Applications of shock wave research to medicine

K. Takayama & K. Ohtani
Tohoku University Biomedical Engineering Research Organization

Abstract

Applications of shock wave research conducted in Tohoku University are briefly described. Its is emphasized that underwater shock wave research and its connection to bubble dynamics are one of the most important physical backgrounds to interpret tissue damages occurring during shock wave therapy. In addiction to ESWL, revascularization of cerebral thrombosis by using a laser induced liquid jet and its application to the water jet dissection method are presented. Lastly the development of a laser ablation induced drug delivery system is briefly described. In these applications implicitly and explicitly shock waves and their interaction with the bubble always play an important role.
Keywords: shock wave therapy, water jet, gene delivery.

1 Introduction

In the Shock Wave Research Center of the Institute of Fluid Science, Tohoku University, the first underwater shock wave research was performed in 1975 in conjunction with bubble dynamic studies. Based on these results, in 1982 we initiated a collaboration with the School of Medicine, Tohoku University for exploring extracorporeal shock wave lithotripsy (ESWL), which is a non-invasive disintegration of kidney stones by means of underwater focusing onto kidney stones from outside a human body (Kuwahara and Takayama [12]).

A prototype ESWL device was constructed in 1983 and eventually approved in 1987 for clinical therapy by the Ministry of Health in Japan. The existing device developed at the Dornier Systems employed electrical discharges for shock generation (Chaussey et al [2]), however, in our device shock waves were generated by exploding silver azide pellets. It was probably one of the most unique uses of primary explosive for peaceful purpose (Glass [3]). Despite its

www.witpress.com, ISSN 1743-355X (on-line)

wonderful clinical merits, even though it is very slight, tissues inside kidneys treated with ESWL were damaged (Takayama [15]). Later it is found that the tissue damages caused mostly by spontaneous penetration of micro water jets into tissues at the moment of bubble collapse.

Later we started to be convinced that we could damage soft tissue in a controlled fashion locally by using the bubble collapse. Then the penetration of cerebral thrombosis was one of the appropriate applications. We at first used silver azide pellets weighing from several 10 μg to a few mg for shock generation but later employed the irradiation of pulsed Ho:YAG laser beams in a catheter. The laser beam irradiation created spontaneously a water vapor bubble and its displacement drove an intermittent water jet from the catheter's exit. We named it the laser induced liquid jet (LILJ). Then LILJ effectively penetrated cerebral thrombi even more effectively than the use of explosives. LILJ has been expanded to various dissection purposes and preliminary in vivo studies were performed (Nakagawa et al [13]).

These activities were transferred to the Tohoku University Biomedical Engineering Research Organization (TUBERO), in which we now concentrate to develop shock wave assisted therapeutic devices and at the same time to clarify mechanisms of shock/cell interaction. This paper reports recent developments of shock wave related therapeutic devices performed in TUBERO and a fundamental experiment regarding shock/cell interactions.

2 Underwater shock waves

At the earlier stage of the underwater shock wave research, we used underwater electrical discharges from condenser banks for shock generation. However this method could not be reliable and was difficult to regulate. Then we detonated lead azide pellets weighing a few mg submerged in water and ignited them with irradiation of Q-switched ruby laser beams. This system worked effectively for basic ESWL studies but we felt it awkward to clinically explode them in a position very close to the brain. Hence we started to employ focusing of pulse laser beams.

A Ho:YAG laser has a wave length of 2090nm, which is close to the peak absorption coefficient of light energy in water at 1900nm and, as a source of underwater shock wave generation, is more suitable than using an Nd:YAG laser with 1060 nm wave length (Komatsu [11], Hirano et al. [4]). During the focusing of a Q-switched Ho:YAG laser beam of 200ns pulse duration in water, water absorbing its energy vaporizes instantly or forms plasma clouds, which acts as an expanding spherical piston driving a spherical underwater shock wave. For very short laser pulse duration, due to so-called inverse bremsstrahlung, free electrons absorbing laser light energy are further accelerated, promoting the process of shock formation.

Hosseini et al. [5] introduced a Ho:YAG laser beam into water through a 0.6mm core diameter optical fiber, the end of which was polished into an aspheric lens shape to focus the laser beam in a spot. With a laser energy of 160mJ shock overpressure was 10MPa at 4 mm from the focal point. Figure 1 shows a spherical underwater micro-shock wave. Fringe accumulation at the tip of the optical fiber indicates the region of high temperature.

