Review on Lithotripsy and Cavitation in Urinary Stone Therapy

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(Clinical Application Review)

***Abstract*—Cavitation is the sudden formation of vapor bubbles or voids in liquid media and occurs after rapid changes in pressure as a consequence of mechanical forces. It is mostly an undesirable phenomenon. Although the elimination of cavitation is a major topic in the study of fluid dynamics, its destructive nature could be exploited for therapeutic applications. Ultrasonic and hydrodynamic sources are two main origins for generating cavitation. The purpose of this review is to give the reader a general idea about the formation of cavitation phenomenon and existing biomedical applications of ultrasonic and hydrodynamic cavitation. Because of the high number of the studies on ultrasound cavitation in the literature, the main focus of this review is placed on the lithotripsy techniques, which have been widely used for the treatment of urinary stones. Accordingly, cavitation phenomenon and its basic concepts are presented in Section II. The significance of the ultrasound cavitation in the urinary stone treatment is discussed in Section III in detail and hydrodynamic cavitation as an important alternative for the ultrasound cavitation is included in Section IV. Finally, side effects of using both ultrasound and hydrodynamic cavitation in biomedical applications are presented in Section V.**

***Index Terms*—Cavitation, histotripsy, hydrodynamic, shock wave, ultrasound.**

I. Introduction

THE PROPAGATION of an acoustic wave with the frequency from few tenths of kilohertz to several hundreds of megahertz refers to the term "ultrasound." In liquids, the propagation of longitudinal waves causes local oscillatory motions of particles around their initial positions, resulting in local changes in liquid pressure. Depending on the frequency, the level of acoustical energy and/or pressure can be targeted to the desired area, thereby enabling the use of ultrasound in therapeutic applications. Because of its ability to exert localized energy from surface of the skin into soft tissues, ultrasound has attracted much interest as a noninvasive and targeted therapeutic treatment [1].

According to the exposure conditions such as frequency, pressure, or duration, ultrasound can prompt thermal, acoustic radiation force, and cavitational effects, which are important parameters to improve therapeutic effectiveness of ultrasonic cavitation in various biomedical applications [2]–[5]. The release of energy by ultrasound leads to an increase in temperature, and in biomedicine; this can be increased from the absorption of the ultrasound waves by tissue, which could limit direct tissue damage but could be still sufficient for drug delivery in thermoresponsive carrier systems [6], [7]. Acoustic radiation force effects of ultrasound cause acoustic wave propagation through tissues [8]. This net force tends to push particles away from the ultrasound transducer, and thus, enhance diffusion of particles into tissue, which gives an advantage of the use of ultrasound treatment in solid tumors [2], [3]. Cavitational effects of ultrasound are provoked by acoustic excitation of microbubbles in the target tissue, and it is usually used to enhance contrast in diagnostic ultrasound imaging [4], [9], [10]. Because of its safety, low cost, and easy accessibility, ultrasound imaging has been one of the most popular medical diagnostic techniques [11]. In this technique, ultrasound contrast agents (UCA) such as lipid or polymer shells can be loaded within the microbubble or can be conjugated directly to the surface of the shell. These microbubbles are designed to collapse and release UCA within the target tissues under ultrasound-induced cavitation [12]–[15]. Today, there are many commercially available and biodegradable microbubbles, and importantly, they can be detected and mapped noninvasively using the conventional B-mode ultrasound [16]. During cavitation phenomenon, microbubbles respond to acoustic excitation in two different ways, namely, noninertial (stable) or inertial (transient) [17]. Noninertial cavitation is the process in which microbubbles are forced to oscillate linearly or nonlinearly in size or shape due to several acoustic cycles without collapsing. This behavior of microbubbles has been found to result in microstreaming, which enables the use of them in ultrasound drug delivery systems through micropumping of drugs [18], [19]. Inertial cavitation occurs when pressure becomes large to initiate unstable bubble growth, resulting in rapid microbubble collapse, and therefore, tends to generate heat, free radicals, shock waves, and shear forces [20], [21]. In fact, these physical

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outcomes allowed the efficient use of ultrasonic cavitation for biomedical purposes.

Hydrodynamic cavitation is another candidate for biomedical treatment. It is a progressive cycle of vaporization and bubble generation under low local pressures and bubble implosion following release to a higher pressure environment. It is initiated with local static pressure reduction below the saturated vapor pressure of the liquid and subsequent recovery above the vapor pressure. Similar to inertial ultrasound cavitation, in hydrodynamic cavitation, bubbles collapse due to rapid successive reduction and increase in local static pressure, which leads to a high-energy outcome, thereby generating highly localized, large amplitude shock waves. Hydrodynamic cavitating flows could be initiated using a microchannel and microorifice design. By using this design, several studies have been successfully shown the unique properties of hydrodynamic cavitation flow at the microscale [22]–[26], and it has been considered as an important alternative to ultrasonic cavitation over the last decade. Due to its cost effectiveness and energy efficiency, there is a growing interest in biomedical applications of hydrodynamic cavitation.

Even though biomedical uses of cavitation phenomena are rapidly increasing, a recent comprehensive review on its physical and/or biological effects and clinical applications in biomedical sciences is missing in the literature. This review focuses on recent studies and advances in the use of ultrasound and hydrodynamic cavitation in biomedical treatment. Physical properties and currently available applications are reviewed, and exponentially growing new approaches are discussed. Improved understanding of this field is of vital importance and would open a new area for the development of novel theurapeutic techniques.

II. Cavitation Phenomenon

Cavitation is a direct consequence of static pressure reductions down to a critical value (vapor pressure), and leads to the formation of inchoate vapor/gas bubbles (cavitation inception) or large-scale attached cavities (supercavitation) [27]–[29]. Cavitation is associated with the explosive growth and subsequent catastrophic collapse of vapor bubbles. Therefore, it is a dynamic phenomenon and its occurrence is not restricted to the fluid medium.

Cavitation occurs when a liquid is subjected to high pressure fluctuations. The pressure drop in ultrasound cavitation is a consequence of acoustic fields with sufficient intensity, while low local pressures as a result of constriction in the liquid flow direction generate hydrodynamic cavitation. The liquid is compressed in positive half cycle of the sound in a small region and is expanded during its negative half cycle. The generated vapor bubbles in the positive cycle collapse in the negative half cycle, and therefore, lead to a shock wave in the liquid as a result of energy released from the collapse of ultrasound cavitation bubbles. The additional pressures by the ultrasound cause an augmentation in the acoustic pressure in cavitation bubbles and make the collapse, and hence, fragmentation quicker, which is exploited in the disintegration of stones using ultrasound cavitation. The generated cavitation bubbles can experience low energy fluctuations as a result of the sound effect, which is called as noninertial cavitation (stable cavitation). The inertial cavitation (transient cavitation) starts to form when the bubbles undergo higher energy fluctuations. There is a threshold depending upon parameters relating to acoustic sound field and bubble behavior, which determines the incipient of inertial cavitation. The population of bubbles plays an important role in determination of stable and transient cavitation. While many applications such as cavitation erosion, cell killing, and ultrasound shock wave exploit inertial cavitation, noninertial cavitation may also take place depending on the bubble population and sound effect. In addition, if the initial bubble size is small, the bubble growth is affected due to high surface tension. In the case of the large initial bubble size, the bubbles growth would not be able to control the energy released from the collapse of the bubbles [30].

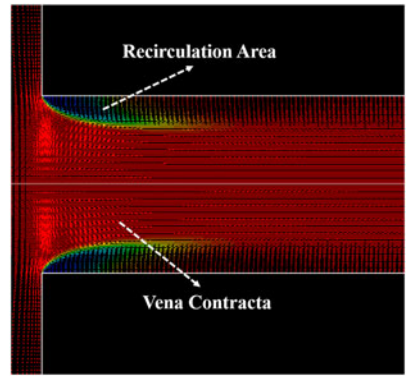

Fig. 1. Schematic of occurrence of cavitation phenomenon in a flow restrictive element.

The cavitation phenomenon has been investigated in many studies with applications in bioengineering, chemical engineering, micropumps, microvalves, and diesel injection engines [31]–[38]. Cavitation number is the basic parameter accounting for the intensity of cavitation

$$Ca = \frac{p - p_V}{\frac{1}{2}\rho V^2} \tag{1}$$

where p is the local pressure, ρ is the density, p_V is the vapor pressure, and V is the velocity at the flow restrictive element. Additionally, the discharge coefficient, which is another significant parameter in cavitating flows, is defined as the ratio of the actual discharge to the theoretical discharge and is computed using the mass flow rate and pressure drop. A schematic of occurrence of cavitation phenomenon is displayed in Fig. 1, where a recirculation zone is generated as a result of emerging bubbles in a low-pressure region. Above and below the recirculation zone, vena contracta is formed and causes a decrease in the cross-sectional area at the constriction.

