Clinical trial

Tissue reactions under piezoelectric shockwave application for the fragmentation of biliary calculi

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SUMMARY  The tissue reactions that occurred during piezoelectric shockwaves for the fragmentation of biliary calculi were investigated in 10 surgically removed stone containing human gall bladders and in acute (six dogs) and chronic (six dogs) animal experiments. Before and after shockwave (500, 1500 or 3000) in the anaesthetised dogs, computed tomography (CT), magnetic imaging (MRI) and laboratory tests were done; treatment was carried out under continuous ultrasonographic control. Shockwave application to the human gall bladders resulted in disintegration of the stones with no macroscopically or microscopically detectable tissue changes. In acute animal experiments, small haematomas were observed in all six animals at surfaces, but also inside the liver and gall bladder (max diameter 25 mm). Perforation or intra-abdominal or pleural bleeding did not occur. In chronic experiments, no macroscopic, and only slight microscopic residual lesions (haemosiderin deposits) were seen three weeks after shockwave. In almost all instances, the lesions were detected by CT, MRI, and ultrasonography, while laboratory tests were negative.

Non-surgical procedures for the treatment of cholecystolithiasis must be measured against the effectiveness of cholecystectomy and its low morbidity (7%) and mortality (0-4%) rates.1 In contrast with oral chemolitholysis alone, extracorporeal shockwave lithotripsy in combination with chemolitholytic post-treatment, appears to be a promising alternative to cholecystectomy in selected patients.2 Sauerbruch et al adapted a kidney stone lithotripter that worked on the basis of the high voltage spark gap discharge principle to the requirements of the biliary system, and reported a 78% stone free rate in patients with solitary stones (up to 20 mm) after four to eight months.3

Using a new type of lithotripter that generates shockwaves using the piezoelectric principle, we have been able to show that gall stones can be disintegrated reliably and reproducibly.4,5 The present paper describes the preliminary studies necessary before clinical application, on possible tissue interactions induced by piezoelectric shockwave application in vitro using human gall bladders, and in vivo in acute and chronic experiments with animals.

Methods

PIEZOELECTRIC LITHOTRIPTER

A piezoelectric lithotripter manufactured by R Wolf, Inc, Federal Republic of Germany (Piezolith 2200) was used. The shockwaves are generated by a self-focusing piezoelectric acoustic generator that has a bowl shaped configuration and bears a mosaic of more than 3000 ceramic elements on its concave surface. The focus area is 10×5 mm (manufacturer’s data). During treatment, the patient is positioned, prone, over the ‘bowl’ of the acoustic generator, which is filled with degassed water (Fig. 1). The calculus is located ultrasonographically in two planes with the aid of an ultrasonic transducer integrated in
the axis of the acoustic generator ‘bowl’. The pulse sequence can be varied in four steps from 1 to 2.5 Hz: the energy per discharge can be selected from among four settings, the pressure in the shockwave focal area varies between 400 and 1100 bar, depending upon the selected pulse energy.

**IN VITRO STUDIES ON HUMAN MATERIAL**
Ten stone filled gall bladders were submitted to shockwave treatment immediately after surgical removal. The gall bladder was put into a latex condom, which was then suspended in such a manner that the fundus of the gall bladder was located within the ‘shockwave focus’ of the lithotripter. Between 1000 and 4000 shockwaves were applied (intensity setting 4, frequency setting 3). Thereafter, the gall bladder was opened by the pathologist and examined for macroscopic lesions and, subsequently, after fixation in formalin and staining with haematoxylin and eosin, under the light microscope, for possible morphological changes.

**IN VIVO EXPERIMENTS IN ANIMALS**
In acute experiments, six mongrel dogs (weight range: 25–30 kg) were anaesthetised with thiopental sodium (Trapanal®) and then, under ultrasonographic control, positioned in the shockwave focal area of the lithotripter in such a manner that piezoelectric shockwaves could be applied sequentially to the gall bladder, the right lobe of the liver, the spleen, the abdomen (bowel) and the lungs. The number of shockwave discharges applied to each animal was either 500, 1500 or 3000. The entire experiment was controlled by continuous ultrasonography. Two to four hours after conclusion of the experiments, the animals were killed with an overdose of the anaesthetic and immediately autopsied. Tissue samples were obtained from the liver, gall bladder, spleen, small and large bowels, pancreas and lungs for histological evaluation.

A total of six dogs were used for the chronic studies, two further dogs serving as controls. After ultrasonographic location of the gall bladder, it was positioned within the area of the shockwave focus and 500, 1500 or 3000 shockwaves applied. Before, and on days 1, 2, 3, 7, 14, and 21 after shockwave application, the following laboratory parameters were analysed: alkaline phosphatase, gamma-GT, GOT, GPT, GLDH, alpha-amylase, and lipase. In addition, before and after shockwave application, CT and MRI studies of the upper abdominal region were carried out. For the rest, the study was of the same design as in the case of the acute experiments. The control animals were merely anaesthetised with Trapanal, and their laboratory parameters analysed.

