Fifth International Symposium on Cavitation (cav2003)
Osaka, Japan, November 1-4, 2003

CAVITATION IN BIOLOGICAL AND BIOENGINEERING CONTEXTS

Christopher E. Brennen
California Institute of Technology, Pasadena, CA 91125
brennen@its.caltech.edu

ABSTRACT

There are an increasing number of biological and bioengineering contexts in which cavitation is either utilized to create some desired effect or occurs as a byproduct of some other process. In this review an attempt will be made to describe a cross-section of these cavitation phenomena. In the byproduct category we describe some of the cavitation generated by head injuries and in artifical heart valves. In the utilization category we review the cavitation produced during lithotripsy and phacoemulsification. As an additional example we describe the nucleation suppression phenomena encountered in supersaturated oxygen solution injection.

Virtually all of these cavitation and nucleation phenomena are critically dependent on the existence of nucleation sites. In most conventional engineering contexts, the prediction and control of nucleation sites is very uncertain even when dealing with a simple liquid like water. In complex biological fluids, there is a much greater dearth of information.

Moreover, all these biological contexts seem to involve transient, unsteady cavitation. Consequently they involve the difficult issue of the statistical coincidence of nucleation sites and transient low pressures. The unsteady, transient nature of the phenomena means that one must be aware of the role of system dynamics in vivo and in vitro. For example, the artificial heart valve problem clearly demonstrates the importance of structural flexibility in determining cavitation occurrence and cavitation damage. Other system issues are very important in the design of in vitro system for the study of cavitation consequences.

Another common feature of these phenomena is that often the cavitation occurs in the form of a cloud of bubbles and thus involves bubble interactions and bubble cloud phenomena.

In this review we summarize these issues and some of the other characteristics of biological cavitation phenomena.

INTRODUCTION

One of the first people to recognize the occurrence of cavitation in living organisms was E.N.Harvey whose work eventually encompassed many aspects of bubble formation in plants and in animals. His considerations of the state of tension in the sap of trees led him to important deliberations on the ability of a liquid to sustain tension and, consequently, on a model ("the Harvey nucleus") that he used to explain the existence of stable cavitation nuclei in a liquid [1-5]. This model was an important precursor to our current understanding of the existence of stabilized nuclei in the cracks and interstices of solid surfaces in contact with a liquid. Harvey went on to an erudite and broad ranging research career, that included investigations of the existence of cavitation nuclei in blood and in animal tissue [1,2], studies of the "bends" or bubble formation during decompression [6], and investigations of cavitation during wounding by high velocity missiles [7] as well as a host of studies of bioluminescence. He has been called the “Dean of Bioluminescence” but could also be identified as the father of cavitation studies in the biological environment.

Today, we recognize that the processes that involve cavitation in a biological or bioengineering context are so wide-ranging that it would be impossible (and excessively tedious) to attempt a comprehensive review. Rather we will focus on the different types of cavitation that occur or are generated, attempt to find common themes and thereby suggest avenues of basic research that might help advance these applications.

The cavitation that occurs in biological, bioengineering and biomedical contexts can be divided into that which is deliberately induced in order to generate some beneficial effect and that which occurs as an undesirable byproduct of some other procedure or device. We begin by reviewing the former.

ULTRASOUND

By far the commonest deliberate generation of cavitation in medicine is though the use of ultrasound. For a comprehensive recent review of the therapeutic effects of ultrasound the reader is referred to the excellent review by Bailey et al. [8]. Though the normal use of ultrasound is to emulsify unwanted tissue or to pulverize unwanted solid material, it is also beginning to be used for hemostasis (to stop bleeding in internal organs [9] such as the liver [10] and spleen [11]), for tumor necrosis [8] and for immunotherapy [8].

Two different tissue destruction techniques are used and are described in the following paragraphs. In some applications an ultrasonically vibrating probe is placed in close proximity to the tissue or solid material. The cavitation induced at the tip of this probe creates the desired effect when it is placed close to the

tissue or solid material. One of the earliest uses of such an ultrasonic probe was in dentistry, where ultrasonic probes are now commonly used to clean teeth by dislodging plaque [12] with product names such as Cavijet and Cavitron [13].

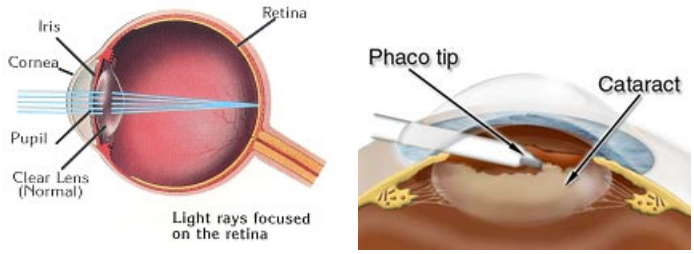

Figure 1. Schematics of the eye and of the phacoemulsification procedure.

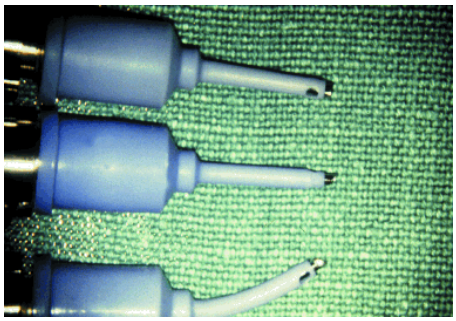

Figure 2. Phacoemulsification probes (from Sabbagh [15]).

Another common application is in phacoemulsification, the procedure most commonly used to emulsify and remove the natural optical lens during cataract surgery. A perfusion and vacuum system is built into the probe in order to remove the emulsified tissue. The invention of the phacoemulsification probe by Charles Kelman in 1967 was, in fact, motivated by the dental plaque-removing tool [14]. The advantage of the phacoemulsification tool is that it can be inserted through a very small incision in the side of the eye and the old lens removed with minimal invasion. The new artificial lens is then inserted in folded form through the same incision and unfolded in place. More than a million such procedures take place each year. However, the WHO estimates that 17 million more people in the world presently suffer from cataracts. While problems with the procedure are rare, the main concerns are collateral damage to surrounding tissue and the possibility of damage to the material of the tool itself which might result in metal debris being left behind in the eye [16].