III. Urinary Stone Therapy Using Lithotripsy and Ultrasound Cavitation

Ultrasound cavitation became an important method in disease therapy because it offers noninvasive and extracorporeal treatment possibilities. In low-intensity pulsed ultrasound, a major method, mechanical energy is transcutaneously transmitted as high-frequency acoustical pressure waves into biological tissues [39]. Today, this medical technology is an established, widely applied intervention for enhancing bone healing in fractures and nonunions [40], [41]. Sonoporation is a well-established ultrasound-based phenomenon for drug delivery, which increases gene uptake into tumor cells. Collapsing bubbles are believed to change the permeability of cell plasma membrane by creating transient holes, allowing efficient delivery. Although ultrasound cavitation has various applications in biomedical sciences, majority of the articles published in this field is concentrated on its biomedical effects in urinary stone treatment. Nonfocused ultrasound might result in hyperthermia in targeted areas and might lead to side effects, such as nerve and vasculature damage in surrounding normal tissues. The usage of high-intensity focused ultrasound (HIFU) or histotripsy methods overcomes these limitations to a certain extent, leading to precise tissue destruction by ultrasound cavitation and utilization in thermal ablation of tumors. Another ultrasound-based noninvasive method is shock wave lithotripsy (SWL), which offers important advantages for the treatment of renal and ureteral stones. The targeted surfaces are successfully destroyed with shock waves with slow rate resulting to reduced renal injury [42]. Recent studies also demonstrated successful therapeutic applications of SWL in orthopedic problems and heart diseases. In this section, recent studies and advances in SWL and histotripsy will be presented.

A. SWL

It is well known that the SWL provides effective biomedical treatment particularly for kidney stone fragmentation. Its effects are based on two fundamental mechanisms, shock wave-related effects and cavitation phenomenon. Mechanical stresses generated by SWL lead to stone fragmentation [43]–[48]. Many researchers proposed new methods to enhance the effectiveness of SWL by intensifying shock waves. Sass *et al.* [49] used kidney stones and gallstones, which were exposed to shock waves, and reported a two-step process in resulting erosion. They showed that first slits formed as a result of the interaction between shock wave and targets, and then, the liquid filled small cracks at the first step. Second, the collapse with cavitation caused significant erosion on the surface of stones, and finally, fragmentation took place. Holmer *et al.* [50] also showed that acoustic cavitation and streaming significantly contributed to the disintegration of stones.

Extracorporeal SWL (ESWL) is a kind of the SWL method, in which the source of the shock waves is outside the body and the shock profile of the ESWL impulse can be determined using a lithotripter device [51], [52]. The main structure of an ESW lithotripter device includes a shock wave generator, a focusing device and a system used for locating the stone [53]. There are three significant sources in ESWL, namely, electrohydraulic, electromagnetic, and piezoelectric sources. The generation of ultrasound cavitation and collapse of the bubbles are of great importance to treat the urinary stones with ESWL. Although effectiveness and safety of this method in urinary treatments were proven by many investigations [54]–[59], and its advantages and/or disadvantages over conventional methods were discussed in several studies [60], [61], investigators have shown that the modern lithotripters were highly ineffective compared to the original devices and might cause severe injury [62].

While ESWL typically works best with stones between 0.4 and 2 cm in diameter, which are located in the kidney, Wu *et al.* [63] in a study on the treatment of the renal stones with a size of 20 mm or bigger on 376 patients reported 64.4% overall stone-free rate and 70.7% efficiency rate after 3 months. They claimed that ESWL is the first choice for the stone with a surface area of 400 mm^2 and for the bigger ones, successive treatments are required. On the other hand, ESWL has a lower rate of success, when stones are located in the ureter. In regards to the guidelines on urolithiasis of the European Association of Urology, ESWL is implementable in minimally invasive endoscopic modalities to treat stones of the upper urinary tract in humans [64]–[67]. Success rate of this method could be increased by using a ureteral stent, which allows for easier passage of the stone by relieving obstruction and through passive dilatation of the ureter. In fact, the results of this method are also dependent on many factors such as shock wave rate, probe to sample distance, and pressure profile [68]–[70].

SWL results in fragmentation of stones due to direct impact imposed by shock waves [71], [72]. Stones, which are fractured with SWL, suffered from dynamic fatigue, squeezing, spallation, geometric superfocusing, shear-induced failure, and cavitation damage [73]–[80]. Stresses and tensions were also generated as a result of the reflection of some waves from the stone [81]. Coleman *et al.* [82] studied stresses generated by shock waves. They revealed that transient echogenicity dramatically increased in kidney tissues under the generated stresses, when the lithotripters output was augmented above a threshold magnitude. Based on the review on using shock waves in orthopedic diseases of Haupt [83], this method was suggested as the most efficient method to treat hypertrophic pseudarthrosis [84]–[86] and the success rate in tendinopathies was reported to be approximately 80%. Howle *et al.* [87] studied shock waves in the kidney stone treatment under the framework of lithotripsy and presented an expression for profile of the ESWL impulse

$$p(t) = \begin{cases} 2p_{\max} \exp^{-t/\tau_1} \cos\left(\dfrac{t}{\tau_2} + \dfrac{\pi}{3}\right) & \text{if } 0 < t < \dfrac{7\pi}{6}\tau_2 \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

where τ_1 and τ_2 determine the profile of the ESWL impulse.

The effect of generated stresses on stone fragmentation was considered by many researchers. Sapozhnikov *et al.* [88] both numerically and experimentally investigated the effect of cavitation and squeezing on generated stresses with lithotripsy. They showed that the highest stress values occurred in the location of stone fracture, and also surface cracks accelerated the comminution. They also showed that stone fragmentation was more pronounced under high stresses for wider high pressure regions.

Another advantage of ESWL, which was proven in many studies, is the fact that extracorporeal shock wave therapy could affect coronary angiogenesis and enhance treatment of myocardial ischemia in patients with intense coronary artery disease [89]–[95]. Hence, this method might have a significant impact on the treatment of ischemic heart diseases [96]–[99]. On the other hand, there are studies on this topic that show SWL is not effective at all by itself but may require stem cells [100]. Although recent studies show that the stem cells do not tolerate sufficiently

TABLE I
PRELIMINARY SIGNIFICANT REPORTS IN SWL

Study	Strategy	Major Findings	References
Gallstones in humans exposed to SWL	An alternative method of gallstone clearance in adults	Using cholecystectomy impacts on biliary physiology as an alternative conservative treatment for cholesterol gallstones	Sauerbruch *et al.* [44]
Exposure of kidney stones and gallstones to shock waves	Visualization of the destruction on the targeted surface	Collapse of the cavitation bubbles as the most significant mechanism in the erosion-Two-step process in resulting erosion	Sass *et al.* [49]
Kidney stone exposure to SWL	Surrounded target to determine the destruction rate	Mechanical effects including acoustic cavitation and streaming effect on stone fragmentation	Holmer *et al.* [50]
Urinary stones treatment using ESWL	Using focused shock waves to fracture calculi instead of surgery (First report)	Reducing the need for surgery with the aid of SWL	Chaussy *et al.* [54]
Immediate focus on the renal morphology after ESWL	Using renography assess renal function in patients after SWL	Signicant acute renal trauma as a result of SWL impose	Kaude *et al.* [66]

the inimical situation of the damaged myocardium but they need some modifications such as applying mesenchymal stem cells [101] and reproducing cardiac stem cell as an alternative to the single stem cell [102]. Recent studies have shown that stem cells fail to adequately engraft and survive in the hostile environment of the injured myocardium, possibly as a result of the absence of the proregenerative components of the secretome (paracrine factors) and/or of neighboring support cells.

The repeated use of SWL in the same patient has been shown to be correlated with an increase in the amount of phosphate in the kidney stone [103]. This is a huge issue in light of the large increase in the number of patients with phosphate stones. There are some studies showing a correlation between SWL number and phosphate content of the resulting kidney stone. Williams *et al.* [104] attempted to correlate the stone fragmentation rate with the structure of the internal stone using brushite stones imposed to SWL. However, their proposed tomography technology did not anticipate any correlation between brushite stones break and SWL. Pramanik *et al.* [105] used the ground stone powder and utilized a three-step extraction method to predict the protein content in the kidney stone. They showed that brushite and apatite stones contain higher amount of protein in comparison to the previous studies. In this regard, Kacker *et al.* [106] investigated the effect of the calcium phosphate stone on the stone-free rate and found that the higher rate of phosphate contains in the renal stone results in the reduction of the stone-free rate. Moreover, Evan *et al.* [107] performed an experiment in pigs showing a rise in urinary pH as a long-term effect of SWL on kidney function as well as changes in renal morphology and tubular changes consistent with a dsyfunctioning thick ascending thick limb. Some important preliminary studies in SWL are presented in Table I.