**Results**

**IN VITRO EXPERIMENTS**
The application of shockwaves (1000–4000 discharges) to freshly surgically removed human gall bladders failed to induce any macroscopic or light microscopic histological changes in the wall of the gall bladder.

**ANIMAL EXPERIMENTS**

**Ultrasonography, CT, MRI. laboratory parameters**
In two of 12 dogs, ultrasonography during shockwave application revealed inhomogeneous, in part echogenic, in part echo poor, lesions in the wall of the gall bladder having a maximum size of 23×11 mm. Computerised tomography and the magnetic resonance image obtained after shockwave application confirmed these findings, and a haematoma in the region of the gall bladder wall was suspected (Figs 2–4). Each of the animals had received 1500 shockwave discharges.

In a further four animals, ultrasonography during treatment revealed echogenic formations of approximately 0.5–1 cm in size, which were pulsatile and drop like and which moved from the gall bladder wall into the gall bladder lumen, where they disappeared. In common with the haematomas, these phenomena occurred after 300 to 700 shockwave discharges. In a single animal, the MR image obtained after shockwave application revealed a decrease in signal intensity in the area of the wall of the gall bladder, which was interpreted as a possible perifocal oedema.

In none of the six animals of the chronic study was any significant rise of the laboratory parameters investigated seen.

**Pathology**

Autopsy of the animals of the acute study revealed a
uniform picture: all the organs to which shockwaves had been applied directly, revealed subcapsular haematomas (Fig. 5). Perforations (pneumoperitoneum, pneumothorax) or intra-abdominal or pleural bleedings were not observed. The suspected diagnosis of haematoma in the region of the gall bladder wall made \textit{intra vitam} on the basis of the imaging procedures in two cases, was confirmed (Fig. 6). The lesions were found to be haematomas of the gall bladder wall measuring $11 \times 7 \times 10$ mm and $25 \times 10 \times 6$ mm, respectively. The gall bladder epithelium was intact. In the remaining four animals of the acute study, macroscopic inspection revealed merely minimal bleeding in the region of the bed of the gall bladder. Coagula indicating haemorrhage into the gall bladder were not to be seen. No correlation was recognised between the size of the haematomas and the number of shockwaves applied.

Histologically, in addition to the known subcapsular haemorrhages, small bleeds within the individual organs (liver, spleen, lungs) were also observed (Fig. 7). No ruptured arterial or venous vessels were seen however. In the region of the haematomas microscopic inspection showed occasional tiny venous thrombi and, to a small extent, spots of necrosis in the liver parenchyma. In one of the six animals, the gall bladder epithelium revealed slight changes, in the remaining five, its integrity remained unimpaired. The suspected perifocal oedema in the region of the gall bladder, observed in one of the animals \textit{intra vitam} in the MR image, was confirmed. Slight oedema affecting the wall of the gall bladder was also found in two further animals.

In the animals of the chronic study, autopsied three weeks after shockwave application and submitted to a macroscopic and microscopic inspection, no noteworthy lesions of the liver or gall bladder were observed. Merely with the aid of special staining (Berlin blue), were scattered haemosiderin deposits demonstrated, possibly representing posthaemorrhage residues (Fig. 7). No scarring was observed in the region of the gall bladder wall.

Discussion
While the application of up to 4000 shockwave discharges to the fresh, surgically removed human gall bladders produced no light microscopically detectable morphological changes in the gall bladder wall, \textit{in vivo}, discharge rates of only 500 already gave rise to unequivocal organic lesions. In common with the microscopic findings in the human gall bladders (\textit{in vitro}), however, no noteworthy destruction of parenchymal tissue was observed in the perfused animal organs: all the lesions induced by piezoelectric shockwave application were bleeds in the region of 'interfaces' – for example, subcapsular,
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Fig. 5 Subscapular liver haematomas after the application of 500 shockwaves (max 23×12 mm).

Fig. 6 Haematoma in the wall of the gall bladder (11×7×10 mm), suspected on ultrasonography, CT and MRI (haematoxylin and eosin, natural size).

Fig. 7 Haematoma within the liver (region of the periportal field) (haematoxylin and eosin).

Fig. 8 Positive Berlin blue reaction in the region of the periportal field three weeks after shockwave application (1500 pulses) (haematoxylin and eosin).

portal fields of the liver, bed of the gall bladder, pulmonary alveoli. Histologically, no definitive signs of ruptured small vessels, or destroyed capillaries were to be seen. This finding is in agreement with the histological studies done by Delius et al after the application of shockwaves to pulmonary parenchyma. Pathophysiologically, it is conceivable that the bleeding lesions are pressure induced diapedetic haemorrhages. Oedema in the periphery of the shockwave focal area, demonstrated histologically and by MRI, are readily compatible with this hypothesis. Corresponding to the morphological findings, in the absence of relevant destruction of organ specific cells (hepatocytes), no significant rise of such typical liver biochemical parameters as GLDH, GOT or GPT occurred. The actual physical mechanisms underlying the tissue damage have, however, not yet been finally established. The most likely candidate are the cavitation effects that occur with all forms of shockwave application.