Figure 3 is a frame from a high-speed video of a phaco-emulsification probe in use. It shows the cavitation on the 0.9mm diameter end face of the probe (or needle) as it approaches a cadaver lens (Anis [17]). Variations in the design of the probe have been deployed in attempts to increase its effectiveness and to minimize collateral damage by confining the cavitation to a well-controlled volume on the face of the device. One particular variation is particularly interesting from a fluid mechanical perspective. Anis [17,18] has developed a probe which not only vibrates at ultrasonic frequency (40kHz in this case) but also rotates (figure 3 is a view of this probe in action). Control over the extent of cavitation is important in minimizing collateral damage. In the absence of such control, cavitation can occur in unexpected locations; for example, figure 4 shows cavitation bubbles formed at the irrigation sleeve around the outside of the tool.

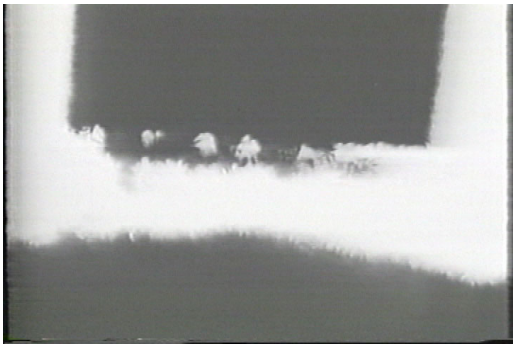

Figure 3. Outline of cavitation bubble cloud (the black images below the black rectangle) on the face of a phacoemulsifier (Anis [18]).

The typical noise generated by a cavitation event on the face of a phacoemulsifier is shown in figure 5 [19]. The pulses shown superimposed on the first high pressure cycle of the ultrasound are very similar to the cavitation event noise measured in other hydrodynamic experiments (for example [24, 25]).

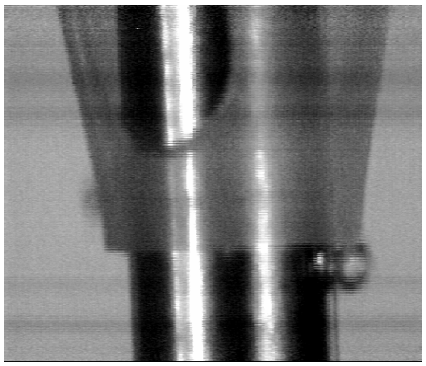

Figure 4. Cavitation bubbles near irrigation sleeve of a phacoemulsifier (from [20]).

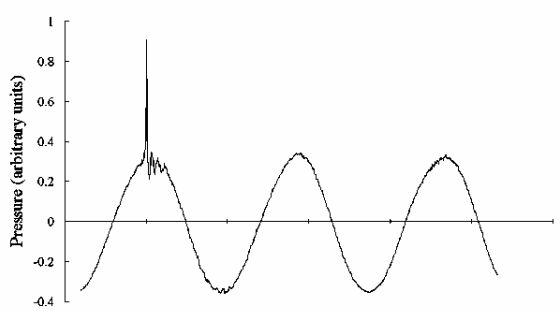

Figure 5. Typical phacoemulsification pressure signal showing a cavitation event during the first high pressure cycle (from [19]).

FOCUSED SHOCKWAVES AND ULTRASOUND

Cavitation is also generated remotely by focusing shockwaves or ultrasound at a target site within the body. For example, focusing is now commonly used in lithotripsy [22, 8, 25, 26], the process which remotely disintegrates kidney and gall stones so that they can be rejected by normal routes. With the patient submerged in a water bath (so that the surroundings closely match the acoustic impedance of the body), shockwaves or strong ultrasonic waves are focused at the site of the stone. Multiple shocks or wavetrains are then used to break the stone into pieces small enough to be ejected by the body. Cavitation may or may not play a role in the disintegration of the stone; it can also cause substantial collateral tissue damage.

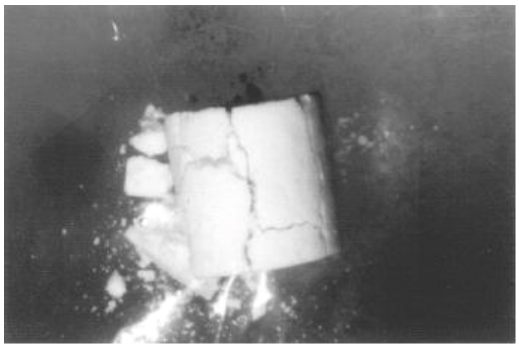

Figure 6. Artificial stone fractured by shockwave lithotripsy [23].

Figure 7. New and damaged artificial renal stone (courtesy of Erin Hatt, Dept. of Anatomy and Cell Biology, Indiana University).

Lithotripsy using shock waves has a long history [26]. Figure 6 exemplifies the fracture of an artificial stone by lithotripsy using strong shock waves. It seems likely that this form of communition results from shock-induced stresses rather than cavitation. On the other hand, the damage shown in figure 7 seems to be quite characteristic of cavitation. Strong shocks do cause widespread cavitation. Frequency dispersion prevents the shock waves from being more narrowly focused and consequently the focal volume is often significantly larger than the target stone. Figure 8 shows the formation of cavitation bubbles on an artificial stone in a shock wave lithotripter. Another illustration, figure 9, exemplifies how widespread the cavitation can be in a focal volume significantly larger than the target stone (the larger black object on the right). Consequently the cavitation generated by the shockwaves causes substantial collateral tissue damage in conventional lithotripsy. Double pulse shock wave lithotripsy can help reduce this focal volume [28] (see also figure 12).