1) Secondary and Tandem Shock Waves in SWL: Secondary shock waves are of great importance in treatment of urinary stones. The implementation of tandem shock waves and the time of sending the second shock wave play a crucial role in SWL. In order to intensify the collapse of the cavitation bubbles, which were produced as a result of the tensile phase of the shock waves, a second shock wave is sent within some 100 μs after the first wave. Cavitation bubbles are nucleated in the presence of the tensile part of the waves, and bubble collapse near the stone generates secondary shock wave leading to erosion [108]. Later on, Delacretaz *et al.* [109] emphasized that in addition to the ordinary stresses on the stone target, there are always second shock waves induced by cavitation collapse, which are more destructive than the initial stresses during SWL. Sheir *et al.* [110] investigated twin-pulse (TP) treatment in eliminating the kidney stone. They conducted the first prospective clinical study with the twin-pulse lithotripter on 50 patients, whose renal stones had the diameters less than 2 cm. The capability of the tandem shock wave was investigated in other studies in the literature [111] and [112]. Loske *et al.* [113] evaluated the capability of the dual-pulse SWL (tandem shock wave) in controlling and collapsing the cavitation bubbles, which were induced by second shock waves. They found that this method was efficient in intensifying bubble implosion. The comminution of stones was increased without any tissue damage in *in vitro* studies. Loske *et al.* [114] tried to enhance cavitation damage on kidney stone during ESWL by generating shock waves with time delays of 50 to 950 μs in their earlier studies. The fragmentation ratio was increased at 250 and 400 μs shock wave delays. Alvarez *et al.* [115] used a modified piezoelectric shock wave generator to produce single-pulse and dual-pulse shock waves and studied the effect of shock waves on the viability of bacteria in solutions. They claimed that tandem shock wave could inactivate the bacteria, while low-pressure single-pulse did not have any significant effect on the bacteria. They also found that tandem shock wave could control bubble growth and prevent their collapse by sending the second shock wave beforehand. Furthermore, tandem shock wave could be used to shorten the SWL process.

The conclusion of the enhancement with strong microjets, which the second shock wave delivers for tenths of microseconds prior to collapsing the bubbles, was reported in the literature [116], [117]. Fernandez *et al.* [118] conducted an *in vitro* study to reduce the SWL time using tandem shock waves. They did their experiments with and without fluid-filled expansion chambers and observed few variations in stone comminution for both single and tandem shock waves in the presence of the fluid field. However, they recorded a significant decrease in SWL time for tandem shock waves.

Recent studies confirm the strong effect of the focused SWL on the cancer treatment. Lukes *et al.* [119] developed a focused tandem SWL (FTSW) generator in order to provide two successive waves with a time delay of 10 μs. The waves generated in this study were at peak positive and tensile pressures of 80 and -80 MPa for first and tandem ones, respectively, while the time delay was adjusted with a parabolic reflector and the electrode structure. They reported a remarkable enhancement of the antitumor effect of chemotherapeutic drugs due to generation and collapse of cavitation bubbles during FTSW process. Tandem shock waves boost attention in pharmaceutical industry. Loske *et al.* [120] used tandem shock wave (underwater) in order to transfer filamentous fungi used in generating antibiotics and

TABLE II
SUMMARY OF TANDEM SHOCK WAVE STUDIES

Strategy	Tandem shock wave significance	Methodology	Outcome	Reference
Comparison between secondary and ordinary waves	Secondary shock wave's superiority compared to ordinary waves	Characterization of cavitation erosion using collapse process to produce secondary shock wave	Critical impact of cavitation on the ESWL	Delacretaz *et al.* [109]
Controlling and collapsing the cavitation bubbles induced by TP	Efficiency of TP in intensifying the bubble implosion	Applied successive shock waves (tandem) to the targets using modified piezoelectric lithotriptor	No reported tissue damage *in vitro* study during comminution increase	Loske *et al.* [113]
Treatment time reduction during ESWL by enhancing fragmentation of the kidney stone	Cavitation damage enhancement on kidney stone	Piezoelectrically generating shock waves with time delays of 50 to 950 μs	Increase in fragmentation ratio for 250 and 400 μs shock wave delays	Loske *et al.* [114]
Investigation on the raise of microorganism death via tandem shock wave generation	Focus on the effect of shock waves on the livability of bacteria in solution	Utilizing piezoelectric shock wave generator to produce single-pulse and dual-pulse shock waves	Tandem shock wave capability in activating bacteria	Alvarez *et al.* [115]
Decreasing the SWL process duration using tandem shock wave via animal model	Significant decrease in SWL time for tandem shock waves	Use of fluid-filled expansion chamber to study the stone fragmentation Standard for single-pulse and tandem shockwaves	Variations in stone comminution for both single and tandem shock waves	Fernandez *et al.* [118]
Application of focused tandem shock waves in cancer treatment	Delay in tumor growth with the aid of tandem shock wave	Using parabolic reflector (cathode) to produce diverging cylindrical pressure wave at a specific point (focused)	Strong interaction between first and second waves at time delay of 8–15μs	Lukes *et al.* [119]
Improvement of DNA transformation to fungal cells using tandem shock waves	Aspergillus niger transformation improvement with tandem shock wave compared to standard one	Using underwater shock waves to transfer filamentous fungi genetically	Genetic transformation of filamentous fungi is significantly affected by acoustic cavitationμs	Loske *et al.* [120]

proteins. They showed a significant superiority of tandem shock wave with a delay of 300 μs in genetic transformation of filamentous fungi compared to standard shock wave. Numerical modeling on the secondary shock wave was also taken into account, and stress and cavitation effects were determined as the key parameters in the fragmentation of the targeted surfaces during tandem shock waves [121]. Some important investigations on the tandem shock wave are presented in Table II.

2) Pressure Field in SWL: Pressure distribution is a very important parameter in SWL and can affect the performance of this method in treating urinary stones. Pressure field was studied in the focal region of SWL in many studies, and the behavior of generated cavitation bubbles in the focal region as a significant mechanism in comminution of stones was investigated in some studies [122]–[124]. Based on these studies, it is proven that geometrical acoustics and shock dynamics play a crucial role for predicting the focal region [125], [126]. Shock dynamics determines the motion of the shock wave without considering the flow field of the shock [127].

Krimmel *et al.* [128] studied pressure field in the focal region of SWL and focused on cavitation formation. They observed in *in vitro* experiments that secondary produced shocks depended upon the pulse repetition frequency (PRF) and the bubble density. They investigated SWL initially in water. They modeled an electrohydraulic lithotripter and considered it as the "gold standard" of the shock wave lithotripters. The kidney stone used in the electrohydraulic lithotripter was placed at the second focus (F2). Meanwhile, the piezoelectric lithotripter array (PLA) was simulated as the piezoelectric lithotripter, and kidney stone was located at the geometrical focus of the truncated spherical cap. Finally, a machine, which was a wide-focus and low-amplitude device, was modeled as the electromagnetic lithotripter. 40 bubbles/cm^3, 0.7 mm, and 280–370 μs were estimated as the bubble density, maximum radius, and the recorded collapse time of the cavitation cloud, respectively. The highest value was obtained as 5% for the void fraction. Multiple bubbles postponed the bubble collapse near F2 (second focus) and lead to a very strong collapse for lower void fractions, and high PRF had a reverse effect on stone fragmentation, which was in a good agreement with the other findings in the literature [129]–[131]. In another study, it was found that cavitation was intensified in the presence of higher PRFs [132]. Lautz *et al.* [133] observed that a decrease in cavitation activity in prefocal region lead to an increase in cavitation activity in the focal region so that more effective stone fragmentation took place. Qin *et al.* [134] studied the effect of focal width on stone fragmentation and found that a shock wave lithotripter with a broad focal width having a low-pressure pick was more efficient than a lithotripter of a high pick pressure with a narrow focal width in *in vitro* treatments. Cleveland *et al.* [135] founded that the tissues had an important role in the formation of pressure waves. Their results in measuring the pressure field in pigs showed that waveforms had similar trends with those measured in water. However, the *in vivo* case had a wider domain in comparison to the *in vitro* case.

