaller values of p^- occurred outside the focus (Table 1), values of p^- have been omitted in Figures 4-7. In pigs with stones, a similar dependency of p^+ and p^- of generator voltage was found.

The mean focal pressures at 19 kV in water were 28.6 ± 1.3 MPa for p^+ and 3.1 ± 0.4 MPa (mean ± SD) for p^-. These were calculated by averaging the means of 10

consecutive measurements performed before and after animal measurements. Mean values of p^+ and p^- at different positions on the Z axis *in vivo* are given in Table 1. Focal pressures were not significantly different in pigs with and without stones; neither were they significantly affected by interposition of the lower ribs between focus and shockwave applicator. In all pigs with stones, a marked decrease of p^+ and p^- was found just distal to a stone positioned at the focus.

Table 1. *Peak-positive and peak-negative pressures in vivo at 19 kV.*

	Peak-positive Pressures (MPa)		Peak-negative Pressures (MPa)	
	Stone Interposition		Stone Interposition	
Position on Z axis	-	+	-	+
Gallbladder (z = 0 mm)	24.1 ± 3.3	25.3 ± 3.9	3.3 ± 0.2	3.4 ± 0.5
Gallbladder (z = 0 mm), with rib interposition	26.2 ± 1.3	23.1 ± 4.6	3.2 ± 0.3	3.3 ± 0.6
Liver (z = 20 mm)	23.7 ± 2.9	8.7 ± 2.0[a]	3.1 ± 0.4	1.6 ± 0.2[a]
Liver (z = 40 mm)	16.5 ± 5.6	11.1 ± 4.0	2.6 ± 0.2	2.5 ± 0.6
Parietal pleura (z = 70 ± 14 mm)[d]	7.1 ± 2.2[b]	5.2 ± 2.0[c]	2.1 ± 0.1[b]	1.9 ± 0.5[c]
Skin (z = 100 - 110 mm)	1.7 ± 0.9[e]		0.7 ± 0.2[e]	

NOTE. Unless stated otherwise, values represent the mean ± SD of averaged (six consecutive measurements) pressures in five pigs.
[a] n=3; [b] z=73 ± 19 mm (mean ± SD); [c] z=68 ± 5 mm (mean ± SD); [d] mean ± SD; [e] n=2.

The distance between focus and parietal pleura was 70 ± 14 mm and between focus and skin 119 ± 13 mm (mean ± SD). Pressures at the exit site from the skin were in general too low to be recorded. In only two of the stone-free pigs, with focus-to-skin distances of 100 and 110 mm, respectively, could exit pressures be measured. In all other pigs, except one with a stone, the focus-to-skin distance was greater than 120 mm.

Figure 5 illustrates three-dimensional plots of the distribution of p^+ on X axis (lateral direction) and Z axis (axial direction). Values on the Z axis correspond to positions behind the focus. The negative and positive values on the X axis correspond to positions on either side of the focus in the focal plane. The focus, characterized by

maximum pressure, is located at the intersection of both axes. Figure 5*A* represents the pressure distribution in water previously assessed *in vitro*.[4] To enable comparison with the pressure distributions *in vivo* (Fig. 5*B* and *C*), the *in vitro* measurements were corrected to 92% of their actual values (correction for different focal pressures and kV setting). Figures 5*C* and *B*, showing the pressure distributions in pigs with and without gallstones, respectively, were constructed by averaging, for each group, the means of six consecutive measurements taken from each point. Pressures were recorded on only one side of the Z axis, symmetry being justifiably presumed because of previous findings (Fig. 5*A*).[4]

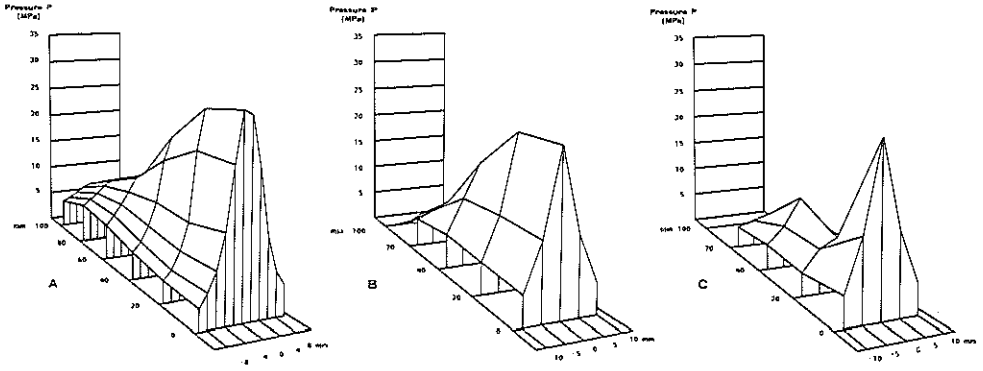

Figure 5. *Positive pressure distribution of the Lithostar on X and Z axes at 19 kV. The X axis (lateral direction) is perpendicular to the Z axis (axial direction). In the focal point, at the intersection of the axes, pressure is maximum.*
A. Pressure profile in water, based on in vitro data[4] (corrected for different focal pressures and kV setting).
B. Pressure profile in pigs without gallstones.
C. Pressure profile in pigs with gallstones.

In Figure 6 the distribution of p^+ on the Z axis *in vitro* as well as *in vivo* are combined and depicted as longitudinal sections of the three-dimensional plots of Figure 5. Pressures *in vivo* (without stones) were 15%-25% lower than in water, but a strong linear correlation ($r = 0.88$; $p \leq 0.01$) between the two was maintained (Fig. 7). However, when a stone was correctly focused, considerably lower pressures were found

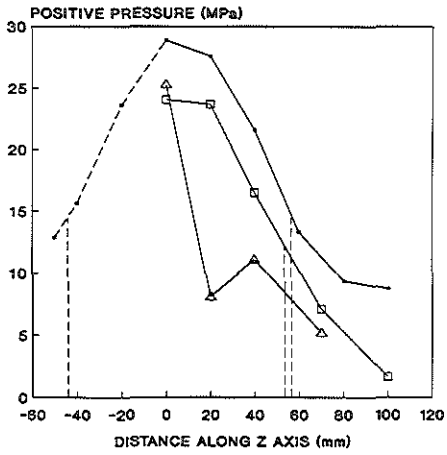

Figure 6. *Positive pressure distribution on Z axis of the Lithostar (19 kV) with indication of -6 dB zone (i.e., the zone in which p^+ is more than half of that of the focus) by vertical dotted lines. The direction of propagation of the shockwaves is from left to right.* ▪ *in water;* □ *in pigs without stones;* △ *in pigs with stones.*

distal to the stone. The -6 dB zones (the area in which p^+ is 50% or more of the maximal focal value) proved to be almost identical when *in vitro* and stone-free *in vivo* measurements were compared.

The distributions of p^+ on the X axis in the *in vitro* study and in pigs without stones are illustrated in Figure 8 as transverse sections of Figures 5*A* and *B*, respectively. The pressure distributions and the dimensions of the resulting -6 dB zones, along the X axis, were almost identical when *in vivo* and *in vitro* measurements were compared.

Table 2 gives the energy values in the focal plane as well as in a parallel plane through the liver, 20 mm distal to the focal point on the shockwave transmission path (Z axis). Calculation of the energies for more distal positions on the Z axis is not permitted because significant changes in waveforms invalidate previous assumptions and derived formulas. Energy disturbance behind a focused stone is so great that meaningful calculations of energy fields cannot be made. Therefore, *in vivo* energy calculations are limited to stone-free pigs.

Discussion

Although negative pressures certainly play a role in the mechanism of ESWL-induced tissue trauma,[5] their absolute values do not vary significantly with acoustic field position and generator voltage setting. Neither is there an appreciable variation in peak-negative pressures of different lithotriptors.[9] The most important parameters

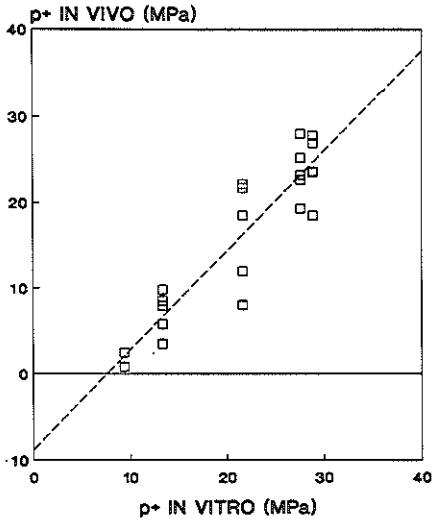

Figure 7. *Correlation between positive pressures in vitro and in vivo (r = 0.88, $p \leq 0.01$, y = 1.12x - 7.78). Each square represents the mean of six consecutive measurements, at one point, in individual stone-free pigs. Pressures in vivo are 15%-25% lower than in water.*

determining the biological effects of ESWL are the peak-positive pressure and the focal pressure distribution of the lithotriptor.[10-14] Characterization of the acoustic field of a lithotriptor is essential for understanding the associated potential hazards of clinical application.

Acoustic fields of several types of lithotriptors have been characterized *in vitro* only.[4,9,15] However, until now it was not known whether *in vitro* pressure profiles could be extrapolated to the *in vivo* situation. This study presents data on shockwave pressures generated during ESWL of gallstones in pigs. The spatial distribution of p^+ *in vivo* was compared with that *in vitro*, which is justified because the same lithotriptor and identical pressure probes have been used.[4,14]

Presently, pressures were measured at a generator voltage of 19 kV. The absolute values of p^+ in the *in vitro* study were obtained at 18.1 kV, resulting in only 1% lower values compared with 19 kV.[4] Furthermore, the mean

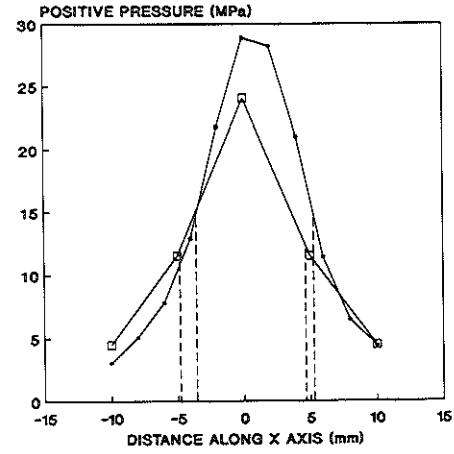

Figure 8. *Positive pressure distribution on X axis of the Lithostar (19 kV) with indication of -6 dB zone by vertical dotted lines. The X axis is perpendicular to the Z axis in the focal plane.*
■ *in water;* □ *in pigs without stones.*

focal pressures in water found in this study were slightly lower than those measured *in vitro* before, which may be caused by variation in calibration and temperature-dependent sensitivity of the pressure probes.[9] To validate the comparison of *in vitro* and *in vivo* data, the former *in vitro* values were therefore normalized to the mean focal pressures in water found in the present study, at 19 kV.

The shape of focal waveforms *in vitro* and *in vivo* were similar. As evidenced by the low shot-to-shot variation, the Lithostar generates shockwaves that are just as reproducible *in vivo* as *in vitro*. The result is a very stable focus. This is an advantage of the electromagnetic shockwave source over spark-gap systems, in which p^+ fluctuates by 25%-45% because of the inherent variability of the electrical discharge.[9,15,16] In pigs, p^+ was found to be dependent on generator voltage just as in water.[15]

Theoretically, interposition of bony structures between focus and shockwave applicator impedes transmission of shockwaves; if this were the case, ESWL of gallstones was considered to be impossible.[1] However, we did not find a significant reduction of focal pressures by interposition of ribs. This observation is clinically important because it justifies coupling of the shockwave applicator onto the lower ribs if the routine ventral approach to ESWL of gallstones cannot be used.

In tissues, p^+ was 15%-25% lower than in water as noted previously.[4,12,17] Apparently, the attenuation of shockwaves is less dependent on the thickness of tissue layers than assumed.[15] This may be explained by the absence of important acoustic interfaces between the various types of tissues.[4]

Focal pressures in the gallbladder of pigs with and without gallstones were not significantly different. This was caused by the difficulty to obtain a stable position of the stone on the shockwave transmission path in front of the focused pressure probe. Significantly lower pressures were measured behind focused stones indicating that most of the shockwave energy is absorbed by the stone. This observation underlines the necessity of accurate focusing to avoid needless exposure of surrounding tissues to shockwave energy.

Using a Dornier lithotriptor (Dornier Medizintechnik GmbH, Germering, Germany), Delius et al. observed lung bleeding as the most serious side effect during the destruction of gallstones in dogs.[12] Even at a distance from the focus of 150 mm on the shockwave transmission path (Z axis), they found gross lung hemorrhages associated with a mean positive pressure of 10.4 MPa. On the X axis, a minimal distance of 40 mm

Table 2. *Energy values.*

Position on Z axis	Energy (mJ)	
	In Vitro	In Vivo
Focal plane (z = 0 mm), (total energy)	76	52
Focal plane (z = 0 mm), diameter 15 mm	18(24)	12(23)
Focal plane (z = 0 mm), diameter 30 mm	37(49)	25(48)
Liver (z = 20 mm), diameter 15 mm	-	11(21)
Liver (z = 20 mm), diameter 30 mm	-	23(44)

NOTE. *In vitro* and *in vivo* energies delivered by a single shockwave front at 19 kV into the focal plane as well as into a parallel plane perpendicular to the shockwave transmission path (Z axis), 20 mm distal to the focal point. Data is expressed as absolute values and as percentages (in parentheses) of the total energy in the focal plane. The energy percentages give a clear guide to the focusing properties of the machine. *In vitro* energies calculated earlier[4] have been corrected because values of p^+ found in this study differed by 8% from those measured previously. *In vivo* values (pigs without stones) are deduced from corresponding *in vitro* values by using a correction factor (f) = $(24/29)^2$ = 0.69 (mean focal p^+ in pigs/mean focal p^+ in water).

from the focus to the lungs was needed to prevent hemorrhage. Mean pressures below 2.5 MPa did not result in lung injury. In contrast to dogs, biliary lithotripsy in humans with spark-gap ESWL systems does not lead to lung hemorrhages.[1,2] In the Lithostar, the pressure distribution on the shockwave transmission path (Z axis) is less wide as in the Dornier because already at a distance of 110 mm from the focus, mean pressures were below 2.5 MPa. Consequently, the probability of tissue damage with the Lithostar should be comparatively lower. Histopathologic data with regard to tissue damage will be published separately.

Not all data from pigs should be extrapolated to humans, because the direction of the shockwave transmission path will be different because of differences in anatomy. Notwithstanding this limitation, the present study improves the understanding of the actual pressure distribution around the gallbladder in ESWL of gallstones.

We consider calculation of the energy within predescribed areas around the focal point, instead of assessing -6 dB or isobar zones, as a more sophisticated method for comparing different lithotriptors.[4] Estimation of energies *in vivo* is important not only for assessment of efficacy but also for safety.

Because the spatial pressure distribution of shockwaves *in vivo* strongly

resembles that found *in vitro*, comparison of different types of lithotriptors can be made by comparing the *in vitro* pressure profiles.

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CHAPTER 5

Biliary Extracorporeal Shockwave Lithotripsy: Short-term and Long-term Observations in an Animal Model

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Abstract

The short- and long-term effects of biliary extracorporeal shockwave lithotripsy (ESWL) using an electromagnetic lithotriptor were investigated in 26 pigs. After implantation of single human gallstones into their gallbladders, all but 4 control pigs were subjected to 4000 or 8000 shockwaves and killed one day (n=9), one week (n=7), or one year (n=6) thereafter. Post-ESWL, no abnormalities of chest radiographs or laboratory tests were detected. Apart from focal injury of the gallbladder and liver, in 4 of 9 pigs subpleural pulmonary hemorrhages were found one day post-ESWL. However, tissue damage was largely reversed within one week and after one year only small hepatic scars came about as permanent damage. Stone fragmentation occurred in 19 (86%) of 22 pigs, and was adequate (fragments $\leq$5 mm) in 9 (41%) pigs. Tissue damage and stone fragmentation after 4000 *versus* 8000 shockwaves were not significantly different. These data warrant further evaluation of this lithotriptor in human studies.