The use of focused ultrasound (rather than shock waves) is more recent and has some significant advantages (see the review by Bailey et al [8]). With a significantly narrower spectrum ultrasound can be focused much more precisely and therefore has the potential for significantly reduced collateral damage.

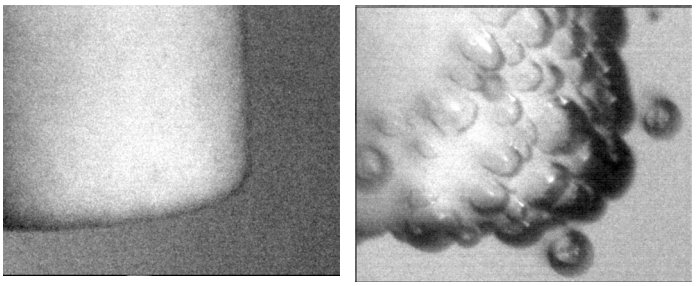

Figure 8. Cavitation bubbles (right) near surface of an artificial stone (left) (courtesy of D. Sokolov, M.R. Bailey, Center for Industrial and Medical Ultrasound, U. Washington)

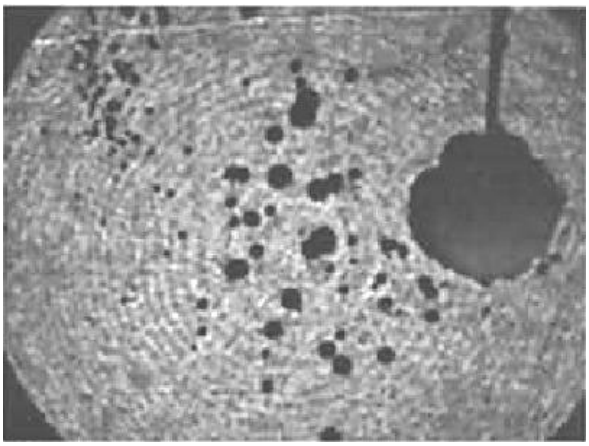

Figure 9. Typical shockwave lithotripsy bubble cloud near stone (larger black object) (from Zhu et al. [24]).

FOCUSED ULTRASOUND

The use in lithotripsy of focused ultrasound (rather than shock waves) is more recent [8, 25] and has some significant advantages. With a significantly narrower spectrum ultrasound can be focused much more precisely and therefore has the potential for significantly reduced collateral damage. It is possible to focus the cavitation on the surface of the stone (figure 10), enhancing the damage potential while reducing the collateral damage. The cavitation generated at the focal point pulverizes the material of the stone, ultimately reducing it to a powder [27].

Figure 11 (from [27]) shows a typical cloud of cavitation bubbles formed at the focal point. During the lecture videos of the damage process on both renal stone and on surrogates [27] will be presented. In these one can clearly see the downward cascades of solid particles generated at the focal point as well as an upward cascade of air microbubbles created by the cavitation.

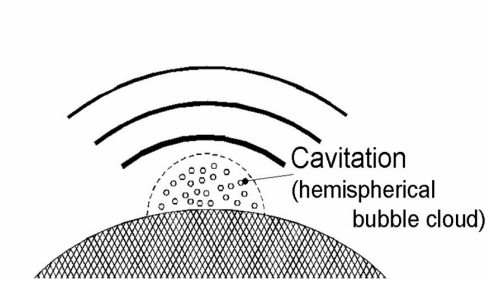

Figure 10. Schematic of the cavitation formed on a target at the focal point of an ultrasonic lithotripter (from [27]).

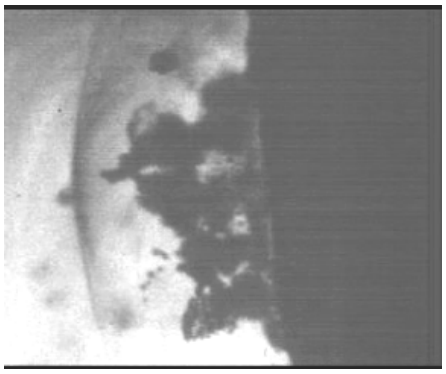

Figure 11. Bubble cloud (center) on face of a target stone (right) (from Matsumoto et al. [27]).

Various techniques have been investigated in order to try to refine lithotripter design. These usually have the competing objectives of limiting the collateral damage by confining the cavitation to a well-defined region while at the same time generating the most damage potential. These are partially competing objectives and the strength of the shockwaves or the ultrasound is usually limited by the need to minimize collateral damage. However, knowledge of the intricacies of bubble dynamics do suggest some superior strategies. Thus, for example, in shockwave lithotripsy multiple pulses [28] may be better than single pulses. As another example, we would note the strategy devised by Matsumoto et al. [27] who found that a period of high frequency ultrasound followed by a few low frequency cycles can be very effective. The high frequency period generates a cloud of small bubbles in the focal region by the process of rectified diffusion [21]. The subsequent low frequency pulses then cause the collapse of this cloud in the manner described by Wang and Brennen [29,30]. Provided the volume fraction in the collapse is high enough the cloud collapse produces a shock wave that propagates into the cloud and strengthens due to geometric focusing. This causes a much more intense shock at the cloud center (and at the surface of the stone in this application) than would be produced by single bubbles [21].

It should be noted that such complex strategies need analytical tools capable of predicting their consequences. Hence there is a need for CFD methodologies capable of predicting these complex bubbly flows. Tanguay and Colonius [31] have addressed this need and their work is exemplified by figure 12 which shows a comparison between the photographs of the bubbly clouds caused in the focal region by a double shockwave lithotripter pulse (photographs by Sokolov, see [28]) and the calculations of the void fraction distribution from the computations of Tanguay and Colonius.