Cathignol *et al.* [136] investigated the effect of the formation of different pressure pulses on the efficiency of cavitation phenomenon using two different shock pressure-time waveforms. The shock waves, which were considered, had successive tensile and compressive waves in inverse steps. The direct-mode pulse reinforced cavitation effects, and overall cavitation collapse had a strong effect on SWL. To have better comminution of urinary stones during SWL, Sokolov *et al.* [137] utilized a dual-pulse lithotripter to amplify cavitation effects. Their suggested method resulted in radial dynamic cavitation patterns. Cleveland *et al.* [138] studied the influence of the sound speed and diameter of the stone on the pressure field inside the stone and found that the stone diameter and internal structure induced negative peak pressures inside a kidney stone. Chitnis *et al.* [139] measured peak pressures on kidney stones for shock waves induced with acoustic emissions from the collapse of cavitation bubbles. Their results illustrated that the effect of the both SWL and cavitation collapse had an important role in the fragmentation of kidney stones. ESWL generates microsecond pulses having 30–150 MPa peak positive pressure and a tensile phase of approximately 20 MPa. The energy released from this process is often between 100 kHz and 1 MHz [115]. The acoustic wave in the SWL intensifies the pressure amplitudes induced by the energy of the ultrasound wave at the targeted area. The produced pressure is defined as the trust per the focal area and further generated pressure as a result of the acoustic wave results in the occurrence of the cavitation bubbles on the medium [140]. Pressure force induced by ultrasound waves is affected by variable parameters in the medium such as the size and the sound speed of the targeted surface and the components of the medium [138].

Pressure distribution using a piezoelectric array was considered in the literature to determine the efficiency of SWL. Based on this approach, Lewin *et al.* [141] developed a technique, which focused on the ratio of pick positive pressure (compressional) to pick negative pressure (rarefactional) to control the cavitation damage and found that reproducible lesions were generated in animals in the *in vivo* studies. They used piezoelectric transducers to generate asymmetrical shock waves, which had a finite amplitude and produced the following wave in an applicable time delay in the same focal zone in order to ensure interaction between waves. In another study, Chitnis *et al.* [142] generated acoustic pressure fields using a piezoelectric array. Their experimental and numerical results related to pressure dispensations with interelement delays showed a reasonable agreement.

3) Cavitation Effects on SWL: Cavitation phenomenon and bubble collapse were considered as important parameters in SWL [143]–[151]. The aim of the studies on this field was to increase the comminution of stones while reducing the tissue injury [152]. The study of the growth and collapse of the cavitation cloud was taken into account by many researchers in the focal region [153]–[157].

Delius and his coworkers are one of research groups contributing to the explanation of the role of cavitation and its biological consequences in ESWL [158]–[161]. They focused on topics such as destruction of gallstones and used ESWL in order to study the behavior of the targeted zones and to investigate the side effects of ESWL. Since lung bleeding is considered as one of the significant side effects of the gallestones destruction in *in vivo* studies, they applied different pressures between the lung and the diaphragm of dogs and observed that low shock waves did not have any important effect on the lung, but higher ones resulted in beagles bleeding. Williams *et al.* [162] observed that gas bubbles existing in the air–fluid interfaces had the potential for serving as cavitation nuclei and found that even small bubbles had an important impact on the lysis of red blood cells during the shock wave exposure. Zhu *et al.* [163] studied the effect of the ultrasound cavitation and stress waves on stone fragmentation. They performed experiments on disintegration of renal calculi in SWL using degassed water and castor oil and found that fragmentation in the degassed water had better results. Fragmentations of 89% and 22% in kidney stones after 200 shocks were achieved in degassed water and castor oil, respectively. The results from the recent studies demonstrated that

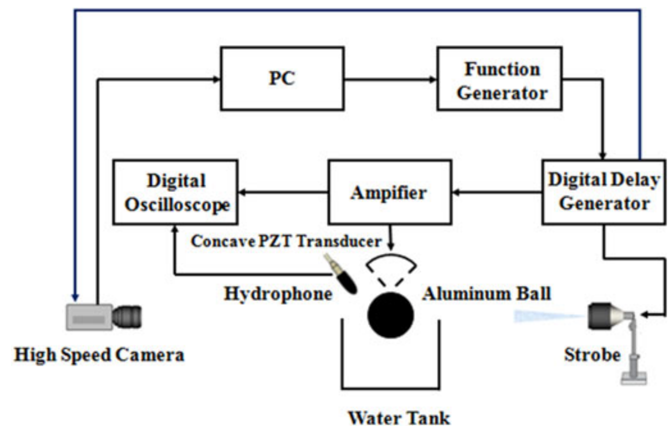

Fig. 2. Schematic of the experimental setup [169]. The setup consists of an acrylic water tank, an ultrasound generation unit, and a data acquisition unit.

the intensity of bubble collapse was reduced by time reversing the lithotripsy pulse. The overpressure and time-reversed waveform led to a reduction in cavitation activity, and the decrease in cavitation damage was reported as a result for these applications in the literature [164]–[167].

The cavitation phenomenon is in a close association with SWL in the processes of formation and collapse of cavitation bubbles. While the acoustic aspect of the lithotripsy induces the cavitation bubbles, cavitation bubbles and clouds dramatically influence the lithotripsy treatment and the pressure distribution in the focal region of the SWL. The collapse of the cavitation bubbles, distance between the applied laser and the targeted stone, the topology of the targeted stone sample are the most significant parameters, which were considered in the literature to control the cavitation phenomenon. Chilibon *et al.* [168] investigated the effect of cavitation in SWL focusing on urinary calculi fragmentation. They claimed that the acoustic term of the lithotripter had a significant effect on inducing cavitation bubbles to target the stone in SWL. Ikeda *et al.* [169] investigated cavitation cloud and its effect on the pressure field. They discovered that the control of cavitation collapse had a big potential in the lithotripsy treatment. They suggested that since the cavitation cloud was the most destructive feature, it had the capability to concentrate intensive pressure fields in the case of acoustically induced collapse of the bubbles (see Fig. 2). It was extensively reported in the literature that the collapse due to cloud cavitation might generate local pressures having a more dominant effect than initial waves [170]–[173]. Yoshizawa *et al.* [174] investigated the effect of the cloud cavitation on HIFU. The energy released from the cavitation bubble collapse induced by acoustic field has the capability of focusing very high pressures. Their method, which included two steps, namely, high-frequency ultrasound (15 MHz), and then, low-frequency ultrasound (100 kHz–1 MHz) with short pulses, offered localization of cavitating bubbles on the stone. Both of the frequencies were applied to the stone surface. However, the second one induced cavitation cloud collapse by generating an oscillating field in the cavitation bubbles and led to powerful shock waves interior the cloud. Thus, the bubbles in the vicinity of the center of the cloud collapsed, and a high-pressure field was generated, which resulted in fragmentation of the stone. Johnsen *et al.* [175] concentrated on the bubble collapse effect on stone comminution. The collapse of shock induced, Rayleigh, and free-field cavitation bubbles led to contributions to stone fragmentation. They recorded high pressures at the stone due to shock-induced collapse and observed a jet near the solid surface due to the collapse of Rayleigh and free-field cavitation bubble.

The collapse of the shock-induced cavitation bubbles and their contributions to SWL were extensively reported [176]–[179]. Johnsen *et al.* [180] founded that shock-induced collapse of air bubbles had a considerable effect on damaging the stone in SWL. Their numerical results were in a good agreement with experimental observations. They showed that bubble collapse near the rigid wall raised the wall pressure (wall pressure determines the damaging power of cavitation bubble collapse), and affected the stand-off distances in kidney stone erosion. Ultrasound cavitation effects are enhanced with delayed second shock waves. Therefore, the importance of intensifying the effect of cavitation collapse is of great interest in this field. Pishchalnikov *et al.* [181] considered cavitation control as an important mechanism in the SWL. The formation of single bubbles resulted in clusters in proximal locations and sides of the stones, and the collapse of each cluster led to erosion and also helped the crack growth. Pishchalnikov *et al.* [182] also proved that stone comminution was more pronounced with a slow rate shock wave lithotripter. They used a U-30 stone with an electrohydraulic lithotripter and showed that the bubble nuclei generated from the stone interacted with later shock waves for the fast rate of SWL. Bubble growth extracted the energy from the negative pressure field of the shock wave during the delivery of subsequent shock waves.