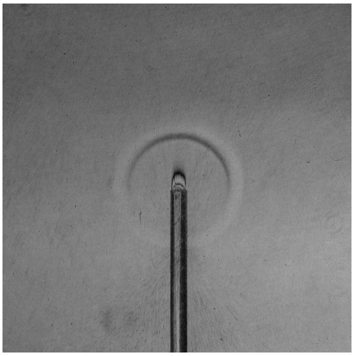


Figure 1: A micro-shock wave by focusing of a Ho:YAG laser in water.

The deposition of laser energy in water created a high-pressure water plasma cloud, which instantaneously drove an underwater shock wave. However, the shock wave is not necessarily uniformly intense to all directions and is the strongest toward the direction of laser beam irradiation. It is nearly a sound wave to the reverse direction and hence we can see the propagation of the compression stress wave along the optical fiber surface. The shock wave so far formed became spherical with its propagation and eventually attenuates to a sound wave. The plasma bubble started to contract oscillate several ms later and when it started to expand, its spherical shape was no longer maintained.

3 Generation of micro water jet

When laser beams are focused at the center of a long capillary tube, the bubble motion is affected by the diameter of the capillary tubes and the laser beam energy. As the dwell time of laser-induced-water vapor bubbles is shorter than that of explosion product gases for quickly forming micro-shock waves, the use of laser focusing is more advantageous for clinical applications than the explosion of micro gram silver azide.

Komatsu [11] focused the Ho:YAG laser beams with energy ranging from 160mJ/pulse to 340mJ/pulse in capillary glass tubes with various diameters, and visualized with a high-speed video recording with one million frames per second and the frame numbers of 16. In the case of a small diameter tube, the bubble shape is cylindrical and fills the entire diameter of the tube. Shock waves are quickly attenuated due to the presence of the solid wall that prevented free expansions. The bubble dwell time increases proportionally to laser energy and decreases with the increase of tube diameter. The displacement of water in a capillary tube drives micro-water jets that are ejected into water from the opening of the capillary tube. The speed of jets is fast enough to penetrate soft objects.

4 Revascularization of cerebral thrombosis

Cerebral embolism occurs when emboli (blood clots) are carried by blood flows from the cardiac artery and choke at cerebral arteries or middle cerebral arteries. If cerebral emboli can be removed mechanically or resolved by introducing a fibrinolytic agent, that is an enzyme and resolves clots, within approximately six hours of the stroke, symptoms will disappear without side effects.

Various clinical methods have been used to remove cerebral emboli, but reliable methods are still needed for this purpose. We noticed, at the earlier stage of our medial research and development, the use of shock/bubble interaction assisted micro-water jets for revascularizing cerebral thrombosis (re-opening blood flows by removing cerebral thrombi in brain arteries). Such micro-water jets were loaded on the surface of artificial thrombi filled inside the Teflon tube, a replacement of cerebral artery (Kodama et al. [10]).

Hirano et al. [4] and Komatsu [11] observed that the laser induced jets could penetrate gelatin layers more deeply than those created with micro-explosions. Komatsu [11] optimized the combination of parameters such as the capillary tube diameter, the stand-off distance that is the distance between the tip of optical fiber and the opening of the capillary tube, and the laser energy and obtained the jet speed of 10 to 16m/s in water. With these optimized combinations of parameters we produced a prototype clinical device by using a 2.0mm outer diameter catheter consisting of a water supply tube, a 0.6mm core diameter optical fiber, and an extended plastic tube for jet formation.

Figure 2 shows a high-speed video observation of a jet released from the extended open end of the catheter into a gelatin layer that is placed in a 4 mm diameter glass tube and attached at the open end of the catheter as an alternative to the cerebral thrombus.