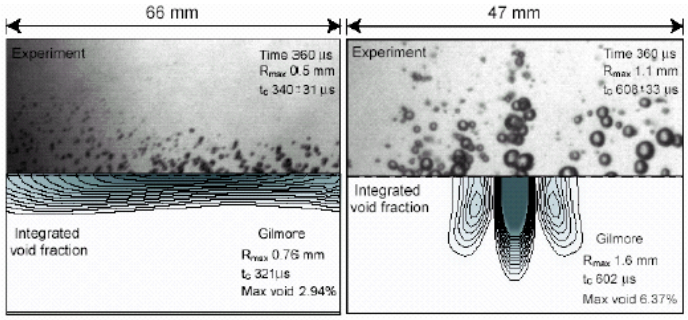

Figure 12. Comparisons between the experimental bubble clouds (upper half of figures, photographs by Sokolov (see [28]) and void fraction distributions from the calculations of Tanguay and Colonius [31]. Single pulse on left, double pulse on the right.

LASER-INDUCED CAVITATION

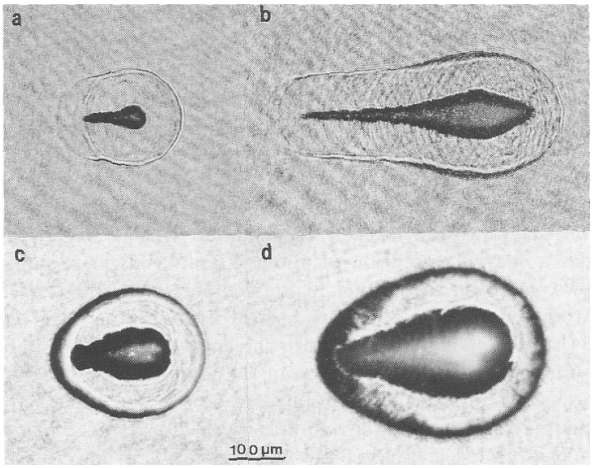

Figure 13. Shockwaves and bubbles formed at the focal point by picosecond laser pulses (a and b) and by nanosecond pulses (c and d). Beam coming from right. From Vogel and Busch [36].

Another method of generating cavitation in a selected region is by means of a focused laser beam. Known as photodisruption, the focused laser light creates cavitation bubbles that cut through tissue and thus generate precise microscopic incisions that are of great potential value in many surgical procedures. Known as "light scalpels", Nd:YAG laser pulses have, for example, become a well-established tool in "non-invasive" intraocular surgery [32-34]. The key to these tools is to produce repetitive, low energy pulses that have a very small damage range and thus limit undesirable collateral damage. As Vogel and his co-workers have demonstrated (see, for example, [35,36]), the extent of the damage is proportional to the cube root of the pulse energy, and therefore the objective is to use the lowest energy laser pulse that still causes cavitation. Vogel and Busch [36] have shown that this can be achieved by reducing the duration of the laser pulses and that picosecond pulses are therefore superior to nanosecond pulses. Some of their photographs are reproduced in figure 13; each frame shows the

extent of both the shock wave associated with the initiation of cavitation and, inside that, the cavitation bubble itself. The laser pulse is arriving from the right and the shape is of the images is, in part, determined by the shape of the focal volume.

Focused laser light is also used in other surgical procedures, for example, laser-induced lithotripsy [37] and in neurosurgery. In the latter, the primary issue is a concern for the limited control of the real-time laser interactions with the neural tissue (see, for example, [38]). Another example of the laser-induced cavitation is the procedure known as percutaneous laser disc decompression [39]. Laser energy is introduced into the nucleus pulposus (the gelatinous core of a spinal disk - see figure 14) through a needle in order to vaporize a small volume of the nucleus and, by removing that volume, reducing the pressure of the disk and thus relieve the pressure on the neural tissue.

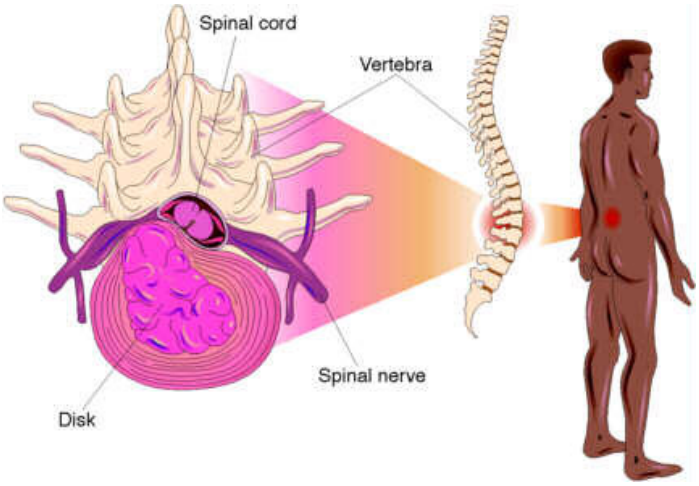

Figure 14. Schematic of the spinal structure (illustration by Electronic Illustrators Group).

ARTIFICAL HEART VALVE CAVITATION

One subject area that has received considerable publicity and therefore some careful attention (see [40-47]) is the issue of artificial heart valve cavitation, a problem whose seriousness did not become apparent until a large number of these valves had been installed. Though cavitation damage to the valve itself is an issue, the rupture of red bloods cells (hemolysis) by the cavitation is the primary concern. Parenthetically we note that attached cavitation appears to be more hemolytic than bubble cavitation [48].

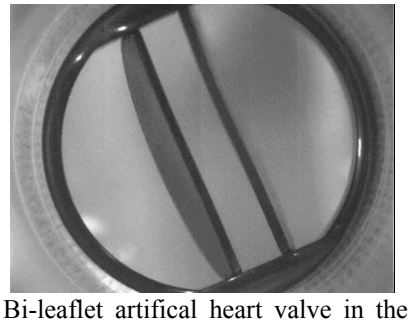

Figure 15. Bi-leaflet artifical heart valve in the open position viewed from downstream (from Rambod et al. [46]).