Another significant issue in the relation between cavitation phenomenon and SWL is the distance between the probe and the targeted area. Fuh *et al.* [183] studied the effect of the distance of laser fiber to stone on the ultrasound cavitation. They studied the effect of the laser fiber proximity on the fragmentation of the stone and examined the distance between the laser fiber and stone target in order to study cavitation bubble behavior. The diameter of cavitation bubbles was increased at larger distances between the stone and fiber. The effect of the collapse of reflected bubbles on rigid bodies was investigated by Calvisi *et al.* [184]. They developed a boundary integral method to study the effect of nonspherical collapse of bubbles influenced by SWL on the near rigid body. They found that the bubble-wall distance had a dramatic effect on dynamics of bubbles collapse in the case of reflection. The results were independent of initial radius of the bubbles. Iloreta *et al.* [185] focused on the effect of the stone topology on cavitation bubbles. They studied bubble dynamics and found that the stone had a strong effect on bubbles when they were in close distance, and this effect was negligible when the bubble was far away from the stone. Smith *et al.* [186] also performed several *in vitro* experiments at the acoustic field of electromagnetic SWL with different fluids in order to determine the role of cavitation. Their results revealed that the type of the stone (hard or soft) changed the thresholds in average peak pressures. Selected studies on the effect of the cavitation on SWL are gathered in Table III.

TABLE III
CAVITATION CONTRIBUTION IN SWL

Strategy	Outcome	Cavitation Contribution	Reference
Cavitation observation in the interface	Even small bubbles affect the lysis of red blood cells	Gas bubbles	Williams *et al.* [153] [162]
Degassed water and castor oil usage in disintegration of renal calculi in SWL	89% and 22% fragmentations in kidney stones after 200 shocks in degassed water and castor oil, respectively	Ultrasound cavitation	Zhu *et al.* [137] [147]
Cavitation collapse control in lithotripsy treatment	The capability of cavitation cloud to concentrate intensive pressure fields. Crack growth in the case of cluster collapse	Cavitation cloud and cluster collapse	Ikeda *et al.* [169] Pishchalnikov *et al.* [181]
Effect of focusing on shock- induce collapse of air bubbles on stone damage	Wall pressure increase and variation in stand-off distances in presence of near wall collapse	Collapse of air bubbles	Johnsen *et al.* [180]
Cloud cavitation effect on (HIFU	Very high pressures concentration due to energy released from cavitation collapse	Cloud cavitation and collapse	Yoshizawa *et al.* [174]

4) Recent Techniques in SWL to Increase the Stone Fragmentation and Decrease the Tissue Damage: Several attempts were made to improve kidney stone comminution. Although it is important to facilitate stone comminution, tissue injury must be prevented in SWL. Some experiments and studies were performed to augment stone fragmentation and to prevent tissue damage at the same time [187], [188]. Zhou *et al.* [189] demonstrated that energy released from the lithotriper in a step-wise way assisted the treatment and yielded better results in stone fragmentation. Loske *et al.* [190] in a new method utilized biofocal and standard ellipsoidal reflectors and concluded that their setup for treatment of the kidney stone had a better performance in breaking up kidney stones while reducing the tissue damage. Zhu *et al.* [191] used an acoustic diode to examine the reduction in tissue injury, while the stone comminution was still taking place. They showed that employing acoustic diode decreased the maximum compressive pressure, maximum tensile pressure, and tensile duration of the lithotripter shock. The tissue injury was significantly reduced after the shock. In the study of Shrivastava *et al.* [140], cavitation bubbles generated from the SWL were capable to quickly collapse with high performance in lithotripters. Increasing the voltage value in ESWL was thus an effective method to improve the treatment with SWL. Maloney *et al.* [192] applied an increasing output voltage for the SWL instead of constant or decreasing output voltage. They proposed a low-valued shock wave to prevent the renal and tissue injury and showed that progressive increase in the SWL voltage led to more stone fragmentation than that for the constant and decreasing output voltage cases. Bhojani *et al.* [193] optimized the treatment parameters and showed that power ramping with a short pause can improve the stone fragmentation and increase the treatment safety. Moreover, they claimed that bigger area for the focal field is crucial for the reduction of the renal tissue injury. Meanwhile, Handa *et al.* [194] showed that there is no need for a pause in the shock wave propagation after the initial wave in order to achieve a better fragmentation and reduced tissue injury. They stated that the SWL depends on its acoustic and temporal properties, so may differ from lithotripter to another one. Ikeda *et al.* [195] attempted to develop a method on the base of HIFU in order to increase the fragmentation rate of the kidney stone. By controlling the cavitation activity in step-wise manner, the effect of the collapse of the generated bubbles would be utilized in the SWL process.

Eisenmenger [196] proposed a new method to study the fragmentation of kidney stones. His suggested technique called as circumferential quasistatic compression or "squeezing" included evanescent waves and initial cleavage surfaces on the basis of the direction of propagated waves. Artificial stones have been used in many studies to imitate natural stones [197]–[203]. McAteer *et al.* [204] used artificial stones (Ultracal-30 gypsum) to simulate SWL. They concluded that the results showed similar shock wave rates compared to the studies with real samples. Both *in vitro* and *in vivo* studies showed that the low rate of SWL transition resulted in an enhancement in the stone fragmentation [198], [205], [206]. Pishchalnikov *et al.* [207] observed that the low value of the shock wave transition resulted in more stone fragmentation, and cavitation occurring on the path to the stone had a great impact on stone fragmentation. They also investigated the effect of firing rate on SWL [208]. They found that the efficiency of SWL in stone fragmentation decreased with firing rate. They claimed that while negative pressure field was intensified by increasing the firing rate, the positive pressure component remained constant. Their results also indicated that stimulation of cavitation bubbles resulted in a decrease in the efficiency of SWL.

The use of piezoelectric arrays is another important method in this field. Fernandez *et al.* [209] studied the effect of presence of the fluid on SWL. They focused on stone comminution when a fluid-filled expansion chamber was used in standard and tandem SWL. They found that water covering the stone had a great impact on stone fragmentation in the case of tandem SWL, which was produced using a piezoelectric lithotripter. A recent enhancement method in shock wave, lithoclast, was implemented in the treatment of renal calculi [210]. This method considerably reduced side damage on the tissues using a minimal surgery and included a unit control, a hand piece, and a set of metallic probes. In this method, the pneumatic lithotripter (lithoclast) and a second ultrasound lithotripter operated at the same time with the aid of a control unit. This method has the potential of being used in capillary deterioration, hypertension (HTN), and other tissue damages [211]–[213]. The advantages of using lithoclast in the treatment of the urinary stones are less operation and postoperation time and the decrease in tissue damage [214]–[220]. Turk *et al.* [221] assessed the efficiency of the urolithiasis diagnosis and conservative management in a study according to EUA guidelines. To detect the renal and ureteral calculi low-dose computed tomography (CT) was implemented. Low-dose CT contributed to rapid diagnosis. They showed that medical expulsive therapy is a suitable choice for stone expulsion. Table IV includes important attempts in the improvement of the SWL.

TABLE IV
SUMMARY OF STUDIES ON ATTEMPTS FOR IMPROVEMENT IN SWL

Purpose	Method	Outcome	Reference
Investigation on the shock wave frequency reduction to increase the SWL safety	Reducing the rate of shock wave for less than 120 shock waves per min	60 shocks per minute results in better fragmentation with treatment time reduction	Pace *et al.* [69] Madbouly *et al.* [129] Kato *et al.* [130] Paterson [198]
Utilizing the energy released from cavitation collapse in stone fragmentation	Characterization of bubble's collapse to study the effect of the ultrasound cavitation in SWL process	Enhancement of stone fragmentation and prevention of tissue injury	Shrivastava *et al.* [140]
Improving the impact of cavitation on stone comminution	Employing acoustic diode	Significant reduction in tissue injury accompanying stone fragmentation raise	Zhou *et al.* [189]
To quantitatively validate the binary fragmentation by quasistatic squeezing	Circumferential quasistatic compression or "squeezing"	Enhancement in Fragmentation of kidney stones-Observation of first cleavage surfaces parallel or perpendicular to the wave bombardment	Eisenmenger [196]
Enhancing the stone fragmentation with altering the shock wave frequency	Increasing the wave frequency with the aid of spark-gap lithotrip	Raising the shocks quantity applied on target by increasing the shock wave frequency from 60 to 117 per minute	Weir *et al.* [205]
Assessment of the significance of chamber filled with water on the fragmentation ratio	Piezoelectric arrays usage to produce tandem shock wave	Beside the fluid-filled chamber, tandem shock wave is necessary for the successful fragmentation	Fernandez *et al.* [209]
Introducing an alternative for standard endoscopic lithotriptors	Lithoclast use in SWL	Less operation and post- operation time	Schulze *et al.* [214] Denstedt *et al.* [215]
Investigation on the efficiency of the lithoclast	using the hands-free in vitro testing system to evaluate the stone fragmentation	Enhancing the penetration time with raising the pneumatic frequency or ultrasonic power	Kuo *et al.* [216]
Study on the combination of ultrasound and pneumatic lithotripsy	ultrasound and pneumatic lithotripsy	Significant enhancement in the efficiency of the combined system and reduction in the treatment time	Haupt *et al.* [219]
Introducing a new lithotripter to increase the fragmentation ratio	Using lithoclast and ultrasound device to produce the new generation lithotripter	Acceptable fragmentation ratio in spite of the various composition of the stone	Hofmann *et al.* [220]

5) Numerical Studies on SWL Treatment: The process of SWL and formation and collapse of cavitation bubbles occur within few seconds. Computer modeling was performed to simulate such processes [222], [223]. Simulations of lithotripters were widely considered with the emergence of advanced computational methods especially for homogeneous fluids [224], [225].