Introduction

Introduced clinically in 1980, extracorporeal shockwave lithotripsy (ESWL) dramatically changed the management of upper urinary stones.[1] The ready acceptance of this new medical technology was facilitated by the low rate of side effects reported in early publications.[2-4] However, there is now a growing awareness that ESWL can induce acute and chronic significant adverse effects.[5-8] Potential long-term damage such as permanently decreased renal blood flow and hypertension reinforce the necessity to define the risks of ESWL.[9]

Since 1986, ESWL has also been used for the treatment of gallstones in selected patients.[10-13] Like the development of ESWL in urology, the quick adoption of ESWL for treating gallstones is based on short-term results. Long-term evidence of efficacy and safety is still lacking. As a result of associated renal damage, the long-term sequelae of biliary lithotripsy may even be similar to those of ESWL of kidney stones.[14]

The acoustic energy output of different types of lithotriptors can vary considerably.[15] Therefore, the effectiveness and potential pathologic effects of shockwaves of each lithotripsy device should be addressed to in animals before evaluation in human studies is justified. In the present study, we investigated the short- and long-term effects of biliary ESWL in a pig model, using an electromagnetic lithotriptor (Lithostar; Siemens AG, Erlangen, Germany). The energy output of this lithotriptor has been assessed *in vitro* as well as *in vivo* previously.[16-17]

Materials and Methods

Twenty-six Yorkshire pigs were used. Matched pairs of human gallstones were collected during cholecystectomies. One stone was used for analysis of cholesterol and calcium content as described elsewhere.[18] The other one was implanted into the gallbladder of the pig. Fourteen days after surgery the pigs underwent lithotripsy under general anesthesia. Interference of lung tissue with the shockwave path was avoided as much as possible. To allow fluoroscopic targeting of the (radiolucent) stones, the gallbladder was opacified by ultrasound-guided percutaneous transhepatic

instillation of contrast (Conray; Byk Nederland BV, Zwanenburg, The Netherlands) using a 18-gauge needle. In five sessions intravenous cholangiography (Biliscopin; Schering Nederland BV, Weesp, The Netherlands) was employed. Shockwaves were discharged at the maximum generator power setting (19 kV) with a frequency of 90-120 shockwaves per minute.

Short-term Study

Twenty pigs (body weight: 19-37 kg) were divided into 3 groups: 8 pigs received 4000 shockwaves, 8 pigs received 8000 shockwaves (administered in 2 doses of 4000 shockwaves on 2 successive days), and 4 pigs underwent the complete regimen including gallbladder opacification except exposure to shockwaves (control group). Nine pigs (5 of the 4000-group; 4 of the 8000-group) were killed one day, and 7 pigs (3 of the 4000-group; 4 of the 8000-group) one week after ESWL. Similarly, pigs of the control group were killed one day or one week after the sham procedure.

To elucidate the relationship between potential tissue injuries and shockwave pressures, ESWL was performed in a similar way as during *in vivo* shockwave pressure measurements whereof we reported elsewhere.[17] The pigs were consistently placed in a prone/oblique position on a support system in a waterbath, such that after focusing the lower ribs were not interposed between shockwave applicator and target. Postero-anterior and lateral chest radiographs, ultrasound examinations of the gallbladder and liver, and blood and urine samples were obtained before, immediately after, and on days 1 and 7 after shockwave application. Laboratory parameters included hemoglobin, free plasma hemoglobin, white blood cell count (WBC), aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), alkaline phosphatase, lipase, amylase, total bilirubin, and creatinine. Post-ESWL results were compared to pre-ESWL baseline values, each animal serving as its own control. Urine for analysis of (microscopic) hematuria was collected by ultrasound-guided percutaneous aspiration of the bladder.

Long-term Study

Six pigs (body weight: 39-42 kg) were divided into 2 groups and treated with 4000 and 8000 shockwaves (administered in 2 doses of 4000 shockwaves on 2 successive days), respectively. The pre- and post-ESWL work-up, and the lithotripsy procedure were

just like that of the short-term study except that no waterbath was used. All animals were killed 1 year post-ESWL.

Assessment of Tissue Effects and Efficacy

At autopsy, the organs of the chest and abdomen were inspected for macroscopic lesions. Both lungs were inflated with air (to differentiate superficial hemorrhages from postmortem blood stasis) before resection, thereafter with 10% buffered formalin. The liver, gallbladder, common bile duct, duodenum, and pancreas were resected en bloc. The efficacy of ESWL was assessed by measuring the total weight and maximum diameters of the recovered fragments. Fragmentation was considered to be adequate when all remaining fragments measured ≤ 5 mm in their largest diameter, and considered unsatisfactory if no fragmentation occurred or if at least one particle was larger than 5 mm. Tissue specimens were taken for microscopy from designated areas of the aforementioned organs and also of the stomach and upper pole of the right kidney. Light microscopy examination was performed by a pathologist, who was unaware of the assigned experimental conditions.

To achieve a qualitative analysis of local tissue injury, the specimens of the gallbladder, liver, extrahepatic bile ducts, pancreatic lymphnodes, and duodenum were scored as discrete variables (absent/present) for various microscopic tissue damage parameters. For these individual organs, the positive scores (presence of tissue change) were summed and divided by the total number of possible scores to calculate cumulative tissue damage indices. Similarly, an overall cumulative tissue damage index was calculated for each treatment regimen separately. To compare the ESWL regimens with the sham procedure, ratios of the cumulative tissue damage indices were calculated. A ratio of 1.0 stands for equal damage, a value >1.0 indicates a proportional increase, a value <1.0 denotes a proportional decrease of damage.

Local tissue damage caused by ESWL was also evaluated semi-quantitatively by grading the microscopic tissue damage parameters on a scale of 0 - 3 (absent, minimal, moderate, or pronounced changes).

The study protocol was approved by the Committee on Animal Research of the Erasmus University Rotterdam.

Data Analysis

Statistical evaluation of the laboratory data and stone characteristics was performed by the Mann-Whitney U-test. Histologic data were compared with the Chi-square or Yates-Cochran tests. Statistical significance was considered at a p value of less than 0.05.

Results

Stone Characteristics

The stones (n=22) implanted into the pigs exposed to shockwaves had a median (range) diameter, weight, and cholesterol content of 13 mm (8-19), 530 mg (180-1300), and 96% (61-98), respectively. The calcium content ranged from 0% to 13% (median: 0.2). The diameters, weights, and cholesterol contents of stones in pigs subjected to 4000 *versus* 8000 shockwaves or in the short-term *versus* the long-term study were not statistically significantly different.

Lithotripsy

Thirty-three ESWL treatments (11 secondary sessions) were performed in 22 pigs. During the 9 treatments of the long-term series, the lungs could apparently be avoided in all cases. Due to the size of the waterbath, however, pigs of the short-term series could not always be positioned in such a way that the long axis of the shockwave field was angled completely away from the lung bases. Accordingly, possible interference of lung tissue with the shockwave transmission path was considered to be present in 13, while this was doubtful in a further 3 of 24 short-term sessions. Nevertheless, post-ESWL chest radiographs did not reveal ESWL-induced abnormalities in any of the 22 pigs. Following ESWL, ultrasonography neither showed pathologic changes, except for thickening of the gallbladder wall noted in one pig.

Laboratory Parameters

In control animals, laboratory tests values did not change throughout the sham procedure. In the animals that underwent ESWL, WBC decreased with 13% ($p<0.05$). Hemolysis did not occur because values of free plasma hemoglobin were

always <0.5 mg/ml. Serum lipase levels remained below the detection limit, and serum amylase did not change after ESWL. AST levels rose two- to three-fold ($p < 0.02$) immediately post-ESWL, but were restored 1 week thereafter. Values in pigs treated with 4000 *versus* 8000 shockwaves were comparable. Results of samples taken one year post-ESWL could not be related to baseline values due to weight gain of the animals. Nevertheless, there was no indication of chronic deterioration. Microscopic hematuria was never detected in post-ESWL bladder aspirates.

Table 1. *Gross findings at autopsy at different times post-ESWL in 16 pigs subjected to biliary lithotripsy with 4000 (n=8) or 8000 (n=8) shockwaves.*

	Time Post-ESWL	
Autopsy Findings	1 Day (n=9)	1 Week (n=7)
petechiae at shockwave entry site	5	-
intraperitoneal bile leakage	1	-
intra-abdominal adhesions	9	7
hemorrhage of gallbladder wall	9	3
subcapsular hepatic hemorrhage	9	3
local erosion of gallbladder epithelium	2	2
hemorrhagic pancreatic lymphnodes	6	-
hematoma in omentum	1	-
stone fragment in cystic duct	-	1
pulmonary hemorrhage	4	2
pulmonary abscesses	2	-

NOTE. Data are given as number of animals.
Tissue damage was not noticeably different for pigs exposed to 4000 vs 8000 shockwaves.

Short-term Study - Autopsy

Table 1 shows the autopsy findings of the short-term study. The nature and extent of gross tissue damage was not noticeably different for pigs of the 4000-group *versus* the 8000-group. The hemorrhages of the gallbladder and the hepatic parenchyma

(adjacent to the gallbladder) measured 2-30 mm and less than 10 mm in diameter, respectively. Of interest is the finding that in two animals a 2-3 cm broad track of petechial bleedings from the ventral to the dorsal part of the liver could be seen, corresponding to the shockwave transmission path. One week post-ESWL, minimal remnants of the acute lesions were found. Gross pulmonary damage manifested in 4 and 2 of the pigs killed one day and one week after ESWL, respectively. These apparent ESWL-related lesions, localized in the lower lobes of both lungs, ranged from <5 mm up to 6x3 cm and appeared to extend into the parenchyma for only 2 to 5 mm.

In the four control pigs, abdominal adhesions due to the stone implantation surgery were the only gross abnormality noted.

Short-term Study - Microscopy

Table 2 gives the absolute numbers of positive scores of microscopic tissue damage parameters. Microscopy specimens are shown in Figures 1 to 6. One day after ESWL, focal hemorrhagic necrosis of the hepatic parenchyma, restricted to a zone adjacent to the gallbladder was found. One week thereafter, this necrosis was completely organized. Endovasculitis and thrombosis were detected in portal blood vessels. Gallbladder damage was confined to mural hemorrhages, slight mucosal inflammation, and mucosal denudation, but epithelial cells in the crypts remained intact. While the acute hemorrhages largely resolved within one week, the epithelial changes persisted.

A qualitative analysis of local tissue injury is shown in Table 3. This table gives the ratios of the cumulative tissue damage indices, compared to the control group. Local tissue damage was mainly restricted to the liver and gallbladder. Furthermore, tissue changes after 4000 or 8000 shockwaves were reversing within one week, regardless of the number of shockwaves.

Figure 7 shows the relative distribution of semi-quantitative tissue damage scores. ESWL-induced damage was slight to moderate, and transient. Statistical evaluation of this semi-quantitative analysis parallelled that of the qualitative analysis (Table 3). Particularly, the extent and severity of tissue alterations were not different for 4000 *versus* 8000 shockwaves.

In all pigs including control animals varying degrees of proliferative pulmonary inflammation were found. These findings were usually restricted to the basal parts of

Table 2. *Microscopic tissue changes found at different times post-ESWL in 16 pigs subjected to biliary lithotripsy with 4000 (n=8) or 8000 (n=8) shockwaves, compared with findings in 4 control animals.*

	Control	4000/8000 sw	
		Time Post-ESWL	
Local Microscopy Findings	(n=4)	1 Day (n=9)	1 Week (n=7)
Gallbladder			
hemorrhage of gallbladder wall	0	8	4
epithelial degeneration / desquamation	2	8	6
cholecystitis	4	9	7
Liver			
hemorrhagic necrosis	0	9	0
scarring	0	0	7
hydropic hepatocytic degeneration	3	8	1
inflammation	1	5	2
vasculitis	0	2	0
thrombosis	0	6	1
degeneration / desquamation of epithelium of minor biliary ducts	1	3	1
cholangitis of minor biliary ducts	1	6	1
hemorrhage of the hepatic capsule	0	7	2
thickening of the hepatic capsule	3	8	4
Extrahepatic bile ducts			
epithelial degeneration / desquamation	4	8	7
cholangitis	1	4	1
Pancreatic lymphnodes			
hemorrhage	0	9	2
ferrous deposition	1	6	4
sinus histiocytosis	4	9	7
cellular degeneration	1	6	1
fibrosis	1	0	1
Duodenum[a]			
epithelial degeneration / desquamation	3	8	5
mucosal inflammation	0	5	1
inflammation of papilla of Vater	1	4	0

NOTE. Data are given as number of animals. Tissue damage was not noticeably different for pigs exposed to 4000 vs 8000 shockwaves.
sw: shockwaves.
[a] data of one control pig not available.

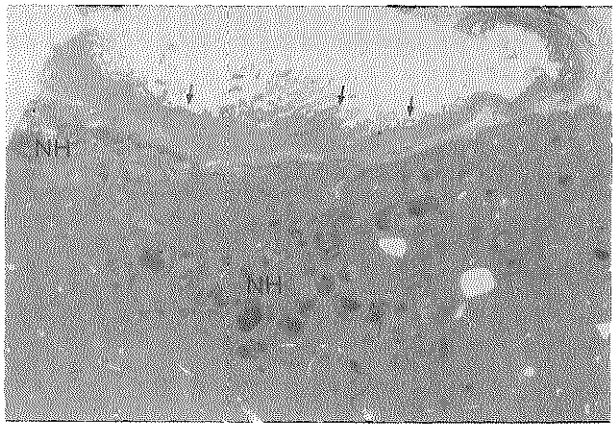


Figure 1. Microscopy specimen (at low power view) of gallbladder and liver parenchyma in a pig killed one day post-ESWL (HAS-staining).
Arrow: epithelial degeneration / desquamation; HN: hemorrhagic necrosis of liver parenchyma adjacent to the gallbladder.

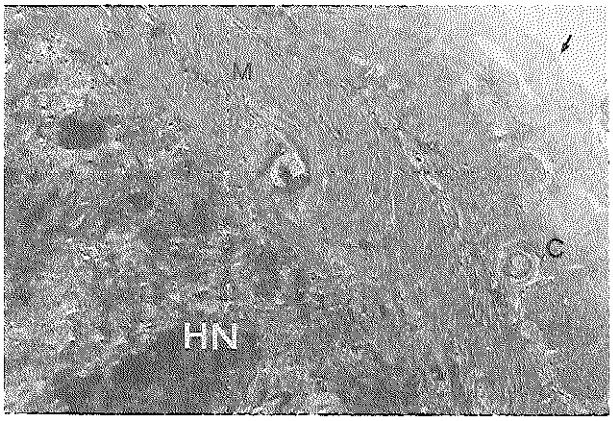


Figure 2. Microscopy specimen (50x) of gallbladder and gallbladder bed in a pig killed one day post-ESWL (HAS-staining).
Arrow: epithelial degeneration / desquamation; M: muscularis mucosae; C: crypt with intact epithelial cells; HN: hemorrhagic necrosis in tissue between gallbladder and liver (gallbladder bed).

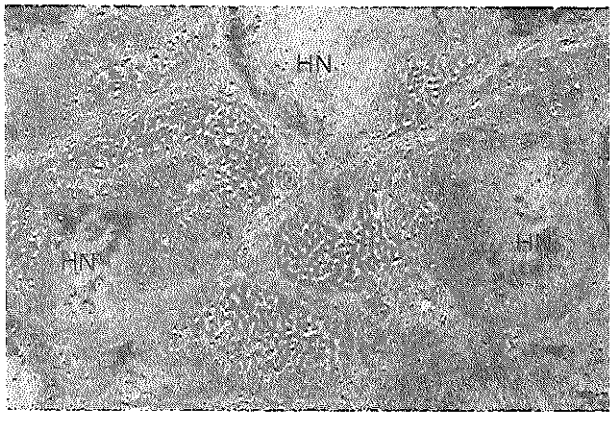


Figure 3. Microscopy specimen (50x) of liver parenchyma in a pig killed one day post-ESWL (HAS-staining).
HN: hemorrhagic necrosis in liver lobule.

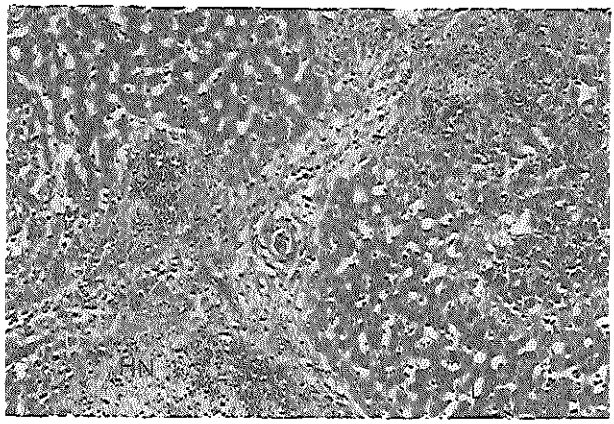


Figure 4. Microscopy specimen (125x) of liver parenchyma in a pig killed one day post-ESWL (HAS-staining).
HN: hemorrhagic necrosis in liver lobule; L: normal liver parenchyma.

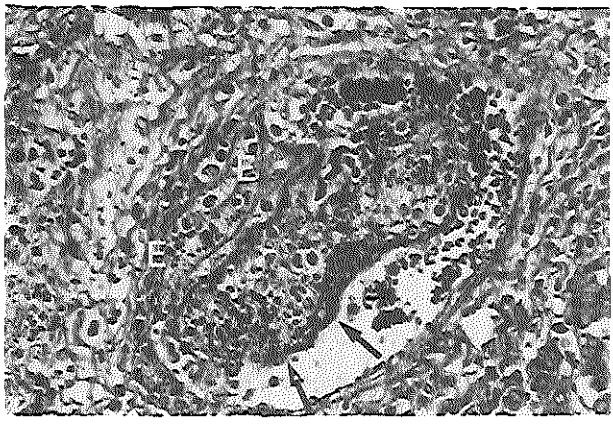


Figure 5. Microscopy specimen (250x) of liver parenchyma in a pig killed one day post-ESWL (HAS-staining), showing endovasculitis and thrombosis.
Arrow: thrombus; E: endovasculitis.