When the gall bladder was in the shockwave focal area, minor bleeds into the bed of the gall bladder regularly occurred, while in two cases largish gall bladder wall haematomas were observed. Of interest for the possible clinical application of the technique is the fact that continuous ultrasonographic monitoring during shockwave application permits the detection of relevant bleeding into the gall bladder wall. Computed tomography and MRI were able to confirm this finding. Whether the ultrasonographic observations of pulsatile echogenic formations which, drop-like, moved from the wall of the gall bladder into the gall bladder lumen, and which occurred already after 300 to 700 discharges, represent bleeding into the gall bladder cannot be definitively established. To clarify this point, special studies of the bile, erythrocyte labelling with radioactive markers, or the investigation of the stools for occult blood, would have to be carried out. A careful macroscopic and microscopic evaluation of the structures surrounding the gall bladder – small bowel, pancreas, common bile duct, and large blood vessels – revealed no pathological changes. This applies in particular also to the distal parts of the lungs, which, in view of the typical
anatomical position of the gall bladder in the dog – directly beneath the diaphragm – were also within the area of shockwave application. In contrast, Brendel et al, using the lithotripter using the high voltage spark gap discharge principle (Dornier system) observed bleeds in the region of the alveoli in these parts of the lungs.8

On the basis of our in vitro experiments, the number of shockwaves applied was selected within the range 500 to 3000. Depending upon the volume, weight and diameter of the stones, but independently of their chemical composition, ‘therapeutically appropriate’ fragmentation was achieved with this pulse range.9

We were unable to find any correlation between the size of the haematoma and the number of shockwaves applied (500 – 1500 – 3000). This is at variance with the observations made by Delius, who, however, used a spark gap discharge type lithotripter, and studied the effect of the shockwaves on kidney parenchyma.6 Nor did we see any destruction with necrosis of the alveolar structure – even after direct application of the shockwaves to the upper fields.6 Under the light microscope, merely intra-alveolar haemorrhages with a largely preserved alveolar architecture were observed.

Further comparisons of tissue reactions, especially in liver, gall bladder and pancreas, induced by shockwaves generated in accordance with the spark gap discharge principle, would be desirable, but, at the present time, are not possible owing to a dearth of reported animal experimental data.10

In the reports by Sauerbruch et al on the use of the spark gap discharge lithotripter system in patients, no mention is made of definitive ultrasonographic, computerised tomographic or biochemical evidence of injuries in the region of the liver/biliary system. On the other hand, in individual cases, cutaneous bleeding and haematuria have been reported, which may well indicate possible traumaisation during shockwave application.23

The role of the different sizes of the shockwave focal area of the two systems’ (piezoelectric focus < spark gap discharge focus), and the consequent difference in the level of the energy transfer (piezoelectric energy < spark gap discharge energy) in the traumaisation of the tissue should be studied in comparative investigations. Apart from the smaller shockwave focus and the reduction in the amount of energy applied, the fact that – in contrast with the spark gap principle – piezoelectric shockwaves in the true sense are generated only in the region close to the focus as a result of the summation of all the piezoelectric waves applied, would appear to be responsible for the pain free nature of the procedure.11 On the other hand, the restriction of the high pressure developed to a smaller focus area than in the case of the spark gap discharge principle means that a larger number of pulses are required for ‘therapeutically appropriate’ fragmentation (≤ 4 mm).11

On the basis of these data obtained in in vitro experiments, we selected – at the maximum energy setting (step 4) – a three to four times larger number of pulses than so far reported in animal experiments with the spark gap discharge principle.8

The results of our experiments on animals show that the application of shockwaves in man should not be used unreservedly. Patients who have a high bleeding risk, in particular, however, patients with severe diseases of the liver – for example, cirrhosis, might have to be excluded from such treatment. Of fundamental significance with respect to the possible clinical application of piezoelectric lithotripsy for gall stone disintegration, however, is the fact that neither intra-abdominal or pleural bleeds, nor perforations (pneumoperitoneum, pneumothorax) were observed in any of the 12 animals investigated. The observation that acute lesions were virtually completely healed within three weeks, would seem to indicate that the clinical application of piezoelectric lithotripsy in man would be justifiable. Continuous ultrasonographic monitoring during lithotripsy represents an additional safety aspect, as it permits the immediate detection of any possible bleeding in the region of the gall bladder.

A preliminary report of a part of this study was presented at the Spring Meeting of the British Society of Gastroenterology, held in Leicester on March 23–25, 1988.

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