In addition to experimental investigations, the collapse of cloud cavitation was taken into account from a numerical point of view in the literature [226]. Bubble formation as a first step of the cavitation phenomenon was mostly considered using the Reyleigh–Plesset equation in the literature [227]. Mihradi *et al.* [228] utilized the continuous finite-element method, and numerically studied the pulse duration of ESWL under the effect of stress elds. They assessed the effect of the pulse duration and also acoustic field on stress evolution inside the stone and reported their significant effect on the location of maxima of the reflected tensile stresses. The interaction between cavitation bubbles and pressure pulse in stone fragmentation was taken into account in some studies. Klaseboer *et al.* [229] numerically studied the dynamic interaction of the generated pressure pulse with oscillating cavitation bubbles near the stone. They showed that medium size bubbles led to better collapse with the largest jet impingement, while the duration of the collapse was almost equal to the shock wave compressive pulse period. Their results illustrated that the interaction between pressure pulse and cavitation bubbles caused stone fragmentation. They also investigated the interaction between a single bubble and shock wave lithotripter. Their computational study confirmed that medium-sized bubbles resulted in a severe collapse and high jet velocity, when the collapse time was approximately equal to the shock wave compressive pulse period.

Tham *et al.* [230] numerically studied modified SWL and showed that both modified and conventional shock waves for direct stress waves resulted in a similar effect on stone fragmentation. Their modification included the bubble collapse intensification using modified single and secondary shock wave pulses. They found that a small period of tandem pulses produced better stone fragmentation than the single pulse lithotripsy. Weinberg *et al.* [231] performed 2-D and 3-D simulations of kidney stones exposed to SWL. They modeled oscillating cavitation bubbles and studied their effects on the distribution of shock waves on the stone. Pressure field generated by shock wave impulse played a significant role in stone fragmentation at first steps.

The effect of the microjet produced with cavitation bubble collapse on the tissue injury was also considered. Freund *et al.* [232] numerically studied the interaction between the produced jet generated by bubble collapse and viscous fluid to measure its effect on tissue injury, while SWL was implemented. They found that the bubbly liquid jet formed after the collapse of the cavitation bubbles was not able to penetrate to simulated viscous fluid having the same property as the tissue. They also showed that larger tissue viscosity significantly decreased penetration length of the jet into the tissue. Jamaloddin *et al.* [233] studied far-field acoustic emission generated by cavitation collapse. They numerically estimated far-field acoustic emissions using the Kirchhoff and Fowcs William–Hawkings (FW-H) formulations. Their method had the capability of extracting far-field emissions characteristics observed in clinical treatment. Coralic *et al.* [234] employed a high-order finite-volume scheme to simulate cavitation bubbles exposed to SWL and studied the behavior of the already existing bubbles in a deformable vessel. Their results showed that pressure and deformation had the highest magnitude for the largest volumetric restriction of the bubbles. Duryea *et al.* [235] focused on behavior of the remnant cavitation bubbles, which affected shock waves at high rates. They developed a model to remove the persistent bubbles by employing a low-frequency acoustic pulse in order to influence their coalescence. They observed that stone fragmentation was accelerated, when the remnant bubbles were successfully removed at higher rates. This was also in agreement with the reduction of bubble excitation captured with optical measurements. Another topic attracting the scientific community is resonant scattering modeling. Owen *et al.* [236] numerically studied the capability of resonant scattering in SWL to identify the difference between the unscathed and fragmented stones. They proved that it was possible to measure the fracture of the stone using frequency analysis.

6) Acoustic Effect of SWL: The acoustic effect of the SWL is significant in fragmentation of urinary stones. There are several parameters influencing acoustic field of SWL, namely, energy density and far-field emission. Detection of cavitation phenomenon as a crucial source of acoustic effect is of great importance [237]. Cleveland [238] investigated the acoustic field of waves generated with SWL. He focused on the effect of physical phenomena on SWL such as sound, distortion, and diffraction. His results illustrated that high rate of shock waves clogged the subsequent wave propagation.

Leighton *et al.* [239] developed a passive device that could measure acoustic signals spread from the targeted body after SWL. Their device had the capability of predicting the stone location and the efficacy of SWL. The device also delivered a real-time feedback of the effectiveness of each shock to the operator. They could monitor the progress of stone fragmentation under the effect of acoustic cavitation. Loske *et al.* [240] studied energy density and its effect on stone fragmentation. In their study, the most significant parameter in stone fragmentation was the energy density. Leighton *et al.* [241] numerically studied far-field acoustic emissions, which were generated by cavitation bubbles during SWL and developed the free-Lagrange method to measure the interaction among bubbles as a function of their separation. They reported vibrational trends of the bubble–bubble interaction with respect to those of single bubbles in SWL.

Alibakhshi *et al.* [242] fabricated piezopolymer-based hydrophone arrays in order to measure acoustic field in SWL. They used such arrays to weight the effect of shot-to-shot variability of the spark discharge on generated acoustic field and recorded its main influence on the location of the produced acoustic field. Lu *et al.* [243] focused on the occurrence of the twinkling artifact (TA) during Doppler ultrasound imaging of kidney stones. They found that the captured random viability among the acoustic signals produced TA, but not electronic signal capture.

B. Histotripsy

Histotripsy is considered as a unique ultrasound method for improving the mechanical fragmentation of stones. It is an invasive method to shorten the time of tissue erosion based on ultrasound cavitation. It generates cavitation cloud with lesion production under the effect of high-pressure pulses. In this method, pressure field in the low acoustic cycles induces the cavitation cloud formation distributing the bubbles [244], [245]. The most significant advantage of this method is offering controllable fragmentation of the tissue in the presence of the bubble cloud [246]–[248]. There are many studies fo-

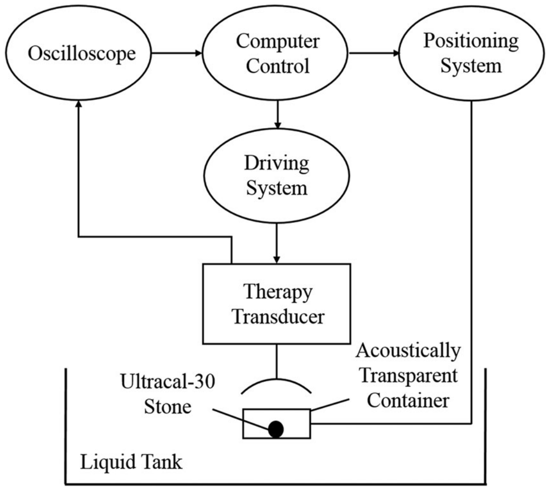

Fig. 3. Experimental setup for the treatment of Ultracal-30 model kidney stones prepared by Duryea *et al.* [271].

cusing on tissue erosion using focused ultrasound (FUS) at high intensity [249]–[251] and short duration [252]–[257] for prostate [258]–[263] and uterus [264], [265]. Moreover, the role of cavitation in HIFU histotripsy was investigated in many studies and the therapeutic applications of HIFU were discussed in the literature [266]–[270].

Duryea *et al.* [271] studied the effect of histotripsy on the erosion of urinary calculi as a pulsed FUS method in which the cavitation activity could be controlled. They claimed that histotripsy might be a subsidiary method for SWL. It could accelerate stone fragmentation and could generate fine debris. The Ultracal-30 gypsum cement was sonicated for 5 min to investigate the efficiency of histotripsy in this study. The cavitation activity was observed to reveal the interaction between the model damage and histotripsy. The real time via B-mode ultrasound imaging was used to identify the ultrasound effect on stone fragmentation (see Fig. 3). Duerya *et al.* [272] also studied the significance of the presence of cavitation phenomenon from a point of view of histotripsy. They found that stone fragmentation was increased due to cavitation collapse, when histotripsy controlled cavitation was present after SWL. Fragmentation of the stone exposed to SWL was accelerated, when controlled cavitation was present before SWL. Wang *et al.* [273] considered histotripsy as a potential method to generate cavitation seeds and tried to remove the cavitation memory in order to establish a method to fragment the stone with fewer pulses. They implemented this approach by removing the cavitation memory in a way that the consecutive pulses were augmented. The stone communition was increased, when cavitation memory removal was successfully performed. The same authors also developed a method in focal region in order to generate more lesions in pulsed cavitation ultrasound therapy or histotripsy [274].