Though there are a number of different designs of prosthetic heart valves we choose to illustrate the phenomenon using the bi-leaflet type shown in figure 15. The flows associated with this valve prior to and during closure are

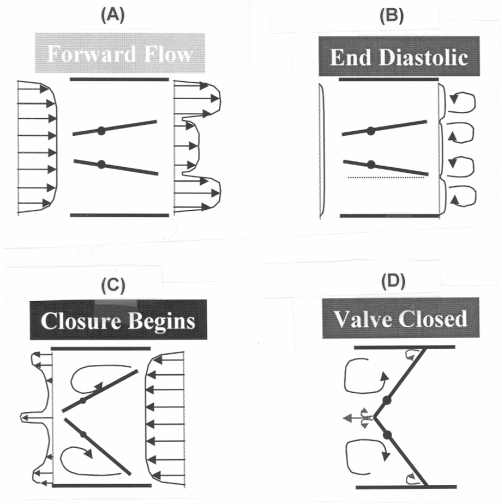

Figure 16. Schematic of the flows associated with the closing of a bileaflet prosthetic heart valve (from [47]).

sketched in figure 16. The two leaflets hinge at roughly the end-on locations shown in figure 15. When first subjected to backflow (stage B, figure 16) these leaflets move in such a way that, just prior to closure (stage C, figure 16), there are narrow passages both along the central diameter and at the circular tips of the leaflets. For a time interval just before and after closure the deceleration of the flow downstream of the valve generates low pressures within the jets and vortices emanating from these temporary narrow passages, thus causing cavitation [47].

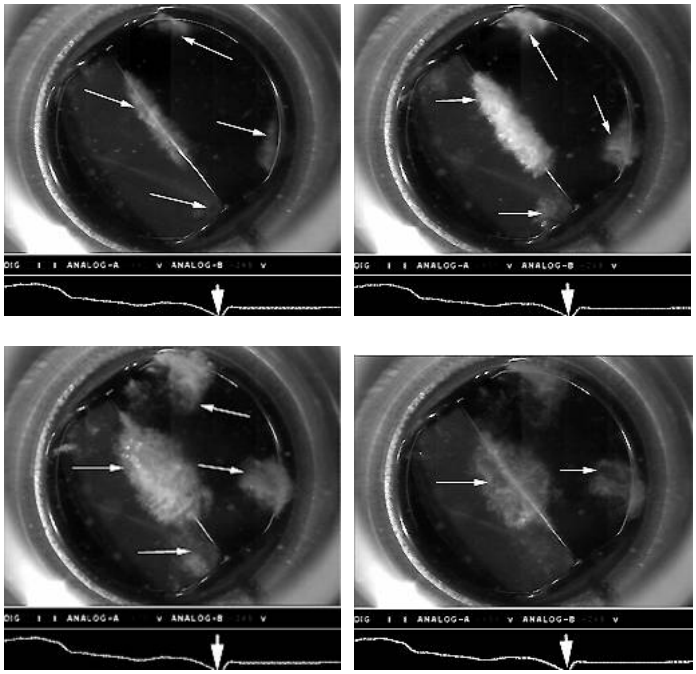

Figure 17. Photographs of cavitation downstream of a closing and closed artificial heart valve (from Rambod et al. [46]).

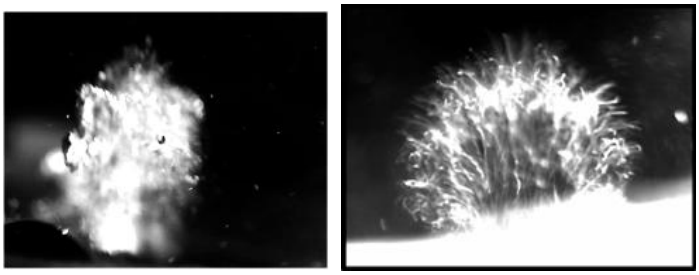

Figure 18. Closeup views of cloud-like cavitation in an artifical heart valve (from Rambod et al. [46]).

The extensive and careful research of the Penn State group [40-45] has done much to elucidate our understanding of this problem. Their observations have shown that both bubble and/or vortex cavitation may occur and that blood is similar to the transparent saline surrogates in so far as its cavitation susceptibility is concerned (Stinebring et al. [40], Garrison et al. [42]). Clearly future improvements in these prostheses will depend on improvements in our understanding of the features that promote or inhibit cavitation as well as an understanding of why they are currently inferior to natural valves. Zapanta et al. [45] provide some useful insights in this regard. They found that both the valve geometry and material have significant effects on the cavitation though the leakage clearance did not. It appears that softer materials provide compliance that reduces the magnitude of the low pressures and reduces the cavitation. This may be the reason that natural valves are superior. Clearly there is a need for better understanding of cavitation in the presence of flexible surfaces.

Prosthetic heart valve cavitation is illustrated herein by the photographs of Rambod et al. [46] reproduced in figures 17 and 18. The growth and collapse of the cavitation both along the central diameter and at the tips can be clearly seen in the sequence in figure 17. Close-ups of these clouds are shown in figure 18. It may be that the fluid used by Rambod et al. [46] contained more cavitation nuclei than some other experiments and hence the prevalence of clouds of cavitation bubbles. The photographs of Stinebring et al. [40] show smaller clouds as well as individual bubbles. However. in experiments conducted at Carbomedics, cavitation events did not occur during every closure and took the form of occasional single bubbles. This is illustrated in figure 19 where just a few individual cavitation

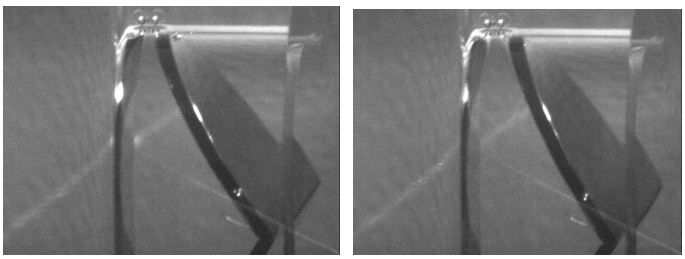

Figure 19. Photographs of a heart valve leaflet (the inclined black plate) just before and at closure showing cavitation bubbles just before closure (left) just downstream of leaflet tip (upper left) (courtesy of Carbomedics). The forward flow is from right to left.

bubbles can be observed near the leaflet tip. Thus it appears that this transient form of cavitation and its consequences may depend not only on the design of the valve and the flow conditions but also on the number of cavitation nuclei present in the fluid and the statistical coincidence of a nucleus with the transient low pressure region. Thus it is clear that more needs to be known about the population of nuclei in the blood.