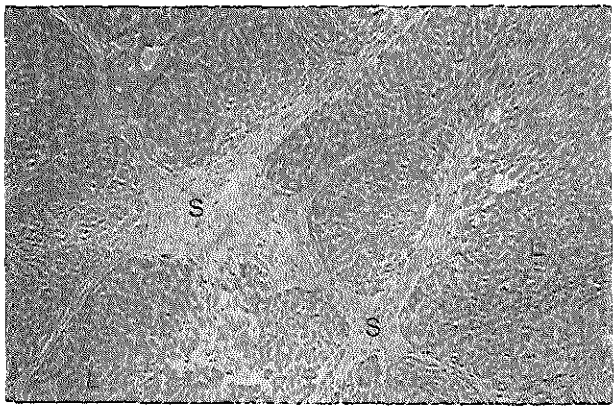


Figure 6. Microscopy specimen (50x) of liver parenchyma in a pig killed one year post-ESWL (HAS-staining).
S: scarring; L: normal liver parenchyma.

the lungs and considered to be unrelated to shockwave treatment. Apart from the gross hemorrhages, focal microscopic subpleural intra-alveolar bleedings were found in 5 pigs. In 3 of these cases this was associated with pleural fibrin exsudates, suggesting a traumatic origin. Retrospectively, in 7 out of 11 pigs with microscopic evidence of pulmonary hemorrhage, basal lung tissue was considered to interfere with the shockwave transmission path, whereas this was dubious in 2 of these 11 pigs. In pigs of the control group no pulmonary bleedings were detected.

Microscopy of the pancreas, stomach, and upper pole of the right kidney did not

Table 3. *Qualitative analysis of local microscopic tissue damage found at different times post-ESWL. Pigs exposed to 4000 and 8000 shockwaves, respectively, are compared to control animals.*

		Ratio of Cumulative Tissue Damage Indices	
		Time Post-ESWL	
Organ	Group	1 Day	1 Week
Gallbladder	4000 vs control	1.7[a]	1.1
	8000 vs control	2.0[b]	1.5
Liver	4000 vs control	2.6[c]	1.0
	8000 vs control	2.8[c]	1.3
Extrahepatic bile ducts	4000 vs control	1.1	0.8
	8000 vs control	1.0	1.0
Pancreatic lymphnode	4000 vs control	1.9[a]	1.1
	8000 vs control	1.9	1.3
Duodenum	4000 vs control	1.7	0.8
	8000 vs control	1.1	0.6
Overall	4000 vs control	1.9[c]	1.0
	8000 vs control	1.9[c]	1.2

NOTE. Values = 1.0 denote equal damage; values <1.0 and >1.0 indicate a proportional decrease respectively increase of damage.
4000 vs 8000 shockwaves at 1 day or 1 week post-ESWL: NS
[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.002$.

reveal traumatic lesions. Cutaneous changes consisted of subepidermal hemorrhagic necrosis extending into the subcutaneous fat with occasional involvement of superficial muscle layers. Both arterial and venous thrombosis and/or vasculitis were observed. The epidermis itself remained unaffected.

Table 4. *Efficacy of ESWL of single human gallstones implanted into the gallbladder of 22 pigs.*

	Overall	Short-term Study		Long-term Study	
Efficacy of Fragmentation	(n=22)	4000 sw (n=8)	8000 sw (n=8)	4000 sw (n=3)	8000 sw (n=3)
Fragmentation[a]	19(86%)	6(75%)	7(88%)	3(100%)	3(100%)
Adequate fragmentation[a] (particles ≤5 mm)	9(41%)	2(25%)	5(63%)	2(67%)	0(0%)
Unsatisfactory fragmentation[a] (particles >5 mm)	13(59%)	6(75%)	3(37%)	1(33%)	3(100%)
Stone clearance (%)[b]	82(17-100)	40(17-100)	92(33-100)	89(57-100)	81(30-89)

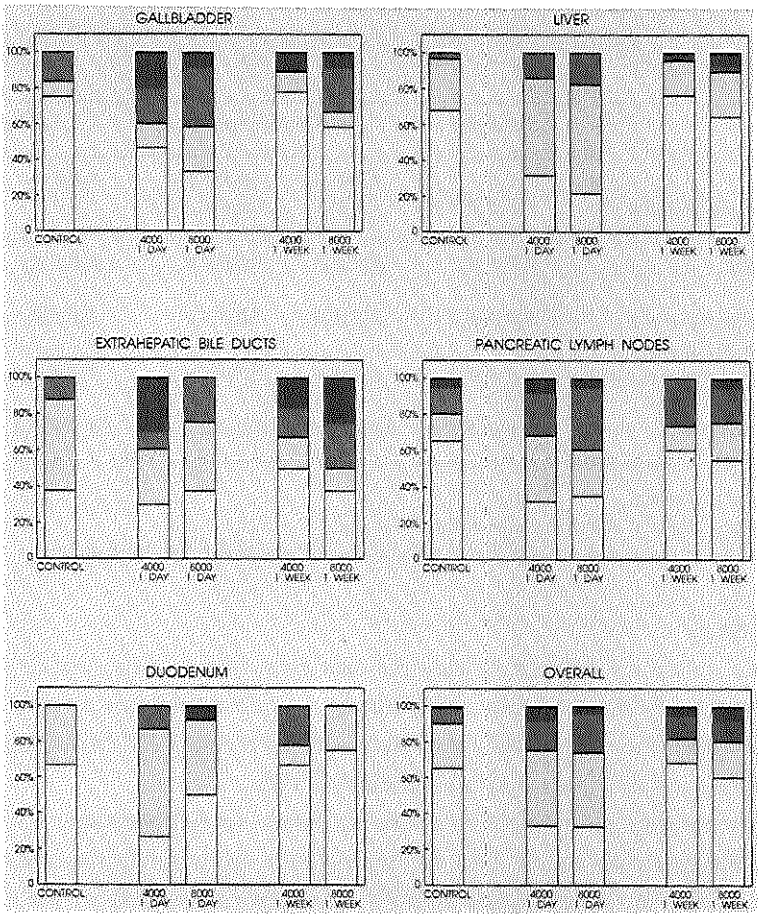
NOTE. sw: shockwaves.
[a] data expressed as numbers (percentage) of pigs.
[b] data expressed as median (range) of original stone weight that had been cleared.

Long-term Study

At one year, abdominal adhesions were the only gross abnormality, similar to those of animals of the short-term study. Particularly, no abnormalities of the liver and gallbladder were noted. Two pigs exhibited signs of recent local bronchopneumonia without indications of chronic lesions caused by ESWL.

Microscopically, pronounced interlobular fibrosis with disturbance of the normal hepatic architecture was found. This was restricted to the parenchyma adjacent to the gallbladder (Fig. 6). In one case, fibrosis clearly corresponded to the shockwave transmission path; in three other pigs, this scarring was associated with focal thickening and slight calcification of the hepatic capsule, an obliterated central vene, and with a partial occlusion of a small arterial branch, respectively. Due to insufficient fixation, histologic evaluation of the gallbladder and bile ducts was not possible. The pancreas, the pancreatic lymphnodes, the duodenum, and the lungs did not reveal ab-

Figure 7. *Relative distribution of semi-quantitative scores of tissue damage of various organs, induced by biliary lithotripsy in 16 pigs. Pigs exposed to 4000 shockwaves, killed one day/week post-ESWL (n=5/n=3), and pigs exposed to 8000 shockwaves, killed one day/week post-ESWL (n=4/n=4), are compared to control animals (n=4).*



NOTE. Data on duodenal damage of one of the control pigs was not available. Tissue damage was scored as: 0 = absent (white), 1 = minimal (light grey), 2 = moderate (dark grey), and 3 = pronounced (black). Statistical analysis: 4000 vs 8000 (irrespective of time post-ESWL): NS; 4000 or 8000, 1 day post-ESWL vs control: $p<0.001$ (overall; liver, 8000); $p<0.01$ (liver, 4000); $p<0.02$ (duodenum, 4000); $p<0.05$ (gallbladder, pancreatic lymphnodes); 4000 or 8000, 1 week post-ESWL vs control: NS.

normalities, except for bronchopneumonia found in two pigs.

Efficacy

Table 4 summarizes the results of fragmentation. Overall, in 19 (86%) of 22 pigs gallstones were fragmented. Adequate fragmentation ($\leq$5 mm) was achieved in 9 pigs (41%), five of which were completely free of stones at autopsy. One year after ESWL, only 1 of 6 pigs appeared to be stone-free, whereas the gallbladders of the remaining pigs harboured at least one fragment >5 mm in diameter in 4 cases.

Irrespective of the number of shockwaves administered, the overall median percentage (range) of initial stone weight that had been cleared was 82% (17-100). The differences between clearance percentages for the 4000-group and the 8000-group were not statistically significant.

Discussion

In the present study, microscopic analysis of tissue specimens revealed that repeated lithotripsy sessions as performed in half of the animals did not result in increased or prolonged tissue damage. This is in agreement with earlier observations of other study groups who were also unable to find a correlation between extent of tissue damage and the number of shockwaves applied.[19-22] Aware of its limitations, we consider our method for semi-quantitative analysis of tissue damage whereby microscopic lesions were subjectively classified into four different grades as justified, because even "pronounced" microscopic tissue damage reflected only minor functional and clinically not relevant adverse effects of biliary lithotripsy. This is corroborated by Deaconson et al., who found on serial section measurements that injury caused by ESWL involved an aggregate volume of less than 1% of the total liver parenchyma.[23]

In a previous study we have assessed the shockwave pressure distribution of the Lithostar *in vivo*.[17] Because of comparable experimental conditions, the histopathologic changes found in the short-term study can now be related to device-specific *in vivo* values of shockwave pressures. So can the present gallbladder lesions, for instance, be associated with a focal *in vivo* pressure of about 25 MPa, corresponding with an energy transmission of 50 mJ.[17] It has been pointed out before that the safety

and efficacy of a lithotriptor are determined by the acoustic energy output, which is proportional with the square pressure of the generated shockwaves.[16,17] Where different energy output settings are applied, it is difficult to assess the applicability of the present data in relation to other studies. The fact that we found more pronounced lesions than Becker et al., using the same lithotriptor, is therefore not explained by the somewhat lower numbers of shockwaves (3000 and 6000) but by the significantly lower generator output setting applied in that study, resulting in at least 20% lower shockwave pressures.[16,19]

Focal damage consistently reported in different animal models included varying degrees of subcapsular and intraparenchymal liver hemorrhages, and bleedings and edema of the gallbladder wall.[19-21,23-28] Abnormalities of the stomach, duodenum, pancreas, and intestines are not documented. Delius et al. observed also petechial hemorrhages on serosal surfaces of the pancreas and duodenum, focal destruction of the liver capsule and capsular adhesions between liver lobes.[24] Apart from gallbladder hemorrhages, Ell et al. identified small bleedings within the liver, spleen, and lungs in dogs, two to four hours after shockwave application.[20] In each animal, however, shockwaves were sequentially targeted to the gallbladder, the right lobe of the liver, the spleen, the abdomen (bowel), and the lungs. Therefore, the potential adverse effects of shockwaves directly focused to a gallbladder(stone) cannot be conclusively determined from these data. Histologically, some studies revealed circumscribed signs of (early) hepatocellular necrosis or the occurrence of venous thrombi in the portal vessels.[20,21,23-25] Thrombi in portal veins tended to occur more often after a fast shockwave administration rate (10 shockwaves per second), which also resulted in increased hemolysis.[29]

Ponchon et al. reported small perirenal and subcapsular renal hematomata following biliary lithotripsy in 2 out of 16 dogs.[25] We found no renal abnormalities nor hematuria, but transient hematuria is described as a usual side effect of the clinical application of biliary lithotripsy.[10-13] This indicates that during biliary lithotripsy renal damage can occur when the kidneys are located in the high-pressure field of the shockwaves, the consequence of which is now recognized as a potential long-term complication.[14]

Hemorrhages in the lower lobes of the lungs attributable to ESWL were evidenced in several animal studies, but were of a silent nature and could in our study

not be detected on chest radiographs.[19,24,25,27,28,30,31] In humans, however, lung injuries have not been reported yet.[10-13] Delius et al. established that the occurrence of pulmonary hemorrhages is pressure-dependent.[31] We measured at the shockwave transmission path at the parietal pleura pressures of about 5 MPa,[17] which is apparently high enough to cause the pulmonary lesions found in this study. Therefore, the lungs should be carefully angled away from the shockwave transmission path. Unfortunately, in contrast to the human situation, in animal experiments these optimal conditions cannot always be achieved because of the specific animal anatomy.

Data about the evolution in time of tissue lesions caused by shockwave therapy are scarce.[20,21,23,25,26] In the present study most lesions were resolving within one week, but in the liver parenchyma discrete and permanent scarring was identified. This corresponds with the observation that hemorrhagic foci in renal parenchyma healed by scar formation within 8 to 10 days after shockwave application.[5] In humans, re-epithelialization of ESWL-induced mucosal damage is assumed to occur from surviving epithelial cells in the mucosal crypts of the gallbladder.[32] This was not noticed in our study pigs, killed one week after ESWL. Due to fixation artefacts, epithelial recovery in pigs of the long-term study could not be determined, but relying on the normal appearance of their gallbladders an unimpaired function can be supposed. This is supported by both experimental and clinical studies showing that gallbladder motility is not modified by extracorporeal lithotripsy.[27,33]

We considered fragmentation to be adequate when residual fragments measured 5 mm or less. This is based on the observation that spontaneous passage of fragments up to 5 mm through the cystic duct and the papilla of Vater appears to be possible and rarely causes clinical and/or biochemical symptoms.[34] Fragments >5 mm are less likely to be cleared spontaneously as evidenced in the long-term series. This underlines the necessity of adjuvant fragment dissolution therapy after biliary ESWL.[13] Overall, fragmentation was achieved in 86% and adequate fragmentation in 41% of animals. Differences after application of 4000 *versus* 8000 shockwaves were not statistically significant. These results were less successful as reported from other animal studies.[23,25] This can be explained by the higher energy output of electrohydraulic devices compared to electromagnetic shockwave sources as well as by the advantage of ultrasonography *versus* fluoroscopy for target imaging. Furthermore, differences of diameters of implanted stones may also account for the differing results of

the various experiments.

The pig model has proved to be an appropriate and viable large animal model to study new treatment modalities of cholelithiasis as also evidenced by this study.[35,36] Nevertheless, it is difficult to draw conclusions from these study data which are applicable to man because the anatomy of pigs is obviously different from that of man. Using the Lithostar, biliary ESWL in pigs was efficacious and associated with discrete but virtually completely reversible soft-tissue injuries without clinical relevancy. Therefore, these data warrant further evaluation of the safety and efficacy of electromagnetic lithotripsy in human studies.

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CHAPTER 6

Electromagnetic Shockwave Lithotripsy of Gallstones in Vitro: The Role of Different Stone Characteristics and Treatment Variables

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Abstract

From 40 sets of five human gallstones obtained at cholecystectomy, four stones were subjected to either 125/250 (maximum generator output) or 250/500 (half-maximum generator output) electromagnetic shockwaves; the fifth stone was used for computed tomography (CT) and chemical analysis. Overall, 130 (81%) of 160 stones fragmented, including 72 (45%) adequately (fragments ≤ 5 mm). After application of 250 shockwaves (maximum generator output), the percentages overall and adequate fragmentation amounted to 95% and 70%, respectively. A significantly higher overall fragmentation rate was obtained in pure cholesterol stones ($p < 0.01$), in stones with a mean CT density ≤ 110 HU ($p < 0.001$), and in stones with a calcified rim ($p < 0.05$). The success of fragmentation was significantly associated with stone weight and diameter ($p < 0.001$), bilirubin content ($p < 0.02$) and calcium content ($p < 0.05$). A weight > 500 mg and a diameter > 10 mm could be defined as stone characteristics being significant negative predictors of adequate fragmentation. High correlations between mean CT attenuation numbers (HU) and cholesterol ($r = -0.87$; $p \leq 0.001$) or calcium ($r = 0.92$; $p \leq 0.001$) content were found. Using a cut-off point of 110 HU, pure cholesterol ($\geq 80\%$ cholesterol) and noncholesterol stones could be discriminated by CT with an overall accuracy of 95%.

Introduction

From 1986 extracorporeal shockwave lithotripsy (ESWL) has been expanding as a nonsurgical treatment for selected patients with gallstone disease.[1-3] Biliary lithotripsy has been performed with electrohydraulic,[4-6] electromagnetic,[7,8] or piezoelectric[9,10] lithotriptors. The acoustic energy output of the respective systems, however, can vary considerably.[11] This depends on the employed techniques of shockwave generation and focusing. It is thus conceivable that the performance of different types of ESWL devices may vary.