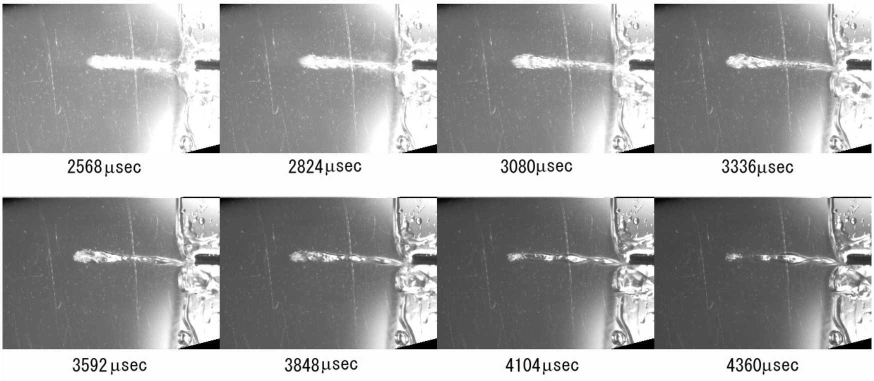
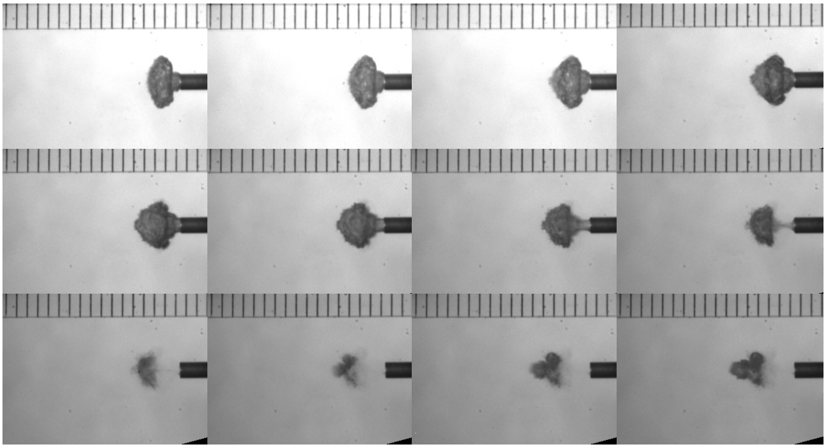


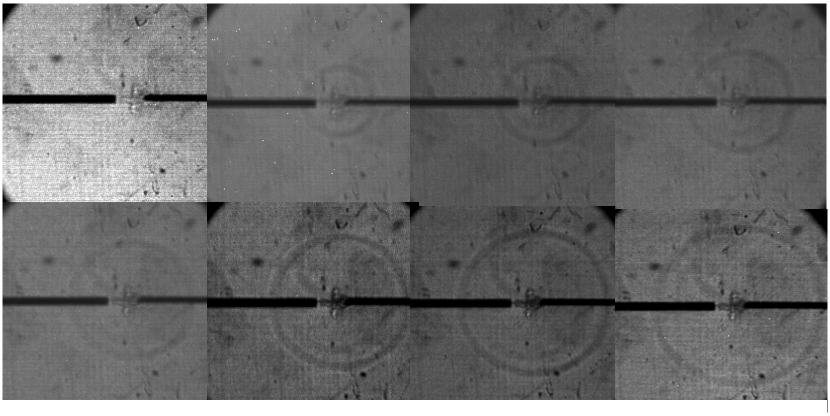
Figure 2: High-speed video observation of a Ho:YAG laser induced water jet (Komatsu [11]).

The peak penetration depth decreases gradually for increase in the stand-off distance. This implies that the attachment of a thin extension tube to the exit of the catheter would elongate the reach of micro-water jets to thinner cerebral arteries. At the stand-off distance of 10 mm, we obtain the jet penetration depth of 9 mm for a single run. Hirano (2003) eventually succeeded in treating thrombi beyond middle cerebral arteries by connecting a 200 mm long micro-catheter to the main catheter exit. Minute fragments so far created during the jet penetration into thrombi are removed effectively with a suction mechanism.

Free discharge of micro-jets in quiescent water created cavitation bubbles with diameters in the order of magnitude of 100μm at about a 4mm distance from the catheter exit. Bubble collapse then generated micro-shocks with overpressures of about 13MPa. Nakagawa [13] used their resulting micro-jets to interaction to deliver liquid resolved drug into artery surface. Figure 3 shows the sequential observation of bubble collapse induced micro-shock waves.



(a) Jet formation in water (interframe time 32 μs)



(b) Shock generation in water jet (interframe time 1 μs)

Figure 3: Generation of micro-shock waves.

5 Drug/gene delivery system

For introducing DNA into a cell, genes are carried by vector viruses or liposomes. However, these carriers are not always reliable nor do they exhibit undesirable characters, for instance, vector viruses trigger cancers and liposomes are toxic. Historically existing mechanical methods are applied to plant cells and totally unsuited for therapeutic use inside human bodies. Hence, a safe and reliable and mechanical method best suited for clinical use should be developed.

Kambe et al. [7] applied an intense ultrasound wave focusing to human clone cancer cell lines in saline solution and observed the disappearance of microvilli (small spikes on the cell line) and dents and perforations on the cell membrane, through which bleomycin (an anticancer agent) was introduced. However, the formation of dent and perforation was not clear. In the shock focusing method or ultrasound wave focusing, the role of shock wave interactions with minute structure has not been investigated from a gas-dynamic viewpoint.