HEAD INJURIES AND WOUNDS

Other subject areas in which the dynamics of cavitation are believed to be important are in head injuries and in wounds caused by high velocity bullets. These are lumped together only because they involve massive trauma and not because the pertinent mechanics are similar.

It has long been known that liquid-filled containers can experience cavitation when the container is subject to impact and/or high accelerations. The resulting pressure waves within the liquid cause momentary regions of low pressure within which the liquid may cavitate. In so far as such dynamics are concerned, the skull is effectively a liquid-filled container and, moreover, one which contains delicate structures. Thus, when subject to a external impact, head injuries are often compounded by cavitation of the cerebral fluid. Goldsmith and his coworkers conducted extensive experiments and analyses of the dynamics of head injuries [49,50]. The collapse of such cavitation bubbles could cause significant secondary damage during a head injury.

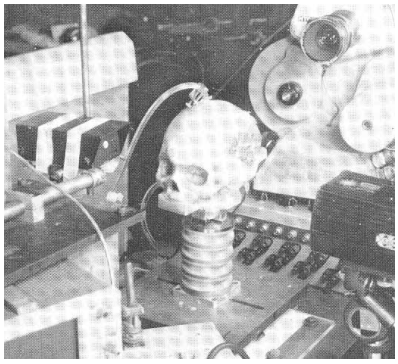

Figure 20. Cadaver skull replica used by Lubock and Goldsmith [51].

When an approximately spherical liquid-filled container is impacted on one side, thus creating a high pressure in the liquid on that impact side, the subsequent transmission and reflection of the pressure waves can generate low, even negative, pressures at other locations within the container (see, for example, [52]). Typically the lowest pressures occur at the contrecoup position on the side opposite the impact. Lubock and Goldsmith [51] studied the occurrence of cavitation in these low pressure zones using both simple spherical shells and cadaver skull replicas (see figure 20). They observed a number of interesting forms of cavitation. An example is shown in figure 21 which illustrates the ring patterns of cavitation bubbles that were observed to occur in water-filled spherical shells. Though cavitation was observed to occur with water, it was not observed when gelatin was used. Consequently, the extent to which cavitation magnifies the damage in head injuries remains uncertain.

The origin of the cavitation damage caused by high velocity bullets is different. When such an object passes through fluid-like tissue it creates a vapor-filled wake, a transient attached cavity. This tends to grow as the bullet progresses, in much the same way as occurs with water-entry cavities [53]. Consequently the exit wound is usually much larger than the entrance wound. Harvey [7] may have been among the first to investigate such phenomena.

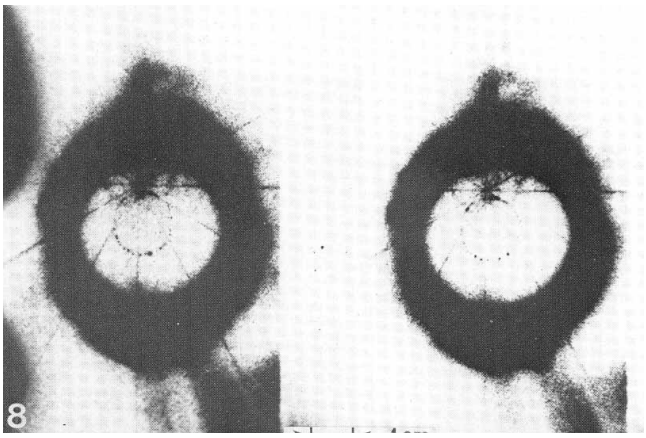

Figure 21. Ring patterns of cavitation bubbles in water-filled acrylic spherical head-neck model subjected to impact (from Lubock and Goldsmith [51]).

NUCLEATION SUPPRESSION

Many of the preceding examples have demonstrated the importance of cavitation nucleation sites in biological systems. Though far-fetched, it may therefore be of value to consider ways in which one might be able to control that site population and thereby modify the cavitation characteristics of a device. The author was recently involved with a project in which bubble nucleation suppression was remarkably successful [54,55]. The context is a system designed to inject a highly supersaturated aqueous solution of oxygen into the bloodstream in order to minimize tissue damage caused by oxygen deprivation in the aftermath of a heart attack or stroke. The aqueous solution of oxygen is prepared at very high pressure (100s of atmospheres) and then is injected through very small capillaries (100s of micrometers) at high speed (m/s). The trick is to accomplish mixing with the receiving fluid without the formation of gaseous oxygen bubbles; this is achieved as follows.

Because of the high speed and high pressure gradient within the capillary, only a short length close to the exit has a pressure below the saturation level. Consequently only nucleation sites within this short length have the potential to produce bubbles. Observations [54,55] showed that there were typically only of the order of 10 such sites in drawn silica capillaries. Moreover these sites could be deactivated by the simple expedient of flushing ethanol through the capillary while it was underwater. Apparently, the ethanol preferentially wets the interior surface of the site and removes the buried nucleation bubble/site. The ethanol may also help dissolve the gas in the nuclei since the solubility in ethanol is about an order of magnitude larger than the solubility in water.

This process of "ethanolization" of the surface was remarkably successful in suppressing nucleation. Moreover, it was made compatible with medical injection by preparing the capillary with an interior coating of benzalkonium heparin laid down in ethanol.

This remarkably successful example of nucleation suppression suggests that similar strategies might be successfully employed in other contexts though the precise mechanism requires more investigation before it can be thoroughly understood.