In contrast to the electrohydraulic and piezoelectric systems,[12-14] gallstone fragmentation and the role of different stone characteristics have not been systematically studied *in vitro* for electromagnetic systems. The aims of the present study were to evaluate the potential for gallstone lithotripsy of a recently developed electromagnetic shockwave source under various treatment regimens and to assess the significance of different stone characteristics in predicting stone fragmentation *in vitro*.

Methods

Stones

Forty sets of five gallstones were obtained from 40 patients who underwent elective cholecystectomy for symptomatic gallbladder stones. By gross observation the stones comprising one set were comparable in morphology and size and were assumed to be of similar chemical composition, because they came from the same patient. The stones were stored at 4°C in phosphate buffered saline (PBS), containing 50 000 IU/l penicillin and 50 000 μg/l streptomycin. One stone from each set was used for examination by computed tomography followed by chemical analysis. The remaining four stones from each set were used for lithotripsy experiments.

Computed Tomography

Computed tomography (CT) was performed with a Somatom CR (Siemens AG, Erlangen, Germany) at settings of 125 kV and 450 mAs. Contiguous sections of 2-mm-thickness were made through a cylindric plexiglas phantom containing eight chambers

filled with physiologic saline, in which the stones were immersed individually. For each stone, mean CT attenuation values, expressed in Hounsfield Units (HU), were obtained by the method described by Brakel et al.[15]

At CT examination, gallstones were categorized as calcified or noncalcified according to Brakel et al.[15] Calcified stones were subdivided into three groups: calcified rim (type I), calcified core (type II), or other pattern of calcification (type III). Noncalcified stones were subdivided into two groups: detectable (type IV), and nondetectable (type V) (iso-attenuating with surrounding fluid).

Chemical Analysis

Gallstones were washed, dried superficially, and weighed to the nearest 0.1 g. After drying to constant weight (48 hours at 37°C), the stones were weighed again to calculate water content. Gallstones were ground in a mortar, and the resulting powder was used for analysis of cholesterol, calcium, and bilirubin. The methods of determination of cholesterol, calcium, and bilirubin contents have been described elsewhere.[15,16]

Shockwave Device

For shockwave lithotripsy of the gallstones the Lithostar Plus (Siemens AG, Erlangen, Germany) was used. This lithotriptor is based on the electromagnetic principle. At maximum generator output setting, the Lithostar Plus generates shockwaves with a maximum positive focal pressure of about 65 MPa *in vitro*; the focal zone (i.e., the zone within which more than 50% of maximum focal pressure occurs) has a length of 40 mm and a width of 3 mm.[17] The maximum acoustic energy output (total energy delivered into the focal plane by a single shockwave generated at maximum generator power) amounted to 70 mJ *in vitro*.[17]

Lithotripsy Experiments

The shockwave applicator was coupled by means of ultrasound coupling gel to a nonattenuating elastic membrane sealing off a window of a water-filled test basin. After measurement of the maximum diameter and weight, individual stones were placed in a small plastic net (1.5 mm meshes) suspended in the water such that the stone was exactly focused.

The four stones of each set used for *in vitro* lithotripsy were subjected to different

Table 1. *Chemical and CT analysis of 40 human gallstones.*

Type of Gallstone	No.	Cholesterol[a] (%)	Calcium[b] (%)	Bilirubin[c] (%)	Mean CT density[d] (HU)
All	40	93.2(0-99.9)	0.7(0-32.7)	0(0-23.6)	41(7-584)
Pure cholesterol (≥80%)[e]	30	95.4(82.3-99.9)	0.2(0-3.9)	0(0-1.8)	29(7-111)
Mixed (≥25%-80%)[e]	4	54.7(38.0-64.9)	14.7(3.3-19.3)	0(0-11.4)	273(117-516)
Pigment (≥25%)[e]	6	0(0-11.4)	2.1(0.8-32.7)	10.2(1.2-23.6)	179(84-584)
Calcified[f]	22	84.1(0-96.4)	1.6(0.2-32.7)	0(0-23.6)	106(21-584)
Noncalcified[f]	18	96.2(91.8-99.9)	0.1(0-1.2)	0(0-0.5)	21(7-41)
CT pattern I	8	91.9(11.4-96.4)	0.8(0.2-16)	0(0-23.6)	79(21-284)
II	4	91.8(85.8-94.7)	0.8(0.6-1.3)	0(0-1.3)	56(49-63)
III	10	19.9(0-90)	3.0(0.8-32.7)	4(0-22.1)	155(102-584)
IV	16	96.2(91.8-99.9)	0.1(0-1.2)	0(0-0.5)	22(13-41)
V	2	97.7(95.5-99.9)	0.1(0-0.1)	0(0-0)	8(7-8)

NOTE. Data are given as median values with ranges in parentheses.
[a,b,d] pure vs mixed, [a-d] pure vs pigment, [c] pure vs pigment: $p < 0.05$.
[a-c] calcified vs noncalcified: $p < 0.05$.
[a,b,d] I vs IV/V, [b] II vs IV, [a,d] II vs V, [a-d] III vs IV/V: $p < 0.05$.
[e] percentage of cholesterol.
[f] on CT scan.

numbers of shockwaves, generated at a generator voltage setting of either 20.3 kV (maximum focal shockwave pressure [100%]) or 16.9 kV (half-maximum focal shockwave pressure [50%]):

treatment I: 125 shockwaves, focal pressure 100% (20.3 kV);

treatment II: 250 shockwaves, focal pressure 100% (20.3 kV);

treatment III: 250 shockwaves, focal pressure 50% (16.9 kV);

treatment IV: 500 shockwaves, focal pressure 50% (16.9 kV).

Application of shockwaves was stopped before completing the intended number of

shockwaves when the net was completely emptied. If necessary, the net was gently shaken during lithotripsy to allow the fragments to pass through the meshes. Fragments remaining in the net after maximum shockwave application were sieved using a metal sieve with a 2.5 mm grid. All fragments not passing through this grid were collected and their diameters measured. Fragmentation was considered to be adequate when all remaining fragments measured ≤ 5 mm in their largest diameter, and was considered unsatisfactory if fragmentation did not occur, or if at least one particle was larger than 5 mm at the end of the experiment. If all treatment regimens failed to fragment the stones, a total of 1500 shockwaves generated at maximum generator output setting was administered.

Data Analysis

Differences between diameter or weight between stone sets, and differences between chemical composition or CT density *versus* treatment regimen were analyzed with the Kruskal Wallis (multiple comparison) test. Relations between CT density and chemical composition were examined with Spearman's rank-correlation test. Categorized fragmentation results were compared using the Chi-square test or Mann-Whitney U-test, where appropriate. The determination of the optimal cut-off point for CT density in predicting chemical composition was performed using ROC-analysis.[18]

Results

The median diameter and weight of the 160 stones used for lithotripsy were 8 mm (range: 6-17) and 230 mg (range: 20-1840), respectively. Diameters and weights of the 40 subsets of stones allocated to the different treatment regimens were equal. Taken together, within particular sets of four stones the diameters and weights differed on average 1.0 mm (range: 0-6) and 72 mg (range: 0-870), respectively.

Chemical and CT analysis of single gallstones of the 40 stone sets are given in Table 1. The stones were divided into three groups, depending on cholesterol content: pure cholesterol ($\geq 80\%$ dry cholesterol weight), mixed ($\geq 25\%$ and $< 80\%$), and pigment stones ($< 25\%$).

From the 22 stones (55%) which were calcified at CT, 8 stones (20%) were

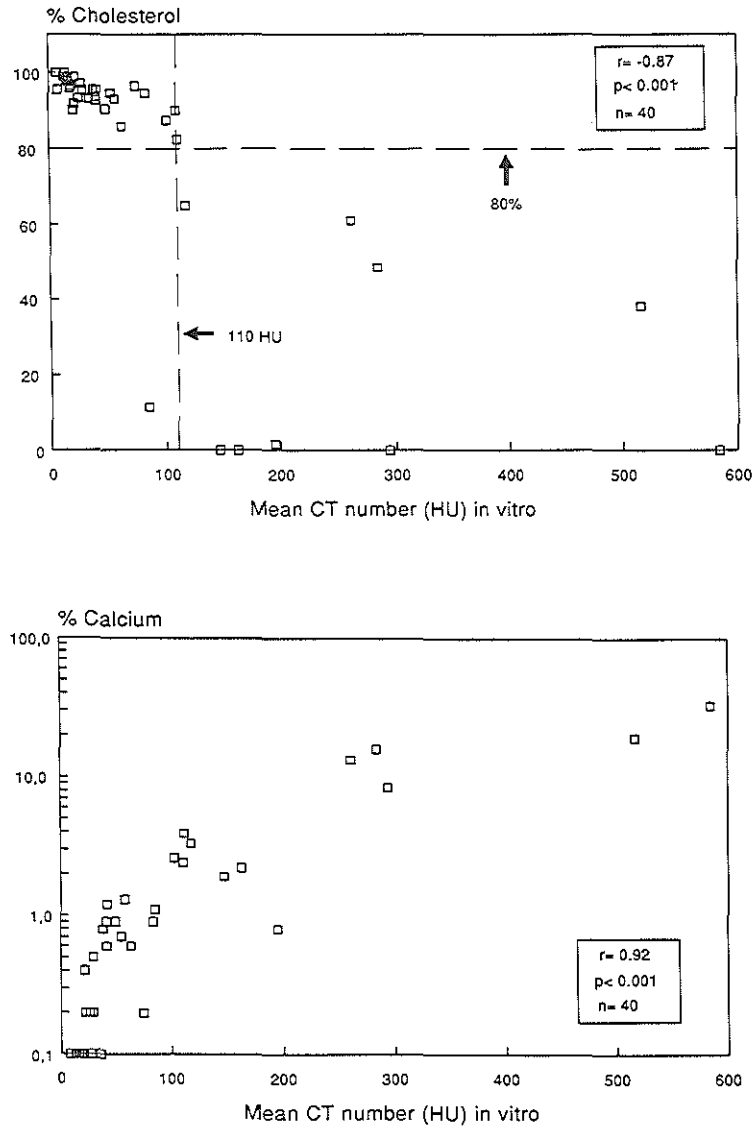

Figure 1. *Correlation between cholesterol (top) respectively calcium (bottom) content and mean CT attenuation numbers (HU) in vitro of 40 gallstones.*

classified as type I, 4 stones (10%) as type II, and 10 stones (25%) as type III. From the 18 stones (45%) categorized as noncalcified, 16 stones (40%) were of type IV and 2 stones (5%) of type V. Stones of type II as well as noncalcified stones (types IV and V) were pure cholesterol stones, but cholesterol stones could also present CT patterns of type I and III. Pigment and mixed stones assorted to type I (n=2) and type III (n=8).

Figure 1 shows a high correlation between mean CT attenuation numbers and cholesterol ($r=-0.87$; $p \leq 0.001$) and calcium ($r=0.92$; $p \leq 0.001$) content, respectively. The optimum cut-off point for pure cholesterol stones was defined by receiver-operating characteristic (ROC) analysis at 110 HU (Fig. 2), because at this value specificity and sensitivity were maximized.[18] Using this cut-off point, CT discriminated between pure cholesterol and noncholesterol (<80% cholesterol) stones with a specificity of 0.90, a sensitivity of 0.97, a positive predictive value of 0.97, a negative predictive value of 0.90, and an overall accuracy of 0.95.

Table 2. *Results of in vitro ESWL of gallstones according to treatment regimen.*

Treatment Regimen	No.	Fragmentation	Maximum Particle Size at End of Experiment[a]		
			≤2.5 mm	>2.5 mm and ≤5 mm	>5 mm
I	40	32(80%)	7(18%)	8(20%)	25(62%)
II	40	38(95%)	14(35%)	14(35%)	12(30%)
III	40	28(70%)	3(8%)	9(22%)	28(70%)
IV	40	32(80%)	11(27%)	6(15%)	23(58%)
Overall	160	130(81%)	35(22%)	37(23%)	88(55%)

NOTE. Data are given as numbers of stones with percentages in parentheses.
[a] I vs II, II vs III/IV: $p < 0.05$.

Irrespective of treatment regimen, 130 (81%) of 160 stones fragmented. Adequate fragmentation (all fragments ≤5 mm) was achieved in 72 stones (45%). Unsatisfactory results were obtained in 88 calculi (55%), including 30 stones (19%) which did not fragment at all. The results of the various treatment regimens according

to different categories of remaining particle size are given in Table 2. Figure 3 depicts the percentage overall as well as adequate and unsatisfactory fragmentation. The highest percentage of (adequate) fragmentation was achieved at a generator voltage setting of 20.3 kV (focal pressure 100%) with 250 shockwaves (treatment II). At this generator voltage, significant better results were obtained after application of 250 (treatment II) *versus* 125 (treatment I) shockwaves ($p < 0.05$). At 16.9 kV (focal pressure 50%), doubling the number of shockwaves from 250 (treatment III) to 500 (treatment IV) also improved the results albeit not significantly. Halving of the focal pressure was not fully compensated for by administration of twice as many shockwaves as evidenced by comparing the results of treatment I and IV, for instance; the number of shockwaves must be increased four-fold to achieve comparable results.

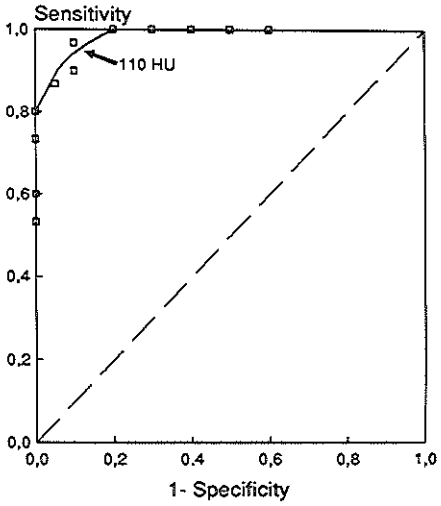

Figure 2. *Receiver-operating characteristic graph of CT attenuation cut-off numbers for classification of gallstones. Specificity and sensitivity of CT to discriminate in vitro between pure cholesterol (≥80% cholesterol) and noncholesterol stones were maximized using a cut-off point of 110 HU.*

Table 3 shows different stone characteristics according to results of fragmentation, irrespective of treatment regimen. Only the stone diameter and weight ($p < 0.001$) as well as the bilirubin content ($p < 0.02$) and calcium content ($p < 0.05$) were significantly associated with adequate fragmentation.

Independent of treatment regimen and without regard to fragmentation outcome, a significantly higher percentage of pure cholesterol stones ($p < 0.01$), stones with a mean CT density ≤110 HU ($p < 0.001$), and stones with a calcified rim ($p < 0.05$) fragmented as shown in Table 4. Except for a stone weight >500 mg and a diameter >10 mm, other stone characteristics which were significant negative predictors of adequate fragmentation, however, could not be identified.

Thirty-two stones from 14 different stone sets did not fragment, but in only 3 sets fragmentation failed with treatment II. In 2 sets (pigment stones, CT type III) all treatment regimens failed to fragment the stones. In these cases, application of 1500 shockwaves (focal pressure 100%) was still insufficient in the one, whereas this resulted in adequate fragmentation in the other case.

Discussion

In this study a single stone of each set from one patient was used for chemical and CT analysis because we assumed that this stone would be representative. This is justified by the observation that the chemical composition of multiple stones obtained from the same patient varied with only 2.5%.[19]

The utility of computed tomography for predicting gallstone composition is an unsettled issue yet.[20,21] In the present study, however, pure cholesterol stones were reliably identified (overall accuracy 95%) by mean CT attenuation numbers using a cut-off point of 110 HU. Brakel et al. achieved a similar overall accuracy using a cut-off point for pure cholesterol stones of 140 HU.[15] Because HU values are device-dependent, the cut-off points for different CT systems cannot be compared unless a reference calibration phantom is used by which CT numbers can be converted to equivalent values of milligrams of K_2HPO_4 per ml.[15] We found an inverse relation between CT attenuation numbers and cholesterol content, confirming earlier *in vitro* as well as *in vivo* observations.[13,15,22-24] Unlike Baron et al., but corroborating other studies, we also found a good correlation between CT attenuation and calcium content.[13,15,24,25]

The various CT patterns of the gallstones in this study were similar to those described previously.[13,15,22,25,26] Stones which were noncalcified by CT appearance (type IV and V) and stones with a calcified core (type II) invariably were pure cholesterol stones, in accordance with the findings of Baron et al.[22] The other CT patterns (type I and III), however, may correspond with cholesterol as well as with mixed and pigment stones. Therefore, qualitative CT analysis of gallstones based on different CT patterns provides some insight into the chemical composition, but does not allow a definite distinction in stones with a high cholesterol content and those with a low cholesterol content.