Klein et al. [8] proposed for the first time a mechanical delivery system by using a powder gun, which was named a particle gas gun. Gene-coated 4μm tungsten particles were attached on the frontal surface of a 5mm diameter and 8mm long nylon cylinder on the frontal surface and were accelerated by the combustion of smokeless powder. At the sudden stop of the cylinder at the gun muzzle, the tungsten particles were ejected at 430m/s, penetrating into the cells placed at a distance of 100mm to 150mm from the gun muzzle. This was the first and successful application of ballistic technology to gene delivery and eventually achieved successful DNA recombination to plant cells (Sanford et al. [14].)

Sanford et al. [14] summarized possible particle delivery technology before 1990, but none were applicable to therapeutic purposes. Du Pont patented a gene delivery system named Balistics, in which gene-coated metallic particles were accelerated by pressurized helium. This particle acceleration idea is based on a shock tube operation and its structure consists of a chamber containing pressurized helium, a particle holder that contains gene-coated metallic particles, a quick opening valve separating the chamber from the particle holder, and a targeting specimen that is plant cells. The quick valve opening generates a shock wave and high-speed flow behind it, which efficiently accelerates particles penetrating into the specimen.

Following this idea, Bellhouse et al. [1] invented needle-free drug delivery systems, which essentially drive dry drug particles with pressurized helium at 6MPa. This system was named the Powder Jet and is commercially available. Kendall et al. [9] investigated the mot ion of particle clouds and their penetration into soft tissues and recently converted this system to gene delivery. However, this system cannot be used inside the human body because of the use of pressurized helium.

We developed a laser ablation assisted drug delivery system. When a Q-switched laser beam is irradiated on a metal foil, a plasma cloud is formed spontaneously which jets in the reverse direction to the laser irradiation, which results in a shock formation in the metal. When it reflects from the other side of the metal foil, its reflected wave is an expansion wave or unloading wave and hence the metal foil will bulge or punch out instantaneously flying at high-speed.

Jagadeesh et al. [6] irradiated a Q-switched Nd:YAG laser beam (SAGA 220, 1.65J/pulse and pulse duration 6.5ns) on a metal foil creating its high speed deformation. To optimize laser-induced plasma confined in a relatively small space, the laser beam was focused on a 0.1mm thick aluminium foil surface backed up with a 5mm thick fused quartz plate. With such a controlled energy deposition, very high-speed deformation of metal foils effectively ejected drug particles or gene coated metal particles at a speed ranging from 1 to 5km/s. We named this as a laser ablation-assisted particle delivery system.

An agarose cell layer was a target material in vitro tests, which was facing against the metal foil at a 6mm stand-off distance. Then the penetration depth of 6mm was achieved when the metal foil was ruptured and it was about 1 mm for un-ruptured metal foil. This system is not only robust but also compact enough to be combined with an endoscope.

It should be noticed that in the Biolistics and the Powder Ject the impingement of free flight particles on the surface of a target material is not controllable, however, in this system particles is distributed on metal foils in a controlled fashion so that their impingement and penetration depths are precisely regulated. In order to determine the spatial distribution of particle impingement holes and penetration depth, we started to investigate particles' free flight. Suppose the free flight of one-micro particle at Mach number 5 in air, the corresponding Reynolds number is about 100. This is a Stokes flow and at hypersonic speed range. In addition to this, the corresponding Knudsen number is about 0.01 so that the continuum flow approximation is just acceptable. To evaluate effect of aerodynamic heating and enormously high acceleration on the particle motion and also change of characteristics of attached gene, we conducted numerical simulations. However, the free flight distance is a few mm and hence the dwell time of particles at high speed is at most in the order of magnitude of one-micro sec. The bow shock building up around particles are no longer discontinuous relative to particle size and the contribution of these effects is physically negligible. Figure 4 shows the result of a preliminary experiment, a one-micron diameter tungsten particle penetrated well into a cell line in saline solution.

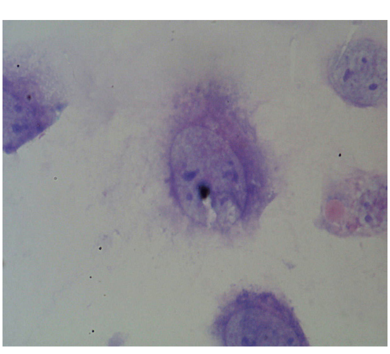


Figure 4: Penetration of a tungsten particle into a cell line.