CONCLUSIONS

While this survey has been both episodic and superficial it nevertheless seems to reveal several common themes that, in turn, suggest areas of cavitation research that would prove valuable in the biological and bioengineering contexts:

Control of Cavitation:

The first (and perhaps most challenging) feature involves the need to control or manage cavitation. It seems clear that the desirability of such control is almost universal. The dual motivations are an increase in the effectiveness of the procedure and a reduction in the collateral damage. However, the methods devised for this control vary greatly. In phacoemulsification spatial control is sought through the design of the ultrasonic probe and the deployment of additional features such as rotation. In other circumstances, temporal rather than spatial control is attempted. Thus in lithotripsy, multiple pulses are used and more sophisticated strategies such as the Matsumoto et al. sequencing are being investigated. A different temporal control approach is embodied in the picosecond laser pulses of Vogel and his co-workers. It seems clear that much could be gained by exploration of more of these temporal and spatial control strategies especially when the full range of possible bubble and cloud dynamics are taken into account.

Stochastic Nature of Cavitation:

Most of the cavitation phenomena described above involve bubble cavitation in transient low pressure regions. Consequently the cavitation is governed by the coincidence of a nucleation site with the occurrence of that low pressure in space and time. In my opinion we need to know more about these stochastic aspects of cavitation and we need to devise experiments and experimental devices that would allow measurement of these statistical processes.

Of course, a key input to these processes is the distribution of nucleation sites. While much is now known about the nuclei distributions in water, very little is known of their existence in biological fluids or structures [46]. It may also be possible to alter or control the nucleation process [55].

Cloud Cavitation:

Many of the cavitation phenomena described also involve multiple bubbles or clouds of bubbles in which the interactions between the bubbles are critical to the cavitation dynamics. More needs to be learnt about the collapse of such bubble assemblages especial in the presence of solid structures. An important

component of this research will be the ability to accurately simulate these multiphase flows computationally.

Final Comment:

As a final comment, this author was surprised to learn of the wide range of biomedical and bioengineering contexts in which cavitation is utilized for beneficial effect. However, this wide range is very splintered and there is little crosstalk that could initiate new strategies and devices. Perhaps the fluids engineering community could play a role in providing some such unifying forum.

ACKNOWLEDGMENTS

Many individuals provided me with valuable assistance in the preparation of this review, including Tim Colonius, Allan Acosta, Yoichiro Matsumoto, Aziz Anis, Michel Tanguay, Brant Maines, Morteza Gharib and Larry Crum.

REFERENCES

[1] Harvey, E.N., Barnes, D.K., McElroy, W.D., Whiteley, A.H., Pease, D.C. and Cooper, K.W. (1944). Bubble formation in animals. I, Physical factors. *J. Cellular and Comp. Physiol*., **24**, No.1, 1--22.

[2] Harvey, E.N., Whiteley, A.H., McElroy, W.D., Pease, D.C. and Barnes, D.K. (1944). Bubble formation in animals. II, Gas nuclei and their distribution in blood and tissues. *J. Cellular and Comp. Physiol*., **24**, No.1, 23--24.

[3] Harvey, E.N., Barnes, D.K., McElroy, W.D., Whiteley, A.H. and Pease, D.C. (1945). Removal of gas nuclei from liquids and surfaces. *J. Amer. Chem. Soc*., **67**, No.1, 156--157.

[4] Harvey, E.N., Cooper, K.W., Whiteley, A.H., Pease, D.C. and McElroy, W.D. (1946). Bubble formation within single cells. *Biol. Bull*., **91**, No.2, 236--237.

[5] Harvey, E.N., McElroy, W.D. and Whiteley, A.H. (1947). On cavity formation in water. *J. Appl. Phys*., **18**, No.2, 162--172.

[6] Harvey, E.N. (1945). Decompression sickness and bubble formation in blood and tissues - Harvey lecture. *New York Acad. Med*., **21**, No.10, 505--536.

[7] Harvey, E.N. (1948). The mechanism of wounding by high velocity missiles. *Proc. Am. Phil. Soc*., **92**, 294--304.

[8] Bailey, M.R., Khokhlova, V.A., Sapozhnikov, O.A., Kargl, S.G. and Crum, L.A. (2003). Physical mechanisms of the therapeutic effect of ultrasound (a review). *Acoust. Phys*., **49**, No.4, 437-464.

[9] Vaezy, S., Martin, R., Mourad, P. and Crum, L.A. (1999). Hemostasis using high intensity focused ultrasound. *European J. Ultrasound*, **9**, 79--87.

[10] Vaezy, S., Martin, R., Schmiedl, U., Caps, M., Taylor, S., Beach, K., Carter, S., Kaczkowski, G., Keilman, G., Helton, S., Chandler, W., Mourad, P., Rice, M., Roy, R. and Crum, L.A. (1997). Liver hemostasis using high intensity focused ultrasound. *Ultrasound in Med. and Biol*., **23**, 1413--1420.

[11] Vaezy, S., Martin, R., Keilman, G., Kaczkowski, G., Chi, E., Yaziji, E., Caps, M., Poliachik, S., Carter, S., Sharar, S., Cornejo, C. and Crum, L.A. (1999). Control of splenic bleeding using high intensity ultrasound. *J. Trauma*, **47**, 521--525.

[12] Williams, A.R. (1983). *Ultrasound: biological effects and potential hazards*. Academic Press.

[13] http://www.dentsply.co.uk/products/products/cavitronselect.htm

[14] Kelman, C.D. (1967). Phaco-emulsification and aspiration; a new technique of cataract removal; a preliminary report. *Amer. J. Ophthalmol*., **64**, 23-35.

[15] Sabbagh, L.B. (1999). Lasers in phaco: challenging the standard. http://www.revophth.com/1999/November_articles/1199%20phaco.htm

[16] FDA CDRH (1996). FDA Center for Devices and Radiological Health, Office of Science and Technology Annual Report, Section 18. http://www.fda.gov/cdrh/ost/index.html

[17] Anis, A.Y. (2003) Personal communication.