Table 3. *Characteristics of gallstones according to results of in vitro ESWL, irrespective of treatment regimen.*

Stone Characteristics	Maximum Particle Size at End of Experiment		P Value
	≤5 mm (n=72)	>5 mm (n=88)	
Diameter of implant(mm)	7.7 ± 0.2	9.5 ± 0.3	< 0.001
Weight of implant (mg)	228 ± 25	470 ± 46	< 0.001
Cholesterol (%)	77.6 ± 3.7	75.3 ± 3.9	NS
Bilirubin (%)	0.8 ± 0.4	3.5 ± 0.7	< 0.02
Calcium (%)	5.1 ± 1.1	1.2 ± 0.2	< 0.05
Mean CT density (HU)	128 ± 20	70 ± 8	NS

NOTE. Data are given as mean ± SEM values.

Evaluating our results, it should be considered that the use of a net to contain the gallstones and the encouragement of the passage of the fragments through the mesh during *in vitro* lithotripsy is not fully representative of the situation *in vivo*. During *in vivo* lithotripsy fragments are known to impede both the visualization and possibly the transmission of the shockwaves. Therefore clearance of these fragments during *in vitro* analysis probably artificially improves the results obtained.

We defined the endpoints of fragmentation as adequate (all remaining particles ≤5 mm) *versus* unsatisfactory (no fragmentation or at least one residual particle >5 mm). The rationale for this stratification is based on the observation that spontaneous passage of fragments up to 5 mm through the cystic duct and the papilla of Vater appears to be possible and rarely causes clinical and/or biochemical symptoms.[28] Furthermore, post-ESWL oral dissolution therapy resulted in a significantly higher stone-free rate when all residual fragments measured ≤5 mm.[5]

Comparable *in vitro* gallstone fragmentation studies have been performed using both electrohydraulic[12,13] and piezoelectric shockwave devices.[14] Schachler et al. achieved adequate fragmentation (≤5 mm) in 42 of 51 solitary stones (82%) after application of at most 1500 shockwaves.[12] In the study of Barkun et al. a mean number of more than 2000 shockwaves was administered to achieve fragmentation in 68 of 85 stones (80%), adequate fragmentation (≤5 mm) occurring in only 27 stones (32%).[13]

Ell et al. applied a maximum of 4000 shockwaves which effected fragmentation of all stones (n=177), 86% of which fragmented "appropriately" ($\leq$4 mm).[14] In the present study overall fragmentation was attained in 81% and adequate fragmentation in 45% of the stones. However, it must be emphasized that in our study 4 different treatment regimens were followed, applying considerably lower numbers of shockwaves than in the aforementioned studies. We are aware that the number of shockwaves used is not representative for the number of shockwaves normally used in the clinical setting. The reason that we have decided to use such a small number of shockwaves is that otherwise it might have been impossible to establish any relationship between energy setting and the number of shockwaves. Considering only the results of treatment II (highest effectiveness), 38 out of 40 stones (95%) fragmented, including 28 (70%) adequately. It is thus conceivable that these results would have been even better if a higher number of shockwaves had been applied.

There are several possible explanations for the varying results obtained in the various *in vitro* experiments. Firstly, the employed shockwave devices differ in acoustic energy output which is directly related to the effectiveness.[11] As shown in this experiment, lower energy settings (resulting in lower focal shockwave pressures) can be compensated for by increasing numbers of shockwaves, but the relation between the energy and the number of shockwaves required for stone fragmentation seems to be not linear but exponential.[27] Secondly, the respective stone populations are not fully comparable with respect to stone size. Particularly in the present study, the median stone diameter was relatively small, probably because these stones were collected from patients with multiple stones. This is of interest because stone size is shown to be an important determinant of the outcome of fragmentation, which became also apparent from this study.[4,5,10,12-14] Thirdly, it cannot be excluded that the treatment geometries in the various fragmentation experiments have been different.[29] Finally, the differing numbers of shockwaves applied in the various studies might have been of importance in determining the results.

Confirming previous observations,[12-14] we did not find any relationship between chemical composition, mean CT density, or CT pattern and adequate fragmentation except that bilirubin and calcium content may play a certain (minor) role. Nevertheless, some stone categories (pure cholesterol stones, stones with a CT number $\leq$110 HU,and stones with a calcified rim) seem to fragment easier than other ones (Table 4).

Table 4. *Results of in vitro ESWL according to different stone categories.*

Stone Categories	No.	Fragmentation[a]	Maximum Particle Size at End of Experiment[b] ≤5 mm (n=72)	>5 mm (n=88)	P Value
Weight:					
≤ 500 mg	126	105(83%)	67(53%)	59(47%)	NS
> 500 mg	34	25(74%)	5(15%)	29(85%)	< 0.001
Diameter:					
≤ 10 mm	129	107(83%)	66(51%)	63(49%)	NS
> 10 mm	31	23(74%)	6(19%)	25(81%)	< 0.001
Cholesterol:					
≥ 80%	120	104(87%)	53(44%)	67(56%)	NS
< 80%	40	25(65%)	19(48%)	21(52%)	NS
Mean CT density:					
≤ 110 HU	120	105(88%)	53(44%)	67(56%)	NS
> 110 HU	40	25(63%)	19(48%)	21(52%)	NS
Calcified on CT					
+	88	68(77%)	37(42%)	51(58%)	NS
-	72	62(86%)	35(49%)	37(51%)	NS
CT pattern:					
I	32	29(91%)	15(47%)	17(53%)	NS
II + III	56	39(70%)	22(39%)	34(61%)	NS
II	16	14(88%)	5(31%)	11(69%)	NS
I + III	72	54(75%)	32(44%)	40(56%)	NS

NOTE. Data are given as numbers of stones with percentages in parentheses.
[a] cholesterol ≥80% vs <80%, mean CT density ≤110 HU vs >110 HU, CT pattern I vs II + III: $p < 0.05$.
[b] weight ≤500 mg vs >500 mg, diameter ≤10 mm vs >10 mm: $p < 0.05$.

Barkun et al. established a stone diameter ≤15 mm, the presence of an angular stone shape and a stone density distribution index ≥60 HU as strong determinants of satisfactory fragmentation (≤5 mm).[13] In our study, a stone weight >500 mg and a stone diameter >10 mm were identified as categorical variables determining the result

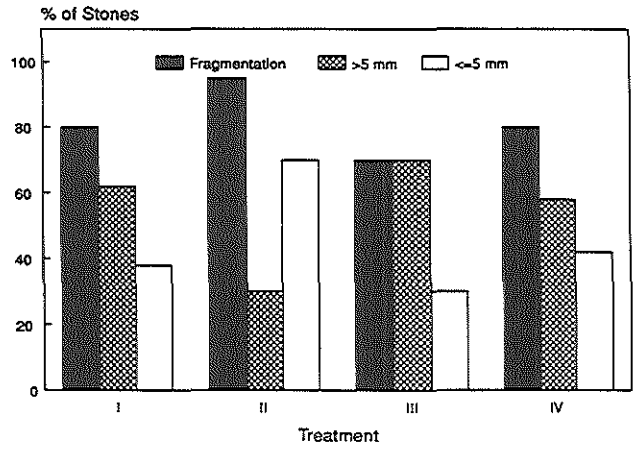

Figure 3. *Percentage of total, adequate (fragments ≤5 mm), and unsatisfactory (fragments >5 mm) in vitro fragmentation of 40 sets of gallstones for 4 different treatment regimens (I: 125 shockwaves, 100% focal pressure; II: 250 shockwaves, 100% focal pressure; III: 250 shockwaves, 50% focal pressure; IV: 500 shockwaves, 50% focal pressure).*

of fragmentation in a negative way.

In conclusion, the fragmentation efficacy of electromagnetic ESWL is mainly determined by the energy output of the lithotriptor and by the size, but not by chemical composition and CT characteristics of the stones. Quantitative CT analysis can provide reliable prediction of gallstone composition and therefore may play an important role in the selection of patients where primary or adjuvant chemolitholysis is considered as nonsurgical treatment. The present data warrant further clinical validation.

Acknowledgements

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CHAPTER 7

In Vitro Comparison of Different Gallstone Dissolution Solvents

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Abstract

Extracorporeal shockwave lithotripsy (ESWL) of gallbladder stones leaves residual fragments that need to be dissolved by chemical solvents. In this study we compared the *in vitro* dissolving capacity of methyl tert-butyl ether (MTBE), mono-octanoin, limonene, and limonene/mono-octanoin (70%/30%). From nine sets of five human gallstones obtained at cholecystectomy, four stones were used for dissolution and the fifth was used for chemical analysis of cholesterol, calcium and bilirubin contents. Eight sets were cholesterol stones with a mean (SD) cholesterol content of 89.9(5.6)%. These stones dissolved completely in either solvent, often leaving sand-like debris, with the exception of one stone. MTBE dissolved cholesterol gallstones 100 times faster than mono-octanoin and 10 times faster than limonene or the limonene/mono-octanoin mixture ($p < 0.001$). The combination of limonene and mono-octanoin was as effective as limonene alone. Of the four solvents, MTBE is the best one to evaluate for dissolution of residual fragments after ESWL treatment of gallbladder stones.

Introduction

Extracorporeal shockwave lithotripsy (ESWL) is a promising nonsurgical treatment for selected patients with cholecystolithiasis.[1] To achieve complete stone clearance, however, ESWL must be combined with adjuvant oral cholelitholysis by chenodeoxycholic or ursodeoxycholic acid, or both. Notwithstanding its simplicity and harmlessness, oral dissolution treatment is expensive and must be continued for at least 6 to 12 months after primary therapy by ESWL.[1] The use of dissolution solvents for direct percutaneous gallbladder perfusion may therefore afford a favourable alternative and is of renewed interest.

Mono-octanoin was found to be a useful substance for direct dissolution of retained cholesterol bile duct stones by either T tube infusion[2-6] or by percutaneous transhepatic catheterisation.[3] It is also used through an endoscopically positioned nasobiliary catheter.[7]

Rapid dissolution of cholesterol gallstones with methyl tert-butyl ether (MTBE) has been described recently.[8] MTBE is structurally related to diethylether but unlike diethylether, which vaporises at body temperature, it remains liquid because of its higher boiling point (55.2°C).[9] It can be delivered to the gallbladder or the common bile duct by a nasobiliary or a percutaneous transhepatic catheter.[8,10-14]

The monoterpene, limonene, is obtained from the peel of citrus fruits. It seemed to be an excellent dissolution solvent *in vitro* on human cholesterol gallstones.[15] Complete dissolution of duct stones was reported by Igimi et al. in 13 of 15 patients using a 97% d-limonene solution.[16] More recently, the authors changed the prescription of the d-limonene preparation to 70% d-limonene and 30% middle chain monoglyceride to improve efficacy and reduce the side effects of the previous preparation.[17] *In vitro* studies showed extraordinary synergism when d-limonene and mono-octanoin were used in a 3:2 mixture to dissolve cholesterol stones.[15]

In this study we compared the gallstone dissolving capacity of four different dissolution solvents *in vitro*: MTBE, mono-octanoin, a 97% limonene preparation and a limonene/mono-octanoin mixture.

Materials and Methods

Stones

Nine sets of five gallstones were obtained from nine consecutive patients who underwent elective cholecystectomy for symptomatic gallbladder stones. By gross observation, the stones comprising one set were comparable in morphology and size, and assumed to be of similar chemical composition. The stones were stored at 4°C in phosphate buffered saline (PBS), containing 50 000 IU/l penicillin and 50 000 μg/l streptomycin. One stone from each set was used for chemical analysis of cholesterol, calcium, and bilirubin contents, as described previously.[18] The remaining four stones were used to study dissolution by different solvents.

The 36 stones used for dissolution were placed on blotting paper and allowed to dry in air for one hour before weighing and measuring the maximum diameter of each stone. A Mettler PK 300 digital balance (Mettler Instrumente AG, Greifensee, Switzerland) was used for weighing.

Table 1. *Percentages of dry weight of cholesterol, calcium, and bilirubin in nine different sets of gallstones.*

Set No.	Cholesterol (%)	Calcium (%)	Bilirubin (%)
1	92.3	0.8	0.5
2	91.4	0.0	0.7
3	92.8	0.7	0.1
4	86.3	2.0	0.1
5	96.9	0.0	0.1
6	0.0	#	10.0
7	91.3	0.0	0.1
8	78.1	#	0.4
9	90.2	1.3	0.2

NOTE. One stone from each set was used for chemical analysis.
amount of material insufficient for chemical analysis.

Dissolution Solvents

The following dissolving agents were used: mono-octanoin (glyceryl-1-mono-octanoate, Capmul 8210, from Stokely USA Inc, Oconomowoc, Wisc, USA); methyl tert-butyl ether (MTBE, from Merck-Schuchardt, Schuchardt, Germany); d-limonene (d-p-mentha-1,8-diene), Tween 80 (polyoxyethylene-sorbitan-mono-oleate), and Span 80 (sorbitan-mono-oleate) (from Sigma Chemical Company, St Louis, MO, USA).

The 97% limonene preparation was prepared by adding 2.1 parts of Tween 80 and 0.9 parts of Span 80 to 97 parts of d-limonene. The limonene/mono-octanoin mixture was prepared by adding 70 parts of d-limonene to 30 parts of mono-octanoin.

Dissolution Experiment

The stones were immersed individually in test tubes containing 10 ml of one of the four different solvents. The tubes were sealed off, placed in a constant temperature (37°C) waterbath, and gently agitated. For reweighing, the stones were lifted out of the solutions using a spatula or by filtration in the case of multiple residues. Stones were blotted dry before weighing every 10 minutes up to two hours; hourly up to six hours; daily from 24-72 hours, and then at three to four day intervals up to 14 days. At the same intervals aliquots (100 μl) of the dissolution solvents were taken for determination of the cholesterol content by the CHOD PAP method.[19] After weighing, the

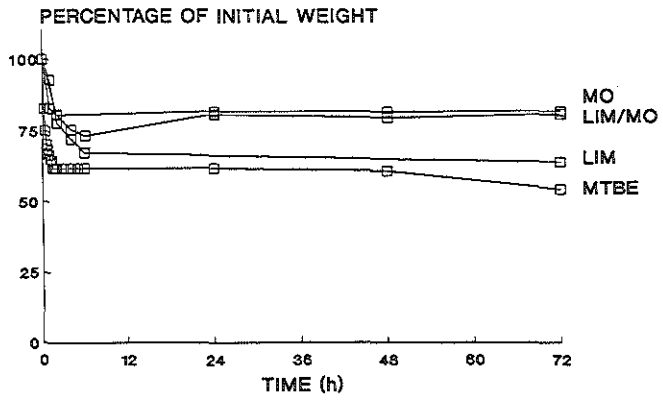

Figure 1. *Relative reduction in weight of pigment stones (set 6) achieved by methyl tert-butyl ether (MTBE), mono-octanoin (MO), limonene (LIM), and limonene/mono-octanoin (LIM/MO).*

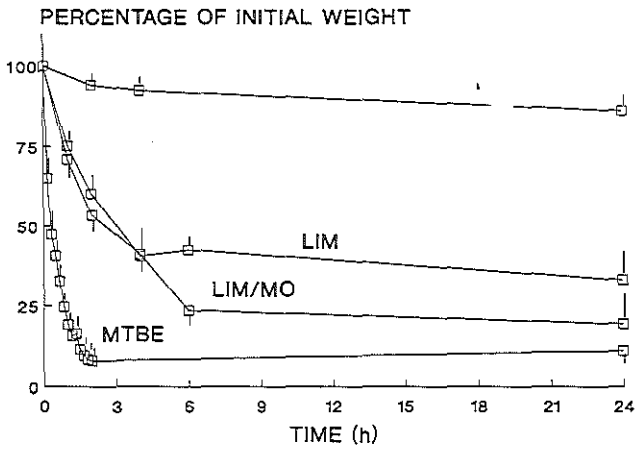

Figure 2. *Relative reduction in weight of eight sets of cholesterol stones in four different solvents, expressed as the percentage of initial stone weight for methyl tert-butyl ether (MTBE), mono-octanoin (MO), limonene (LIM), and limonene/mono-octanoin (LIM/MO). Data are mean (SEM) values.*

stones or residues were returned to the original test tubes. The different solvents were not replaced during the study. Dissolution was defined as a reduction in stone mass, the residual debris not exceeding 2 mm in diameter.

Data Analysis

Stone weights at set times were expressed as percentages of the initial stone weight. The relative reduction in stone weight over time was related to the relative recovery of cholesterol from the medium. The 25% and 50% dissolving times were calculated by solving a four parameter logistic equation[20] using ALLFIT 2.7 (software kindly provided by Dr D Rodbard, NIH, Bethesda, MD, USA). Data were compared using non-parametric analysis of variance (Friedman's test) and the Mann-Whitney test.