6 Concluding remarks

We describe interdisciplinary applications of shock wave research to medicine. We expect that various shock wave-assisted therapies will be well defined because shock wave therapy evolves as an independent physical approach for medicine. However, for shock wave dynamics to contribute to these research fields we still need more careful surveys for resolving shock waves in complex media.

Acknowledgements

The author would like to acknowledge the staff and students of the Shock Wave Research Center, Institute of Fluid Science, Tohoku University and Tohoku University Biomedical Engineering Organization for their devotions to interdisciplinary shock wave research. Interdisciplinary shock wave research in SWRC has been supported by the Grant-in-Aid for Science Research 12CE2003 offered by the Ministry of Education, Science, Culture, Sport, and Technology in Japan.

References

[1] Bellhouse BJ, Quilan NJ, Ainsworth RW., Needle-less delivery of drug, in dry powder form, using shock waves and supersonic gas flow, In: Houwing AFP, Paul A, Boyce RR, Danehy PM, Hannemann M, Kurtz JJ, McIntyre TJ, McMahon SJ, Mee DJ, Sandeman RJ, Tanno H. (eds) *Proc. 21st Int Symp on Shock Waves*, pp. 51-56, 1997.

[2] Chaussey C, Schmiedt E, Jocham D, Walter V, Brendel W, Forssmann B, Hepp W., *Extracorporeal Shock Wave Lithotripsy*, Karger, Germany, 1982.

[3] Glass II., Some aspects of shock wave-research, Dryden Lectureship in Research, *AIAA J.* **25**, pp. 214-229, 1987.

[4] Hirano T, Komatsu M, Saeki T, Onodera O, Takayama K, Takahashi A, Uenohara H, Yoshimoto T., Enhancement of fibrinolytics with a laser-induced liquid jets, *Laser Surg. Med.* **29**, pp. 360-368, 2001.

[5] Hosseini SHR, Hirano T, Onodera O, Takayama K, Takahashi A, Uenohara, Yoshimoto T., Study of laser driven underwater shock waves for medical application, *Proc. Japanese Shock Wave Symposium* ed. K Takayama, pp. 613-616, 2000.

[6] Jagadeesh G, Kawagishi J, Takayama K, Takahashi A, Cole J, Reddy KP., A new micro particle delivery system using laser ablation, In: Lu F (ed) *Proc. 23rd Int Symp Shock Waves Fortworth USA*, pp. 859-866, 2001.

[7] Kambe M, Ioritani M, Shirai S, Kambe K, Tezuka F, Kaji M, Saitoh T, Murakami Y, Kuwahara M, Funato T, Gamo M, Takayama K, Orikasa S, Kanamaru R., Macroscopic pores opened by shock wave on cancer cell surfaces: Morphological and functional features, *Jpn. J. Endourol ESWL*, **9**, pp. 161-167, 1996.

www.witpress.com, ISSN 1743-355X (on-line)

[8] Klein TM, Wolf ED, Wu R, Stanford JC., High-velocity microprojectiles for delivering nucleic acids into living cells and tissues, *Nature* **7**, pp. 70-73, 1987.

[9] Kendall MAF, Quilan NJ, Thorpe Sj, Ainworth RW, Bellhouse BJ., The gas-particle dynamics of a high-speed needle-free drug delivery system, In: Ball GJ, Hillier R, Roberts GT (eds) *Proc. 22nd Int. Symp. on Shock Waves*, pp. 605-610, 1999.

[10] Kodama T., Takayama K., Uenohara H., A new technology for revascularization of cerebral embolism using liquid jet impact, *Phys. Med. Biol*., 42, 2355-2367, 1997.

[11] Komatsu M., Study of applications of shock waves to medicine, Doctor Thesis, Graduate School of Tohoku University, Aerospace Engineering, 2002.

[12] Kuwahara M, Takayama K., Extraxorporeal microexplosive lithotripter, Sate-of- Art Extracorporeal ShockWave Lithotripsy, Furutura Pub Comp Inc Mount Kisco NY, pp. 97-110, 1984.

[13] Nakagawa A., Application of shock waves as a treatment modality in the vicinity of brain and skull, *J. Neurosurgery*, **99**, pp. 156-162, 2003.

[14] Sanford JC, Klein TM, Wolf ED, Allen N., Delivery of substances into cells and tissues using particle bombardment process, *Prt. Sci. Tech.* **5**, pp. 27-37, 1987.

[15] Takayama K., Applications of shock wave research to medicine, In: Ball GJ, Hillier R, Roberts GT (eds) *Proc. 22nd Int. Symp. on Shock Waves*, pp. 23-32, 2000.

www.witpress.com, ISSN 1743-355X (on-line)