Schade *et al.* [275] carried out a study on capability of histotripsy in prostatic urethra homogenization and focused on the pulse number and PRF. They recorded an increasing rate for ureteral disintegration, while the histotripsy PRF was gradually increased at a constant dose of pulse rate. Roberts *et al.* [276] investigated the effect of histotripsy after the treatment from a local and systematic point of view. Their *in vivo* experiments were performed on ten male dogs. The after treatment behavior was investigated using transrectal ultrasound. The histotripsy generated prostate debulking in all experiments. Lin *et al.* [277] studied histotripsy from a different aspect and measured the peak negative pressure for a high amount of cavitation cloud. They considered a dense cavitation cloud induced by supra-intrinsic threshold pulses and concluded that the generated lesion increased under the effect of increasing peak negative pressure.

TABLE V
SUMMARY OF STUDIES ON HYDRODYNAMIC CAVITATION IN BIOMEDICAL APPLICATIONS

Method	Target	Effect	Reference
Rayleigh-type hydrodynamic simulation of interaction between bubbles and tissue	Soft tissue made of CAM	Preventation of tissue damage using concave endoprobes	Palanker *et al.* [280]
Bubbly cavitating flow effect on cell cultures	Kidney chalk specimens and cancerous cells.	Significant reduction in cell livability	Kosar *et al.* [282] Hydrodynamic cavitation exposure on target area
Hydrodynamic cavitation exposure on target area	Kidney stone samples	Considerable erosion rate in an optimum probe- specimen distance	Perk *et al.* [283]
Hydrodynamic cavitation exposure on target area	Prostate cells and BPH tissue	Hydrodynamic cavitation as an alternative to ultrasound cavitation in treatments involving BPH tissues.	Itah *et al.* [284]
Hydrodynamic cavitation exposure on target area	Lysozyme structure	No irreversible effect No deactivation	Turkoz *et al.* [285]

IV. ALTERNATIVE FOR ULTRASOUND CAVITATION: HYDRODYNAMIC CAVITATION

While hydrodynamic cavitation has been extensively studied in applications involving hydromachinery, potential biomedical applications were recently considered as an emerging research area particularly in microscale. Although ultrasound cavitation is very popular in disease therapeutics, side effects caused by ultrasound cavitation motivated researchers to seek for different, local, and efficient methods, such as hydrodynamic cavitation (see Table V). In a very early study, Rooney [278], [279] founded that hydrodynamic cavitation had the capability of generating high-intensity jet flows, which could be used in order to fragment stone and damage the tissues. Then, Palanker *et al.* [280] used a 2-D Rayleigh-type hydrodynamic simulation in order to study the interaction between a jet containing bubbles and a soft tissue made of chorioallantoic membrane (CAM). They tried to avoid generating cavitation bubbles, which might cause considerable damage to tissues using concave endoprobes. Their results were obtained under the condition of a maximum velocity of 80 m/s and tissue distance up to 1.4 mm. They indicated that concave endoprobes could be used to prevent tissue

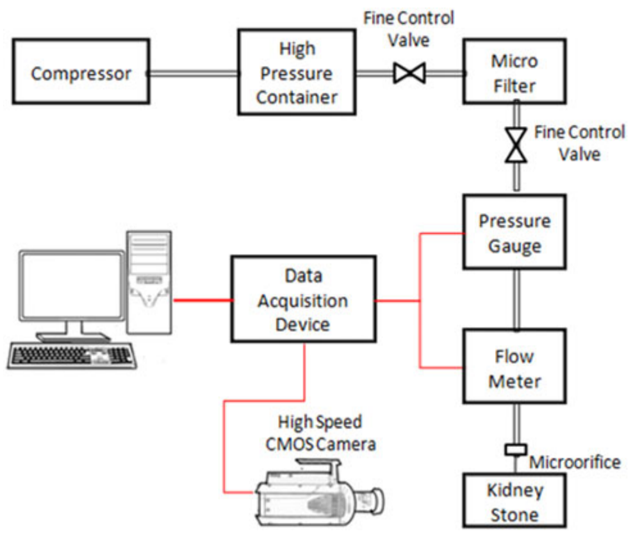

Fig. 4. Hydrodynamic cavitation setup used to fragment kidney stones [283].

damage by slowing down the bubble back boundary diffusion. Toytman *et al.* [281] investigated hydrodynamic interactions among simultaneous cavitation bubbles originating from multiple laser foci, which are widely used in ophthalmologic surgery. If multiple cavitation bubbles were produced at once, with a target tissue trapped between them, cutting efficiency was enhanced. Focusing problem by a series of pulses could be solved.

Different from previous studies, experimental setup that was used in the study of Koşar *et al.* [282] did not include any moving part, and their experiments were carried out at various inlet pressures while visualizing bubbly cavitating flow patterns (see Fig. 4). The authors studied the impact of released bubbles on kidney chalk specimens and two different leukemia cells. On chalk specimens, they observed that the penetration in the chalk medium increased with time. The distance between the microprobe and the specimen was an important parameter. The penetration depth was larger for closer distances due to stronger bubble specimen surface interactions. The interaction between emerging bubbles (from the microprobe) and the chalk surface caused significant erosion and created rough local spots on the surface leading to augmented roughness on chalk surfaces. The findings implied that the erosion resulting from the exposure to bubbly cavitation was produced by micrometer-size bubbles rather than the shear effect of the liquid flow. Moreover, the authors measured the size of the eroded stone debris and maximum debris size was found to be 50 μm. On the other hand, the data of Koşar *et al.* [282] with leukemia cells showed that after bubbly cavitation exposure cancer cells died as a result of two different mechanisms: 1) first effect was seen shortly after exposure in which most of the cells lost their membrane integrity and 2) second effect was the late effect on cell survival. Although the short-term effects of cavitation caused a form of cell injury following with premature cell death due to the mechanical forces of cavitation, the late effects might be controlled by a programmed cell-death mechanism.

As an extended study, Perk *et al.* [283] assessed the capability and applicability of the hydrodynamic cavitation method for kidney stone treatment utilizing 18 kidney stone samples made of calcium oxalate. The authors used phosphate buffered saline (PBS) solution as the working fluid. At a cavitation number of 0.017 and a probe to specimen distance of 1 mm, their experiments resulted in an erosion rate of 0.31 mg/min. By using a similar experimental design in the study of Itah *et al.* [284], the authors investigated the destructive effects of hydrodynamic cavitation on prostate cancer cells and benign prostatic hyperplasia (BPH) tissues as well [284]. Here, the detailed molecular mechanisms hydrodynamic cavitation effect were also analyzed using prostate cancer cells. The microorifice was a polyether ether ketone with an inner diameter of 147 μm, while the pressure at the inlet was varied from 50 to 150 psi for cell culture experiments, and the physiological solution was PBS. The results on prostate cancer cells PC-3 and DU-145 exposed to hydrodynamic cavitation showed the destructive effect of bubbly cavitation in a pressure- and time-dependent manner. There was a further increase in dead cells after 24 h since the cavitation exposure. There was no evidence of the activation of apoptotic programmed cell death, shown by the analysis of nuclear changes, caspase activation, PARP cleavage, sub-G1 fraction cells, and DNA laddering. Additionally, activation of other type of programmed cell death, autophagy, was also not observed. These results indicated that hydrodynamic cavitation damaged prostate cancer cells instantly and pulverized cells upon exposure. Moreover, the authors proved significant damage and penetrating effect of hydrodynamic cavitation to exposed BPH tissue specimen compared to the noncavitating conditions, which suggests that hydrodynamic cavitation could be a viable alternative in BPH tissue treatment. Similar experimental setup was used to show the effect of hydrodynamic cavitation on protein structure [285]. In this study, the authors had chosen Hen egg-white lysozyme as a protein model. Via biochemical and biophysical methods, they found that hydrodynamic cavitation had no significant effect on lysozyme structure and function. The authors revealed a reversible change of hydrodynamic diameter and bioactivity outside the cavitation regime. Their results suggested that side effects of the application due to local protein damage is expected to be minimal. Studies on hydrodynamic cavitation in biomedical treatment are summarized in Table V.