Results

Table 1 gives the results of chemical analyses of a single stone from each set. The stones comprising set 6 were black in colour and had an irregular surface - typical

criteria for pigment stones. These stones consisted of 10% bilirubin and did not contain any cholesterol. The remaining sets were smooth surfaced, rounded or faceted, and for the greater part yellowish stones, largely composed of cholesterol. The mean (SD) percentage of cholesterol in the latter stones was 89.9(5.6)%.

Table 2. *Dissolving times of methyl tert-butyl ether (MTBE), mono-octanoin (MO), limonene (LIM), and limonene/mono-octanoin (LIM/MO) at which the initial weights of eight cholesterol stones were reduced by 25% and 50%.*

	Dissolving Time (h) to Achieve Weight Reduction of	
Solvent	25%	50%
MTBE	0.2(0.1-0.2)	0.3(0.2-0.5)
MO	21.1(13.4-25.2)	45.5(34.8-61.8)
LIM	1.2(0.7-2.2)	3.4(1.7-5.1)
LIM/MO	1.0(0.6-2.2)	2.1(1.3-4.0)

NOTE. Values represent medians with 25th - 75th centiles in parentheses.
MTBE vs MO, LIM, and LIM/MO: $p<0.001$; MO vs LIM, and LIM/MO: $p<0.001$; LIM vs LIM/MO: NS.

In each of the four solvents, the pigment stones (set 6) disintegrated partly or completely into multiple fragments. The weights of these stones were reduced by 20% to 35% within the first two to six hours; thereafter a further decrease in weight did not occur (Fig. 1).

The remaining cholesterol stones incubated in MTBE, mono-octanoin, limonene, and limonene/mono-octanoin had mean (range) weights of 845 (110-1634), 702 (132-1563), 787 (123-1854), and 787 (79-2046) mg, respectively. The mean (range) diameters were 13.7 (6.5-20.5), 12.7 (6.8-19.1), 13.7 (6.8-21.0), and 12.8 (6.0-18.1) mm, respectively. For the four different solvents, the weights and diameters of the stones did not differ significantly.

During dissolution of the cholesterol stones in MTBE, limonene, and limonene/mono-octanoin most stones broke into multiple fragments; in mono-

octanoin this occurred in two cases only. All cholesterol stones dissolved completely in either solvent, except one stone from set 9, which was reduced by only 50%. The stones from set 5, which had the highest percentage of cholesterol (Table 1), dissolved completely without leaving any residue. Dissolution of the other stones resulted in a sand-like debris (except for stones from set 9).

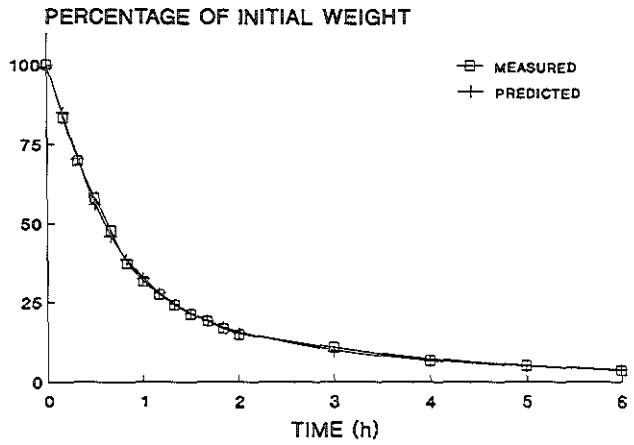

Figure 3. *Relative reduction in stone weight in methyl tert-butyl ether (MTBE) (set 8), compared with the predicted reduction in stone weight by the four parameter logistic equation.*

Figure 2 shows the results for the eight sets of cholesterol stones for each time point; data are expressed as the mean percentage of the initial stone weight. In MTBE, stones dissolved within two hours. In mono-octanoin, limonene, and limonene/mono-octanoin, however, ±85%, ±40%, and ±20%, respectively, were still left after 24 hours. Dissolution with mono-octanoin was completed after 10 days.

In Table 2 the median 25% and 50% dissolving times are given. MTBE dissolved cholesterol gallstones 100 times faster than mono-octanoin ($p < 0.001$) and 10 times faster than limonene or limonene/mono-octanoin ($p < 0.001$). The combination of limonene and mono-octanoin was as effective as limonene alone.

The four parameter logistic equation proved to be an adequate mathematical description for the weight reduction of the stones in either solvent. A typical example is shown in Figure 3.

Figure 4 illustrates the relative reduction in stone weight and the relative

recovery of cholesterol from mono-octanoin, limonene, and limonene/mono-octanoin, expressed as a percentage of the initial stone weight. Data on MTBE are not available due to technical difficulties caused by the volatility of the solvent. The reduction in stone weight paralleled the recovery of cholesterol, showing that the reduction in stone weight was due to dissolution of cholesterol.

Discussion

The combination of chenodeoxycholic and ursodeoxycholic acid has been shown to be effective and safe in dissolving cholesterol stones in selected patients.[21,22] However, the slow process of stone dissolution,[15,23] the high recurrence rate after stopping treatment,[24] and the low percentage of patients that fulfil the selection criteria[25] are considerable disadvantages of oral dissolution therapy.

Recently, oral cholelitholysis has become more important as adjuvant treatment after ESWL of gallbladder stones for dissolution of the residual fragments.[1,26] Dissolution therapy with bile desaturating agents is enhanced considerably by preceding stone fragmentation.[27] Nevertheless, the expensive adjuvant oral dissolution treatment is still lengthy. This may reduce the cost-effectiveness of combined ESWL and chemolytic treatment as an alternative for cholecystectomy. Therefore, notwithstanding its more invasive nature, percutaneous dissolution treatment might be optional for dissolving the fragments remaining after ESWL.[28-31] For patients with large or numerous stones, who are currently excluded from ESWL treatment, contact dissolution may broaden the applicability of ESWL.[1]

In a model dissolution system, it seemed that the initial stone diameter and matrix content determined the dissolution rate rather than the cholesterol content.[32] Fragmentation of gallstones increases the surface for solvent-crystal contact thereby accelerating stone dissolution. Furthermore, disruption of concentric rings of matrix within stones may also contribute to the ease of dissolution. Laser fragmented gallstones dissolved *in vitro* significantly faster in MTBE than did intact stones.[33,34] Calcified stones cannot be dissolved by MTBE. Nevertheless, when calcium is distributed in an outer shell or inner core, mechanical fragmentation increases the efficacy of MTBE dissolution.[28,34] We found a significant acceleration in gallstone

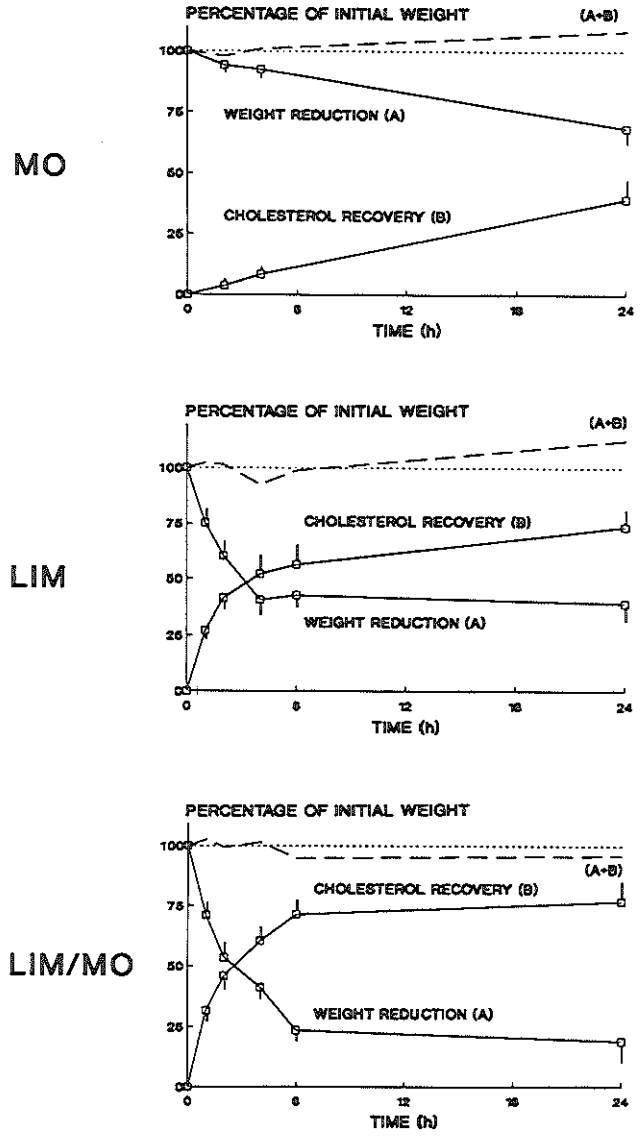

Figure 4. *Relative reduction in stone weight and relative recovery of cholesterol from medium, expressed as percentage of initial stone weight for mono-octanoin (MO), limonene (LIM), and limonene/mono-octanoin (LIM/MO). Data are mean (SEM) values.*

dissolution by MTBE after ESWL in a pig model, irrespective of stone calcification (Vergunst et al.; unpublished observations).

In this study we compared four different solvents possibly suited for post-ESWL contact dissolution. The cholesterol dissolving capacity of different limonene preparations *versus* MTBE and mono-octanoin, respectively, had not previously been compared *in vitro*.

We found that MTBE dissolved cholesterol stones *in vitro* more than 100 times faster than mono-octanoin. This finding corroborates the previously reported superior dissolving capacity of MTBE compared with mono-octanoin, even for stones with a cholesterol content of only 40%.[35] Compared with the limonene preparations MTBE dissolved comparable stones 10 times faster. It has been reported that pigment stones are not dissolved by MTBE.[35,36] The pigment stones in our study, however, were partly dissolved by either solvent. Since these stones did not contain any cholesterol, the weight reduction must be caused by dissolution of other organic constituents.

In conclusion, MTBE, which has been used clinically for dissolution of gallbladder stones without severe side effects or complications,[8] is the most potent cholesterol solvent now available. Combining ESWL and contact dissolution therapy probably renders more patients with cholecystolithiasis eligible for nonsurgical treatment. Of the four solvents, MTBE is the best one to evaluate for dissolution of residual fragments after ESWL.

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CHAPTER 8

Sequential Treatment of Gallbladder Stones by Extracorporeal Shockwave Lithotripsy and Methyl Tert-Butyl Ether: Assessment of Safety and Efficacy

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Abstract

To achieve complete stone clearance after extracorporeal shockwave lithotripsy (ESWL) of gallbladder stones adjuvant fragment dissolution is advocated. In this study the contribution of post-ESWL contact dissolution with methyl tert-butyl ether (MTBE) to the success of ESWL was investigated in the pig model. Couples of similar human gallbladder stones were surgically implanted into 30 pigs. All pigs underwent ESWL using an electromagnetic lithotriptor. Half of the animals were adjuvantly treated with MTBE during 2 hours immediately following ESWL. All pigs were killed 1 week after treatment. Adjuvant MTBE dissolution led to superimposed damage of the gallbladder but no systemic side effects were observed. For all kind of stones, adjuvant MTBE treatment improved the results of ESWL with 30% ($p < 0.01$), whereas for pure cholesterol stones this improvement amounted to approximately 40% ($p < 0.01$). Irrespective of treatment regimen, the weight, diameter, or cholesterol content of the stones did not affect the outcome. These data warrant clinical evaluation of the applicability of combined ESWL and MTBE dissolution therapy for symptomatic gallbladder stones.

Introduction

In the past decade, new therapies for the management of symptomatic gallstone disease have emerged.[1] Extracorporeal shockwave lithotripsy (ESWL) was introduced in 1985.[2] In the same year initial human experience with percutaneous contact dissolution of gallbladder stones by methyl tert-butyl ether (MTBE) was reported.[3] Both forms of therapy appeared to be safe and effective in selected patients with radiolucent gallbladder stones.[4,5]

Following ESWL of gallbladder stones the spontaneous discharge of residual fragments is unlikely to be complete in the majority of patients.[6] To achieve complete stone clearance, gallstone lithotripsy is therefore combined with oral bile acid dissolution therapy.[4,7-12] The need of this adjuvant medication restricts lithotripsy to patients with cholesterol stones in a functioning gallbladder.[13,14] Furthermore, because oral chemolitholysis is expensive it substantially impairs the cost-effectiveness of ESWL for the management of cholecystolithiasis.[15] Therefore, it has been suggested that adjuvant percutaneous dissolution with MTBE might be a favorable alternative.[16] Although invasive, MTBE dissolves cholesterol gallstones - of any size or number - much more rapidly than oral bile acids whether or not it is preceded by lithotripsy.[5,17] Consequently, adjuvant therapy with MTBE might render gallstone lithotripsy more cost-effectively than when combined with oral cholelitholytic agents. Moreover MTBE also may broaden the applicability of ESWL to patients with large or numerous stones who have been excluded thus far, as well as to patients with partially calcified cholesterol stones.[18]

In the present study, the feasibility of sequential treatment of human gallstones with ESWL, using a recently developed electromagnetic lithotriptor, and contact dissolution with MTBE was assessed in a pig model.

Materials and Methods

Stones

Fifteen different sets of three gallstones matched for morphology and size were obtained during cholecystectomies in 15 patients. One stone from each set was used

for chemical analysis as described elsewhere.[19] Depending on cholesterol content, the stones were divided into pure cholesterol stones (≥80% dry cholesterol weight) (n=11) and noncholesterol stones (<80%) (n=4). The cholesterol stones had a median (range) cholesterol, calcium, and bilirubin content of 95.5% (82.3-99.9), 0.2% (0-3.9), and 0% (0-1.3), respectively. The corresponding percentages for the noncholesterol stones were 6.6% (0-61.0), 4.8% (0.8- 13.3), and 7.6% (0-23.6). After measurement of the maximum diameter and weight, the remaining two stones were individually implanted at laparotomy in the gallbladders of 30 Yorkshire pigs (body weight:19-26 kg; mean, 23.3), thus forming 15 weight matched couples. Because the stones comprising one set came from the same patient, the pigs of each couple were assumed to have implanted stones of similar chemical composition.[20]

Shockwave Device

For lithotripsy the overhead module of the Lithostar Plus (Siemens AG, Erlangen, Germany) was used, an electromagnetic lithotriptor equipped with an integrated in-line sonographic target imaging system. *In vitro*, shockwaves with a maximum positive focal pressure of about 65 MPa are generated.[21] *In vivo*, pressures are 15% to 25% lower than those measured *in vitro*.[22] The focal zone (50%-zone) has a length of 40 mm and a width of 3 mm *in vitro*, which is equal *in vivo*.[21,22] The maximum acoustic energy output amounted to 70 mJ *in vitro*.[21]

Lithotripsy

Fourteen days after surgery the pigs underwent ESWL under general anesthesia. The shockwave applicator was coupled by means of ultrasound coupling gel onto the epigastrium with the animals placed in an oblique-supine position, such that the lower ribs were not interposed between shockwave applicator and target. Possible interference of lung tissue with the shockwave path was avoided by angling away the long axis of the shockwave field as far as possible from the bases of the lungs. All animals were exposed to 1500 shockwaves (maximum generator power; 60-120 shockwaves/min). Chest radiographs, ultrasound examinations (Siemens Sonoline XM; 5 MHz sector-scanner) of the gallbladder and liver, and blood samples for chemistry and hematology profiles were obtained before, immediately after, and 1 week after ESWL. Post-ESWL results were compared to pre-ESWL baseline values, each animal serving as its own

control. All pigs were killed one week after treatment.

Adjuvant Contact Dissolution

From each couple, one pig was adjuvantly treated with MTBE immediately following lithotripsy, the other pig was not. Gallbladder access was obtained by ultrasound-guided transhepatic puncture of the gallbladder with a 22-gauge needle. After insertion of a guide wire, the needle was removed and replaced by a 6-French polyethylene pigtail catheter, positioned in the gallbladder fundus. After complete aspiration of the content of the gallbladder, 10 to 50 ml (mean, 26.8) contrast was injected to rule out leakage and to determine the overflow volume by fluoroscopy. Over a 2-hour period continuously volumes of 4 to 18 ml (mean, 8.5) MTBE were manually instilled, left in the gallbladder for 11-17 min (mean, 13.2) and then evacuated and replaced by a fresh amount of MTBE. Finally the gallbladder was rinsed with saline and the catheter removed. At the end of the procedure blood samples were obtained for laboratory examinations.

Assessment of Tissue Damage and Efficacy

At autopsy the lungs were inflated with air (to differentiate superficial hemorrhages from postmortem blood stasis) before resection, thereafter fixed with 10% buffered formalin. The liver, gallbladder, common bile duct, duodenum, and pancreas were resected en bloc. Tissue specimens were taken from designated areas for light microscopy, which was performed by a pathologist who was unaware of the assigned experimental conditions.

To achieve a comparative qualitative analysis of local tissue injury, the presence/absence of predefined microscopic tissue damage parameters was scored. For individual organs, the positive scores (presence of tissue change) were added up and divided by the total number of possible scores to calculate cumulative tissue damage indices. Similarly, overall cumulative tissue damage indices were calculated for the distinct treatment regimens.

To evaluate the effectiveness of lithotripsy, the total weight and maximum diameters of the fragments recovered from the gallbladder at autopsy were measured. Fragmentation was considered to be "adequate" when none of the fragments measured more than 5 mm in its largest diameter, and "unsatisfactory" if at least one particle was

larger than 5 mm.

The study protocol was approved by the Committee on Animal Research of the Erasmus University Rotterdam.

Data Analysis

Statistical evaluation of the laboratory data and stone characteristics was performed by the Mann-Whitney U-test. Histologic data were compared with the Chi-square test. The differences were considered to be statistically significant when the p value was less than 0.05.

Results

Stone Characteristics

The stones implanted in the pigs treated by combined ESWL and MTBE *versus* ESWL alone had a median weight and diameter of 270 mg (range: 102-425) and 11 mm (range: 6-18) *versus* 315 mg (range: 144-1387) and 11 mm (range: 8-16), respectively. The weights and diameters of the stones implanted in the pigs of the MTBE(+) and MTBE(-) group were not significantly different.

Lithotripsy

During lithotripsy, obvious fragmentation of the stones did not occur in 3 out of 30 pigs, two of which had noncholesterol stones implanted. It could not be prevented that the shockwaves traversed lung tissue in one animal, while this was doubtful in 5 pigs. In contrast with pre-ESWL radiographs, chest x-rays made immediately after ESWL showed a posterobasal opacification in 14 pigs ($p < 0.001$). One week later, this abnormal radiographic finding was still present in four, and unknown (premature exitus) in one of these 14 pigs. Ultrasonography revealed a thickened gallbladder wall (>3 mm) in 3 MTBE-treated pigs one week after treatment, which was confirmed at sacrifice. Bile duct dilatation was not detected in any case. Immediately after ESWL, 19 of 30 pigs had petechial bleedings at the shockwave entry site, which were resolved already one week thereafter.

Adjuvant Contact Dissolution

Percutaneous catheter placement was accomplished without difficulties in all but 2 pigs, in which repeated punctures were needed. In one of these cases, minor leakage from the gallbladder was identified. This pig died 3 days after the treatment due to bile peritonitis caused by a perforated gallbladder. In 4 pigs the aspirate was slightly hemorrhagic, three of which appeared to have coagula in their gallbladders at autopsy. In one of these pigs the instilled volumes of MTBE could not be completely aspirated.

Laboratory Parameters

A slight transient elevation of aspartate-aminotransferase (AST) ($p < 0.01$) was found immediately after treatment which was restored one week thereafter. Hemolysis did not occur since values of free plasma hemoglobine were always < 0.05 mg/ml. Other laboratory parameters including hemoglobin, white blood cell count, alanine-amino-transferase (ALT), alkaline phosphatase, amylase, total bilirubin, and creatinine did not change either after ESWL or after contact dissolution.

Autopsy Findings

Table 1 summarizes the autopsy findings. The adhesions between liver and abdominal wall noted in almost all pigs are probably caused by the surgical stone implantation. In the pig that died prematurely due to perforation of the gallbladder, 2-3 l abdominal fluid associated with a severe peritonitis was present. After ESWL alone, minimal tissue changes were found whereas combined treatment of ESWL and MTBE resulted in increased injury of the gallbladder. The hemorrhages of the gallbladder and adjacent liver parenchyma were not beyond 5-10 mm in diameter. In 4 pigs, small pulmonary lesions (spots of red discoloration, ranging from < 5 mm up to 20x3 mm) were localized in the basal parts of the lower lobes of both lungs, but could not be identified conclusively as hemorrhages.

Microscopic Findings

In 16 of 30 pigs mild peribronchial inflammation was found. Focal pleural thickening or pleuritis was noted in 9 animals, and pleural fibrin exsudates of uncertain traumatic origin in 7 pigs. Tissue damage probably attributable to shockwaves was found in the basal parts of the lungs of 6 pigs, and included localized small (< 10 mm) subpleural

intra-alveolar hemorrhages or ferrous deposition (n=3), local pulmonary necrosis and fibrosis with endovasculitis and thrombosis (n=1), and intra-alveolar fibrin foci (n=2). Microscopic evidence of ESWL-induced pulmonary damage coincided with suspected interference of lung tissue with the shockwave transmission path during ESWL in only 1, with abnormal chest radiographs in 2, and with autopsy findings in 1 case, respectively.

Table 1. *Gross findings at autopsy one week after ESWL of gallbladder stones with / without adjuvant contact dissolution by MTBE in 30 pigs.*

Autopsy Findings	Treatment Regimen	
	MTBE (+) (n=15)	MTBE (-) (n=15)
intra-abdominal adhesions	15	10
intraperitoneal bile leakage[a]	1	-
(rests of) subcapsular hepatic hemorrhage	2	1
patchy white discoloration of liver adjacent to gallbladder	2	1
slight reddening of duodenum/papil of Vater	2	2
collapsed gallbladder[a]	2	-
perforated gallbladder[a]	1	-
blood clots within gallbladder	5	-
hemorrhage (remnants) of gallbladder wall[a]	6	-
(local) thickening of gallbladder wall	5	-
local erosion of gallbladder mucosa	3	-
pulmonary hemorrhages (?)	1	3
pulmonary abscesses	-	2

NOTE. Data are given as number of animals.
[a] findings in a pig that died 3 days after combined treatment with ESWL and MTBE.

Table 2 gives the positive scores of selected parameters of local microscopic tissue changes. ESWL-induced hepatic scarring was found in a zone of liver

parenchyma adjacent to the gallbladder. In 4 MTBE-treated pigs also puncture-related narrow tracks of scar tissue piercing from the hepatic capsule to the gallbladder were identified. In the gallbladder bed of 8 pigs of the MTBE(+) group, fibrinoid vessel wall necrosis, endovasculitis, and focal foreign-body giant cell reaction were found, which were detected in only 3 pigs of the MTBE(-) group. Typical gallbladder damage in the MTBE(+) group consisted of (resolving) small mural hemorrhages, local mucosal necrosis or ulcers with fibrin exsudates and fibroblast proliferation. The gallbladders of the MTBE(-) group showed no or less severe abnormalities, consisting of slight mucosal inflammation and varying degrees of denudation of the mucosa. In both groups of pigs, also mucosal denudation varying from 10% to 100% of the epithelial lining of the extrahepatic bile ducts was noted. This finding was associated with subepithelial basophilic stroma degeneration without or with only mild inflammatory changes, suggesting a mechanical more than a toxic origin. Mild duodenitis occurred more frequently in the MTBE(+) than in the MTBE(-) group. Microscopy of the pancreas did not reveal traumatic lesions.

The overall cumulative tissue damage indices for ESWL with *versus* without adjuvant contact dissolution therapy were 0.49 *versus* 0.39 ($p < 0.02$) (a higher index score signifies more damage). For the gallbladder, the respective indices were 0.62 *versus* 0.36 ($p < 0.01$), whereas for the other individual organs the cumulative tissue damage indices for the MTBE(+) group *versus* the MTBE(-) group did not significantly differ.

Efficacy

At autopsy multiple fragments were recovered from the gallbladder in 23, single fragments in 5, and no fragments in 2 out of 30 pigs. Assuming that in 2 of the 5 cases with a single stone remnant the original stone size may have been reduced only by contact dissolution, overall stone fragmentation was achieved in at least 28 (93%) of 30 pigs.

Stone fragmentation immediately following ESWL and one week thereafter was sonographically considered to be adequate in 18 (60%) and 20 (67%) pigs, unsatisfactory in 7 (23%) and 4 (13%) pigs, and undeterminable in 5 (17%) and 6 (20%) pigs, respectively. At autopsy, however, it was found that stone fragmentation was adequate in only 8 (27%) pigs. Three (MTBE-treated) pigs seemed to be stone-free at ultrasonography

Table 2. *Local microscopic tissue changes one week after ESWL of gallbladder stones with / without adjuvant contact dissolution by MTBE in 30 pigs.*

Microscopy Findings		Treatment Regimen MTBE (+)	MTBE (-)
Gallbladder			
	hemorrhage of gallbladder wall	4	0
	epithelial degeneration / desquamation	11	5
	cholecystitis	13	11
Liver			
	local hemorrhagic necrosis	1	0
	local scarring	11	9
	hepatocytic degeneration	5	2
	inflammation	9	10
	focal fibrosis	5	6
	vasculitis	5	1
	thrombosis	1	2
	epithelial degeneration / desquamation of minor biliary ducts	1	0
	cholangitis of minor biliary ducts	8	10
	hemorrhage of hepatic capsule	5	3
	thickening of hepatic capsule	13	15
Extrahepatic bile ducts			
	epithelial degeneration / desquamation	12	14
	cholangitis	14	8
Duodenum			
	epithelial degeneration / desquamation	2	4
	mucosal inflammation (slight)	13	4
	inflammation of papilla of Vater	7	8

NOTE. Data are given as number of animals.

one week after treatment, but the gallbladder of one of these pigs harboured 29 fragments <2 mm in diameter.

Table 3 gives the total weights of the residual fragments recovered from the gallbladder at autopsy, expressed as percentages of the original stone weights. Combined ESWL and contact dissolution with MTBE resulted in a 30% higher stone clearance than ESWL alone ($p<0.01$), whereas for pure cholesterol stones this difference even amounted to approximately 40% ($p<0.01$). Irrespective of treatment regimen, the stone weight, diameter, or cholesterol content did not affect the outcome.

Discussion

Initial animal studies suggested the feasibility of sequential shockwave treatment and MTBE dissolution of gallbladder stones.[23-25] To our knowledge, the contribution of post-ESWL contact dissolution with MTBE to the success of ESWL has not been defined thus far. Accordingly, in this study the efficacy and safety of ESWL alone as compared with ESWL combined with adjuvant MTBE dissolution were determined.

One week after ESWL of gallbladder stones using the Lithostar Plus (overhead module), practically no gross abnormalities were found corroborating observations of Malone et al.[26] In an animal experiment using the Lithostar (undertable shockwave generator), we observed gross hemorrhages of the gallbladder and adjacent liver in all pigs one day after ESWL, which were still present in half of the animals killed one week later.[27] It is thus reasonable that the Lithostar Plus induces less severe tissue effects than the Lithostar which is probably related to the optimized shockwave pressure profile of the Lithostar Plus.[21] This is also supported by the less pronounced laboratory changes and the fewer microscopic tissue changes found in this study compared to that observed in the aforementioned study with the Lithostar. However, the nature of the focal ESWL-induced lesions was equivalent in both studies and did not differ from findings reported by other study groups,[28-34] which have been extensively discussed elsewhere.[27]

The transient posterobasal opacification found on chest radiographs in almost half of the pigs indicate that the basal parts of the lungs had been localized in the shockwave transmission path. Nevertheless, microscopic lung changes probably

attributable to ESWL were found in only 6 pigs. Malone et al. also noted some increase in basal opacity on chest radiographs in 7 of 16 pigs.[26] This is related partly to the caudal extension of the pleural sinus in pigs. Furthermore, due to the relative small porcine thorax aperture, optimal focusing often requires coupling of the large shockwave applicator in a cranial direction. Therefore, findings of biliary lithotripsy in laboratory animals with regard to pulmonary damage cannot be extrapolated to humans.[26,27,35,36]

Table 3. *Efficacy of ESWL with / without adjuvant contact dissolution by MTBE of single human gallstones implanted into the gallbladder of 30 pigs.*

Stone Categories	Treatment Regimen	
	MTBE (+)	MTBE(-)
All stones	31(0-58)[n=15]	60(11-81)[n=15][a]
Weight:		
≤500 mg	27(0-56)[n=10]	56(11-75)[n=12][b]
>500 mg	32(16-58)[n=5]	61(59-81)[n=3][b]
Diameter:		
≤10 mm	23(0-56)[n=7]	60(11-75)[n=7]
>10 mm	31(0-58)[n=8]	60(34-81)[n=8][a]
Cholesterol:		
≤80 %	23(0-58)[n=11]	61(11-81)[n=11][a]
<80 %	50(4-56)[n=4]	55(29-66)[n=4]

NOTE. Data are expressed as median (range) percentage of original stone weight recovered from the gallbladder at autopsy. Weight ≤500 vs >500 mg: NS; diameter ≤10 vs > 10 mm: NS; and cholesterol ≥80 vs <80 %: NS.
[a] $p<0.01$; [b] $p<0.05$.

MTBE treatment following ESWL led to superimposed tissue damage as evidenced by the significantly higher overall cumulative tissue damage index. However, this additional tissue damage was confined primarily to the gallbladder and gallbladder bed as might be expected. Although a higher incidence of mild cholangitis and duodenitis was found in the MTBE-treated animals, yet the differences between

the cumulative tissue damage indices of both treatment regimens for the duodenum and extrahepatic bile ducts did not reach statistical significance. The MTBE-induced histopathologic findings in the present study correspond with that in other large animal studies where no ESWL, but only MTBE dissolution was applied.[37,38] Exposure to MTBE caused minimal hemorrhages and mild inflammatory changes of the mucosa of the gallbladder, and incidentally mild duodenitis in dogs.[37] Three to 5 days after MTBE exposure, superficial ulcerations of the gallbladder as well as inflammatory changes of the gallbladder wall, common bile duct, and duodenum were observed in pigs.[38] In rabbits, MTBE caused more severe tissue damage.[39] In humans, MTBE has been shown to cause mild acute inflammatory changes of the mucosa but no gross or histologic mucosal ulceration or scarring of the gallbladder wall.[40]

Data about the safety of combined ESWL and MTBE treatment are scarce. Immediately after treatment, Peine et al. found gross hemobilia on aspiration of the gallbladder, variable mucosal erythema, subserosal ecchymosis, and intraluminal clots in all of 9 dogs, but ESWL did not induce increased absorption of MTBE.[23] In dogs autopsied 1 week after therapy, no gross evidence of injury was detected.[24] Comparable results were obtained using a piezoelectric shockwave device.[25] In preliminary clinical studies with electrohydraulic lithotriptors, no evidence was found that predissolution stone fragmentation with ESWL predisposed the gallbladder to either mucosal damage by MTBE or increased absorption of MTBE.[18,41]

Using the same lithotriptor for an *in vitro* gallstone fragmentation study, we found after only 250 shockwaves (maximum generator output setting) an overall stone fragmentation rate of 95%, including an adequate fragmentation rate of 45%.[42] Irrespective of adjuvant treatment, a comparable overall stone fragmentation rate (93%) was achieved in the present study. In spite of the application of a six-fold higher number of shockwaves than applied *in vitro*, however, at autopsy the percentage of adequate fragmentation (27%) appeared to be considerably lower. Although this may be explained in part by differing stone populations, successful *in vivo* fragmentation apparently requires a much higher number of shockwaves than was chosen in this study. This is in agreement with clinical experience where up to 20 000 shockwaves have been applied to patients whose stones responded well to fragmentation.[43]

According to (repeated) ultrasonography, adequate stone fragmentation was achieved in at least 60% to 67%. This is strongly discrepant with the autopsy findings.

Thus it is reasonable that ultrasonography has limitations in assessing the outcome of biliary ESWL, questioning the value of reported success rates of clinical studies on gallstone lithotripsy. Recently, this shortcoming of ultrasonography and the implicit need for verification has also been recognized.[44,45]

Concerning chemical composition, the stone sets used in this study were representative for the population because the chemical composition of the stones met the distribution of cholesterol and pigment stones in western countries.[46,47] With regard to radiolucency the stones were unselected. It is therefore plausible that also radiopaque stones were included in this study, which are usually excluded from clinical biliary ESWL. Considering that opaque stones can contain six times more calcium than lucent stones,[48] the results of this study must be interpreted accordingly. Perhaps recent progress in the development of solvents for pigment stones may hold future improvements.[49,50]

In the present study, adjuvant contact dissolution with MTBE improved the results of biliary ESWL by 30% to 40%. It must be emphasized that at variance with clinical studies[5,18] MTBE was administered for only 2 hours post-ESWL, because it was not the aim of this study to achieve a complete stone clearance but to demonstrate the value of adjuvant MTBE dissolution. It is conceivable that the results can be further improved when adjuvant contact dissolution therapy will be prolonged and when a microprocessor assisted solvent transfer system will be used.[51]

For pure cholesterol stones the results of the MTBE(+) group were superior to that of the MTBE(-) group. The control group received only ESWL, but no catheter was placed in the gallbladder and no flushing with saline was applied. One could argue that the flushing and the changing of the fluid caused stone fragments to migrate through the biliary ducts. The finding that for noncholesterol stones adjuvant MTBE dissolution did not significantly enhance the results of ESWL, makes it likely that the observed differences in fragment clearance are caused to the action of MTBE itself and not by the instillation and flushing of the fluids through the gallbladder.