V. Side Effects and Limitations in Biomedical Use of Ultrasound and Hydrodynamic Cavitation

Ultrasound cavitation treatment of cells or tissues was reported to have several side effects in various systems. At a cellular level, cell death either resulting in instant cell lysis or in the induction of programmed cell death is the main outcome of ultrasonic cavitation treatment. Cell membrane disruption followed by induction of apoptotic cell death was detected after administration of low-intensity ultrasound cavitation in leukemic cells [286]–[288]. Similarly, *in vitro* application of high-frequency ultrasound has also been shown to lead to irreversible cellular damage via apoptotic programmed cell death [289]. Activation of programmed cell-death mechanism by ultrasonic cavitation was revealed in various human [290], [291] and murine [292] cancer cells.

In addition to cellular damage, the cavitation phenomenon induced by shock waves caused serious injuries in organs of the body. Brujan [293] reviewed the effects of cavitation bubbles in the cardiovascular application of ultrasound and laser surgery as well as the effects of cavitation in mechanical heart valves. He indicated that the interaction between cavitation bubbles and tissue during pulsed laser surgery caused damage to surrounding tissues. The author also emphasized on the effects of bubbles collapse resulting in the generation of shock waves, high-velocity liquid jets, free radical species, and strong shear forces, which might damage the nearby tissues during cardiovascular application of ultrasonic cavitation.

Although the most commonly used technique, SWL, has a good success rate for kidney stone treatment in adults [294]–[296], there are many studies reporting the side effects of SWL. Its destructive effects result in intensification of stone malady due to several shock wave lithotripsies [297]–[300], HTN inception [301], [302], tissue injury [303], [304], hematoma formation [305], [306], scar formation [307]–[310], diabetes [311], nephron, and blood vessel injury [312]–[315]. Furthermore, vascular damages were also observed in a wide range in *in vitro* experiments [316]. Denburg *et al.* [317] tried to evaluate the occurrence rate of arterial HTN and/or chronic kidney disease during the ESWL and ureteroscopy treatment on the patients with urolithiasis. They showed that a particular case with urolithiasis has a risk ratio for HTN in comparison to cases without urolithiasis.

Recker *et al.* [318] investigated vulnerable parts of the body exposed to the effects of shock waves and found that critical intrarenal hematomas were one of the most serious harmful outcomes. Shock waves indirectly stimulated the sciatic nerves, and its consequences were studied by Schelling *et al.* [319]. They found that cavitation caused significant pain during ESWL. Induced shear stress [320] and hydrostatic tension [321] were considered as factors affecting kidney injury in prefocal region. Howard *et al.* [322] demonstrated in an *in vitro* study that bubble collapse had the ability to devastate thin membranes. Their results showed that the energy of implosion of bubbles produced heat-induced free radicals, which could damage nearby cells and tissues. Al-Awadi *et al.* [323] studied the effect of the antioxidation on renal injury. They performed a clinical study to determine how antioxidants could decrease short-term damage of the SWL treatment. Their experiments focused on three groups of patients: patients not taking any antioxidants (control group) and the other two groups taking different amounts of antioxidants capsules, "Nature Made R." Blood and urine samples were gathered during various periods before and after ESWL. The serum albumin amount measured in the group taking antioxidants was higher in comparison to the control group. Their results proved that free radicals were produced during treatment, and antioxidants reduced renal injury in blood generated after ESWL administration. Aksoy *et al.* [324] focused on the effect of SWL on plasma and malondialdehyde (MDA) concentrations and found that this method led to disruption in the renal capillary, which led to renal ischemia-reperfusion (I/R) injury. They also claimed that erythrocyte glucose-6-phosphate dehydrogenase and its catalystic function were considerably reduced one hour after SWL treatment in comparison to the initial values. Clark *et al.* [325] reported that the pretreatment of low-energy SWL in kidney stone treatment could considerably decrease the renal oxidative stress generated by SWL and also inflammation prior to the actual high-energy shock wave. Benyi *et al.* [326] proposed a method, in which a randomized investigation was applied to several patients, and a calcium antagonist (nifedipine) and also a xanthine oxidase inhibitor (allopurinal)

TABLE VI
SUMMARY OF STUDIES ON SWL SIDE EFFECTS

Observation	Side Effects Considered	Reference
In vitro experiments	HTN inception	Janetschek *et al.* [301] Barbosa *et al.* [302]
Renal function observation under SWL	Tissue injury	Connors *et al.* [303] Deng *et al.* [304]
In vitro functional outcome of ESWL	Hematoma formation	Fainas *et al.* [305] Krishnamurthi *et al.* [306]
Renal calculi observation under SWL	Scar formation	Morris *et al.* [307] Koga *et al.* [308] Lechevallier *et al.* [309] Newman *et al.* [310]
Renal and proximal ureteral stones under SWL	Diabetes	Krambeck *et al.* [311]
In vitro observation of renal calculi under SWL	Nephron and blood vessel injury	McAteer *et al.* [312] Handa *et al.* [313] Evan *et al.* [314] Brewer *et al.* [315]
In vitro experiments	Vascular defects	Shao *et al.* [316]
Vulnerable organs observation under SWL	Intrarenal hematomas	Recker *et al.* [318]
Sciatic nerves exposure to SWL	Sciatic nerves	Schelling *et al.* [319]
Prefocal region observation in SWL	Hydrostatic tension and shear stress	Sturtevant *et al.* [320] Bailey *et al.* [164] Zhong *et al.* [321]
Plasma and malondialdehyde (MDA) concentrations observation under SWL	Renal ischemia-reperfusion (I/R) injury.	Aksoy *et al.* [324]

TABLE VII
MECHANISMS OF STONE FRAGMENTATION IN SWL

Mechanism	Advantage and Disadvantage	Implementation	Reference
Tear and shear forces	Restricted to small area target observation	Occurrence of pressure drop and front and distal surface pressure variation	Chaussy [43]
Quasi-static Squeezing	Restricted to large area target observation	Occurrence of pressure gradient in squeezing of the stone	Eisenmenger [196]
Dynamic Squeezing	High accuracy in numerical simulation analysis	Squeezing waves effect on the shear waves generated at the stone corner	Sapozhnikov *et al.* [88]
Cavitation	Privilege in stone fragmentation and shock wave exposure	Pressure drop occurrence in low static pressure and negative pressure wave generation	Crum [108]
Spallation	Restricted to small area target observation	High tension level generation at distal surface of the stone	Zhong *et al.* [117]

were examined on high-energy renal function. They tried to reduce renal damage induced by SWL and found that calcium antagonist could affect the urine rate of albumin in patients exposed to SWL.

Despite the increasing potential of hydrodynamic cavitation, its clinical application has also some limitations. *In vivo* applications might only be possible through the integration of a cavitation tube system into an endoscopy device. This system may require a flow tube in order to generate negative pressure, and the treatment could only be performed in tissues, where the tip of the device can be positioned. Precise manipulation of the endoscopic probe in the body is another critical point. The endoscopy device should allow the application of hydrodynamic cavitation in a localized and targeted manner. Table VI summarizes SWL side effects reported in the literature, while important mechanisms of stone fragmentation in SWL are gathered in Table VII.

VI. Concluding Remarks

In this review, the advances in ultrasonic and hydrodynamic cavitation and their biomedical applications were discussed. Studies from the earliest steps to very recent investigations were included so that a comprehensive review was provided. SWL, tandem, and secondary shock wave were considered, and the most significant findings focusing on these topics were presented in detail. Since the pressure field occupies a very vital area in the ultrasound cavitation and has a significant parameter in the SWL method, it was taken into account in detail. Although most of the investigations regarding ESWL were carried out experimentally, numerical studies were also considered in order to add a numerical perspective to the review. Historipsy and hydrodynamic cavitation, which have been recently implemented as alternatives, were other important subsections of the review.

The data in the literature emphasize on the importance of cavitation phenomenon generated by both ultrasonic and hydrodynamic sources and its potential applications in biomedical sciences. Today, the clinical use and efficacy of ultrasound cavitation are well established, particularly in urinary stones treatment. Alternatively, hydrodynamic cavitation has been recently considered as an emerging research area in biomedical applications, and its efficacy on cell disruption, water disinfection, and urinary stones treatment is proven in *in vitro* studies. However, as discussed previously, *in vivo* implementation of hydrodynamic cavitation has some limitations, and its clinical use is still not available. Therefore, further investigations are needed to better characterize the physical properties, bubble dynamics, and the effects of bubble collapse on tissue or organ system. More precise definition of optimum surgical conditions in hydrodynamic cavitation procedure is required for preventing undesirable consequences. On top of all these, hydrodynamic cavitation should also be tested in other areas such as drug delivery or diagnosis to reveal full potential of this technique. Overall, it is likely that hydrodynamic cavitation offers a substantial promise for biomedical applications.

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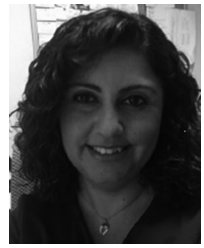

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