In conclusion, treatment of solitary gallbladder stones by ESWL caused only minor tissue effects in pigs. Adjuvant MTBE treatment led to a more extensive damage of the gallbladder without evidence of systemic side effects. MTBE dissolution during a short period was shown to improve significantly the results of ESWL. Nevertheless, these data warrant further clinical studies to evaluate the potential

efficacy, safety, and cost-effectiveness of combined lithotripsy and contact dissolution as a nonsurgical alternative for the treatment of symptomatic cholecystolithiasis.

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CHAPTER 9

General Discussion

Currently a variety of both operative and nonoperative treatment modalities are available for the management of symptomatic gallbladder stones.

Chemical dissolution of gallbladder stones with bile desaturating agents as monotherapy is restricted to patients with a limited number of small (< 10 mm) cholesterol stones in a functioning gallbladder.[1-3] The single use of chenodeoxycholic acid (CDC) causes moderate liver test abnormalities, minor increases in serum LDL-cholesterol, and diarrhea in a considerable number of patients. These adverse effects do not occur as a result of treatment with ursodeoxycholic acid (UDC). The combination of CDC and UDC is preferable, because concomitant administration of UDC offsets CDC toxity and the combination is more effective than either as a single bile acid.[4,5] However, oral dissolution therapy is expensive and must be continued for at least six months to several years, whereas complete dissolution is achieved in only 30% to 60% of patients. Besides, the chance of recurrent stone formation within five years after discontinuation of therapy is about 50%; this is a significant drawback of chemical dissolution of gallstones.[6-8]

Topical dissolution of cholesterol gallstones can be accomplished with methyl tert-butyl ether (MTBE) instilled into the gallbladder through a percutaneous transhepatic catheter.[9,10] This procedure can be carried out under local anesthesia. Potential side-effects include nausea, pain, sedation, acute duodenitis, intravascular hemolysis, and foul breath. By using an automatic pump system precluding overflow of bile and MTBE from the gallbladder into the common bile duct, these adverse effects might be prevented.[11] MTBE is a very powerful lipid solvent and there are no limitations to size and number of stones for successful dissolution. Nevertheless, the procedure is time-consuming, technically demanding and, because MTBE is flammable and potentially explosive, not without hazards.

Various percutaneous interventional techniques enable gallbladder drainage and mechanical stone extraction from the gallbladder with a high success rate and few complications.[12-17] Stones too large to be extracted can firstly be fragmented by different methods of intracorporeal mechanical or contact lithotripsy. When these procedures can be carried out under local anesthesia, thus avoiding general

anesthesia, these approaches are of importance for selected patients with poor operative risks due to advanced age or multiple coexisting diseases. Permanent defunctionalization of the gallbladder by percutaneous instillation of sclerosing agents to prevent gallstone recurrence - which is to be expected after any form of treatment that leaves the functioning gallbladder in place - has been disappointing.[18-20]

Significant cost savings can be realized using modified operative techniques ("mini-cholecystectomy"), allowing patients to be discharged on the first or second postoperative day.[21,22] In selected high-risk patients with complicated cholelithiasis, the combination of surgical minicholecystostomy and radiologic stone extraction may be a safe and effective option.[23] Recently, laparoscopic techniques have been introduced.[24,25] Although its definite place remains to be settled, laparoscopic cholecystectomy will probably become the standard form of therapy for symptomatic cholecystolithiasis.[26] Nonetheless, laparoscopic cholecystectomy is a medium-sized surgical procedure, requiring general anesthesia and carrying with it risks similar to or even higher than those of conventional cholecystectomy.[27] Especially the risk of bile duct injury during laparoscopic cholecystectomy is higher than during "open" cholecystectomy.

From 1985 extracorporeal shockwave lithotripsy (ESWL) is emerging worldwide as a completely noninvasive treatment modality of gallstone disease.[28-30] In combination with oral chemolitholysis it has been shown that ESWL is effective with few adverse events and no mortality thus far.[31-35] Unless repeated treatment sessions with a very high total number of shockwaves are performed,[36] chemical dissolution therapy is a critical addition to ESWL with regard to fragment clearance.[35,37] Only 15% to 30% of patients with symptomatic gallstones are considered to be eligible for combined ESWL and oral bile acid dissolution therapy.[31,38,39] Preliminary reports, however, suggest that the currently accepted entry criteria underestimate the number of patients suitable for this form of therapy.[40,41] Nevertheless, it is unclear yet that with increasing experience and technical and medical improvements the eligibility criteria can be further extended, while maintaining acceptable clinical results. Notwithstanding its noninvasiveness, one group of investigators claimed that gallstone lithotripsy is four times as expensive as elective cholecystectomy.[42] The long-term costs associated with

ESWL may exceed those of surgical treatment.[43] Rational utilization of ESWL for the treatment of gallbladder stones therefore requires critical evaluation with particular reference to symptom relief, long-term outcome and cost-effectiveness.[44] Medical technology assessment (MTA) is the instrument by which this new technology can be compared with conventional or laparoscopic cholecystectomy.

Because MTA can best be performed by using the principle of a randomized, controlled clinical trial,[45,46] the ROGAL study (Rotterdam Multicenter Gallstone Study) was started.[47-49] In this randomized trial the cost-effectiveness and health status outcomes after ESWL followed by oral bile acid therapy are compared with those after cholecystectomy in patients with symptomatic gallstones.

The studies described in this thesis afford experimental evidence of the efficacy and safety of the electromagnetic shockwave sources employed in the Lithostar and the Lithostar Plus (overhead module) for the treatment of gallbladder stones. Because of the sonographic stone targeting equipment, the Lithostar Plus (overhead module) is preferable for (radiolucent) gallbladder stone lithotripsy over the Lithostar which applies fluoroscopic target imaging. Moreover, compared to the Lithostar the shockwave pressure profile of the Lithostar Plus (overhead module) is more appropriate to minimize the chance of ESWL-induced tissue damage.

These data sustain the clinical studies which are undertaken in our institution to validate the applicability of ESWL with the Siemens lithotripsy system, and to analyze the role of this noninvasive treatment in the management of symptomatic gallbladder stones by the on-going randomized ROGAL study.[47-49]

Finally, a few words should be devoted to the future use of extracorporeal shockwave treatment in humans. Apart from the use of ESWL for the treatment of urinary and gallbladder stones, ESWL has been successfully applied for the treatment of common bile duct stones,[50] pancreatic stones,[51] and salivary stones.[52] It has been demonstrated that shockwaves can interfere with the normal pattern of tumor cell proliferation, opening new eras for research in cancer treatment.[53,54] Quite interesting is the experimental application of extracorporeal shockwaves in orthopedics[55] and in the

management of pseudarthrosis.[56,57] Shockwaves as a new physical principle have broadened the surgical armamentarium. To search for other possible applications of shockwaves in medicine remains challenging.

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SUMMARY

The objective of this study was to determine the physical characteristics and biological effects of the lithotriptor to enhance further clinical studies on the role of ESWL in the treatment of symptomatic cholelithiasis, using a newly developed electromagnetic lithotripsy system.

Chapter 2 reviews the implications of preliminary experimental and clinical studies, on the basis of which data the possibilities and limitations of ESWL for the management of gallstone disease are discussed.

Chapter 3 reports on the results of *in vitro* assessment of shockwave pressure profiles of the electromagnetic lithotriptor to obtain a better understanding of the mechanism of operation and the potential risks associated with ESWL. Maximum positive pressure (p^+) in the focus of the Lithostar Plus (overhead module) was twice as high as that of the Lithostar. At maximum generator power setting, the focal zone of the Lithostar had a length of 95 mm and a width of 9 mm. The equivalent values for the Lithostar Plus (overhead module) were 40 mm and 3 mm, respectively. In clinical use, the Lithostar Plus (overhead module) is supposed to cause less tissue damage in surrounding structures due to the optimized focal geometry.

Chapter 4 gives data on *in vivo* measurements of shockwave pressures using the Lithostar in pigs, some of which had human gallstones surgically implanted into the gallbladder. The *in vivo* values were compared with *in vitro* data presented in Chapter 3. Pressures obtained *in vivo* were always 15% to 25% lower than those measured *in vitro* but the spatial distributions of the positive pressure *in vivo* and *in vitro* were almost identical. It is concluded that different types of lithotriptors can be characterized by *in vitro* shockwave pressure profile measurements. These findings indicate that animal experiments for that reason can be substituted by *in vitro* experiments, obviating the need to use animals.

Chapter 5 focuses on the short-term and long-term effects of biliary ESWL studied in pigs, using the Lithostar. The animals were killed either one day, one week, or one year after treatment. Post-ESWL, only minimal focal tissue damage was found which was largely reversed within one week after treatment. After one year, only small

hepatic scars were found as permanent damage. Stone fragmentation occurred in 86% of pigs, and was adequate (fragments ≤5 mm) in 41%. Because the energy output of the Lithostar also has been assessed (Chapters 3 and 4), this study can serve as a reference model from which potential ESWL-induced tissue damage of any type of lithotriptor with a comparable energy output can be extrapolated.

Chapter 6 describes the *in vitro* efficacy of electromagnetic gallstone fragmentation using the Lithostar Plus (overhead module) under various treatment regimens. Overall, 81% of the stones fragmented, including 55% adequately (fragments ≤5 mm). The relationship between chemical stone composition, CT characteristics, and fragmentation results were systematically examined. High correlations between mean CT attenuation numbers (Hounsfield Units) and either cholesterol or calcium content were found. Using a cut-off point of 110 HU, pure cholesterol (≥80% cholesterol) and noncholesterol stones could be discriminated by CT with an overall accuracy of 95%.

Chapter 7 deals with the problem that ESWL of gallbladder stones leaves residual fragments that need to be dissolved by chemical solvents. *In vitro*, the gallstone dissolving capacity of MTBE, mono-octanoin, limonene, and a limonene/mono-octanoin mixture were compared in relation to the chemical stone composition. MTBE dissolved cholesterol gallstones 100 times faster than mono-octanoin and 10 times faster than limonene or the limonene/mono-octanoin mixture. The combination of limonene and mono-octanoin was as effective as limonene alone. Of the four solvents, MTBE is the most effective to dissolve residual fragments after ESWL treatment of gallbladder stones (Chapter 8).

Chapter 8 presents the results of sequential treatment of gallbladder stones with ESWL using the Lithostar Plus (overhead module) and percutaneous contact dissolution by MTBE in the pig model. Adjuvant MTBE dissolution during only 2 hours immediately following ESWL improved the final results by 30% to 40%, causing only minor tissue effects; these were not considered to be clinically relevant. For noncholesterol stones, adjuvant MTBE treatment did not significantly enhance the results of ESWL.

Chapter 9 discusses the scope of the present study with regard to current concepts in the management of cholecystolithiasis.

SAMENVATTING

Deze studie had tot doel de fysische karakteristieken en de biologische effecten van de lithotriptor te bepalen, als basis voor verder klinisch onderzoek naar de betekenis van ESWL voor de behandeling van symptomatisch galsteenlijden. Hierbij werd gebruik gemaakt van een onlangs ontwikkeld elektromagnetisch lithotripsie systeem.

Hoofdstuk 2 geeft een overzicht van initiële experimentele en klinische studies, aan de hand waarvan de mogelijkheden en de beperkingen van ESWL voor de behandeling van galsteenziekte worden besproken.

Hoofdstuk 3 beschrijft de resultaten van een *in vitro* onderzoek, waarin de schokgolf-drukprofielen van de elektromagnetische lithotriptor werden bepaald om een beter inzicht te verkrijgen in het werkingsmechanisme en de potentiële risico's van ESWL. De maximale positieve druk (p^+) in het focus van de Lithostar Plus ("overhead module") was twee maal zo hoog als die van de Lithostar. Bij een maximaal generator vermogen bedroeg de lengte respectievelijk de breedte van de focale zone van de Lithostar 95 mm en 9 mm. De overeenkomstige afmetingen van de focale zone van de Lithostar Plus ("overhead module") waren 40 mm en 3 mm. Op grond van een meer optimale focale geometrie werd verondersteld dat de Lithostar Plus ("overhead module") bij klinisch gebruik minder schade aan de omgevende structuren zal veroorzaken.

Hoofdstuk 4 geeft informatie over *in vivo* metingen van schokgolfdrukken, gegenereerd in varkens door de Lithostar. Bij een aantal dieren werden menselijke galstenen operatief in de galblaas geïmplanteerd. De *in vivo* waarden werden vergeleken met de *in vitro* waarden die in Hoofdstuk 3 werden gepresenteerd. *In vivo* waren de drukken altijd 15% tot 25% lager dan *in vitro*, maar de ruimtelijke verdeling van de positieve druk was *in vivo* bijna identiek aan die *in vitro*. Geconcludeerd werd dat verschillende lithotriptor types gekarakteriseerd kunnen worden door *in vitro* meting van het schokgolfdrukprofiel. Deze bevinding impliceert dat dierexperimenten voor dat doel vervangen kunnen worden door *in vitro* experimenten, waardoor het gebruik van proefdieren overbodig wordt.

Hoofdstuk 5 richt zich op de korte- en lange-termijn effecten van biliaire ESWL,

hetgeen werd bestudeerd in varkens die werden behandeld met de Lithostar. De dieren werden na een dag, na een week, of na een jaar na behandeling afgemaakt. Na ESWL werd alleen minimale weefselschade vastgesteld, die na een week grotendeels hersteld bleek te zijn. Als permanente weefselschade werden een jaar na behandeling alleen kleine littekens in de lever gevonden. Steenfragmentatie vond plaats in 86% van de varkens, adequate vergruizing (fragmenten $\leq$5 mm) vond plaats in 41%. Omdat de energie "output" van de Lithostar eveneeens werd vastgesteld (Hoofdstukken 3 en 4) kan deze studie gebruikt worden als referentie model; de potentiële weefselschade veroorzaakt door een gegeven lithotriptor met een vergelijkbare energie "output" kan hiervan worden geëxtrapoleerd.

Hoofdstuk 6 beschrijft een *in vitro* experiment waarin de effectiviteit van electromagnetische galsteenvergruizing van verschillende behandelingsregimes met de Lithostar Plus ("overhead module") werd bepaald. In het totaal werd 81% van de stenen vergruisd, waarvan 55% adequaat (fragmenten $\leq$5 mm). De relatie tussen de chemische samenstelling van de stenen, bepaalde karakteristieke bevindingen bij computertomografie, en de fragmentatie resultaten werden systematisch onderzocht. Tussen gemiddelde CT getallen (Hounsfield Units) en zowel het cholesterol als calcium gehalte van de stenen bestonden sterke correlaties. Met een "cut-off" punt van 110 HU konden met behulp van computertomografie pure cholesterol stenen ($\geq$80% cholesterol) en "noncholesterol" stenen van elkaar worden onderscheiden met een accuratesse van 95%.

Hoofdstuk 7 heeft betrekking op het probleem dat na ESWL van galblaasstenen fragmenten overblijven die met chemische oplosmiddelen moeten worden opgelost. *In vitro* werd het galsteenoplossend vermogen van MTBE, mono-octanoin, limonene, en een mengsel van limonene en mono-octanoin vergeleken in relatie tot de chemische samenstelling van de steen. Met behulp van MTBE konden cholesterol galstenen 100 keer sneller worden opgelost dan met mono-octanoin, en 10 keer sneller dan met limonene of met het limonene/mono-octanoin mengsel. De combinatie van limonene en mono-octanoin was even effectief als limonene alleen. Van de vier oplosmiddelen is MTBE het meest effectief om steenfragmenten die onstaan na ESWL van galblaasstenen op te lossen (Hoofdstuk 8).

Hoofdstuk 8 geeft de resultaten weer van een dierexperiment met varkens waarin galblaasstenen sequentieel werden behandeld met ESWL, met gebruikmaking van de Lithostar Plus ("overhead module"), en met het percutaan toegediend oplosmiddel MTBE. Aanvullende behandeling met MTBE gedurende twee uur direkt in aansluiting op ESWL verbeterde de resultaten met 30% tot 40%, terwijl hierdoor slechts minimale weefsel effecten werden veroorzaakt; deze afwijkingen werden niet als klinisch relevant beschouwd. Voor "noncholesterol" stenen werden de resultaten van ESWL door aanvullende behandeling met MTBE niet significant verbeterd.

Hoofdstuk 9 bespreekt de strekking van de huidige studie met betrekking tot hedendaagse concepten voor de behandeling van galblaassteenlijden.

ABBREVIATIONS

ALT	alanine-aminotranferase
AST	aspartate-aminotransferase
CDC	chenodeoxycholic acid
CT	computed tomography
ESWL	extracorporeal shock wave lithotripsy
HAS	hematoxylin, azaphloxin, saffron
HU	Hounsfield Unit
kV	kilovolt
LDH	lactate dehydrogenase
MHz	megahertz
mJ	milli-joule
MPa	megapascal
MTA	medical technology assessment
MTBE	methyl tert-butyl ether
p^+	positive pressure
p^-	negative pressure
Pa	pascal
PVDF	polyvinylidene fluoride
UDC	ursodeoxycholic acid
v^+	positive voltage
v^-	negative voltage
WBC	white blood cell count

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