[18] Anis, A.Y. (1999) PhacoTmesis. Chapter 12 in *Atlas of Cataract Surgery* (eds: S. Masket and A.S. Crandall), 89-96, Martin Dunitz.

[19] FDA CDRH (1997). FDA Center for Devices and Radiological Health, Office of Science and Technology Annual Report, http://www.fda.gov/cdrh/ost/rpt97/OST1997AR75.html

[20] Ceccio, S.L. and Brennen, C.E. (1991). Observations of the dynamics and acoustics of travelling bubble cavitation. *J. Fluid Mech.*, **233**, 633-660.

[21] Brennen, C.E. (1995). *Cavitation and bubble dynamics*. Oxford Univ. Press.

[22] Chaussy, C., Brendel, W., and Schmiedt, E. (1980). Extracorporeally induced destruction of kidney stones by shock waves. *Lancet* Ⅱ, 1265-1268.

[23] Eisenmenger, W. (2001). The mechanisms of stone fragmentation in ESWL. *Ultrasound in Med. & Biol*., **27**. No. 5, 683-693.

[24] Zhu, S., Cocks, F.H., Preminger, G.M. and Zhong, P. (2002). The role of stress waves and cavitation in stone comminution in shock wave lithotripsy. *Ultrasound in Med. & Biol*., **28**, No. 5, 661-671.

[25] Coleman, A.J., Saunders, J.E., Crum, L.A., and Dyson, M. (1987). Acoustic cavitation generated by an extra corporeal shockwave lithotripter. *Ultrasound Med. & Biol*., **13**, 69--76.

[26] Sturtevant, B. 1996. *Shock wave physics of lithotripters*. In *Smith's Textbook of Endourology,* Quality Medical , St. Louis, 529-552.

[27] Matsumoto, Y., Allen, J., Yoshizawa, S., Ikeda, T. and Kaneko, Y. (2003). Renal stone communition utilizing cavitation erosion. Manuscript in preparation.

[28] Sokolov, D.L., Bailey, M.R. and Crum, L.A. (2001). Use of a dual-pulse lithotripter to generate a localized and intensified cavitation field. *J. Acoust. Soc. Amer*., **110**, No.3, 1685-1695.

[29] Wang, Y.-C. and Brennen, C.E. (1994). Shock wave development in the collapse of a cloud of bubbles. *ASME Cavitation and Multiphase Flow Forum*, 1994, **FED-194**, 15-20.

[30] Wang, Y.-C. and Brennen, C.E. (1999). Numerical computation of shock waves in a spherical cloud of cavitation bubbles. *ASME J. Fluids Eng* . **121**, 872-880.

[31] Tanguay, M. and Colonius, T. (2002). Numerical investigation of bubble cloud dynamics in shock wave

lithotripsy. *Proc. ASME Fluids Eng. Div. Summer Meeting, FEDSM2002-31010.*

[32] Fankhauser, F., Rousel, P., Steffen, J., Van der Zypen, E. and Chrenkova, A. (1981). Clinical studies on the efficiency of high power laser radiation upon some structures of the anterior segment of the eye. *Int. Opthalmol*., **3**, 129--139.

[33] Aron-Rosa, D., Aron, J.J., Griesemann, M. and Thyzel, R. (1980). Use of the Nd:YAG laser to open the posterior capsule after lens implant surgery: a preliminary report. *Am. Intraocul. Implant Soc. J*., **6**, 352--354.

[34] Steinert, R.F. and Puliafito, C.A. (1985). *The Nd:YAG laser in Ophthalmology*, Saunders.

[35] Vogel, A., Lauterborn, W. and Timm, R. (1989). Optical and acoustical investigations of the dynamics of laser-produced cavitation bubbles near a solid boundary. *J. Fluid Mech*., **206**, 299--338.

[36] Vogel, A. and Busch, S. (1994). Time-resolved measurements of shock wave emission and cavitation-bubble generation in intraocular laser surgery with ps- and ns-pulses. In *Bubble Dynamics and Interface Phenomena* (eds: J.R.Blake et al.), Kluwer Acad. Publ., 105-117.

[37] Steiner, R. (ed.) (1988). Laser lithotripsy. *Proc. 1st Int. Symp. on Laser Lithotripsy*, Springer.

[38] Krishnamurthy, S. and Powers, S.K. (1994). Lasers in neurosurgery. *Lasers in Surg. and Med*., **15**, No.2, 126--167.

[39] Choy, D.S.J. (1998). Percutaneous laser disc decompression (PLDD): Twelve years' experience with 752 procedures in 518 patients. *J. Clin. Laser Med. & Surg*., **16**, No.6, 325-331.

[40] Stinebring, D.R., Lamson, T.C., and Deutsch, S. (1991). Techniques for in vitro observation of cavitation in prosthetic heart valves. *ASME Cavitation and Multiphase Flow*, **FED-109**, 119--124.

[41] Lamson, T.C., Rosenberg, G., Geselowitz, D.B., Deutsch, S., Stinebring, D.R., Frangos, J.A. and Tarbell, J.M. (1993). Relative blood damage in the three phases of a prosthetic heart valve flow cycle. *ASAIO J*., **39**, No.3, M626--M633.

[42] Garrison, L.A., Lamson, T.C., Deutsch, S., Geselowitz, D.B., Gaumond, R.P. and Tarbell, J.M. (1994). An in vitro investigation of prosthetic heart valve cavitation in blood. *J. Heart Valve Dis*., **3**, Suppl.1, S8--S24.

[43] Stinebring, D.R., Deutsch, S., Sneckenberger, D.S., Zapanta, C. and Tarbell, J.M. (1995). Investigations of cavitation in prosthetic heart valves. *ASME Cavitation and Multiphase Flow*, **FED-210**, 95--103.

[44] Zapanta, C.M., Stinebring, D.R., Sneckenberger, D.S., Deutsch, S., Geselowitz, D.B., Tarbell, J.M., Snyder, A.J., Rosenberg, G., Weiss, W.J., Pae, W.E. and Pierce, W.S. (1996). In vivo observation of cavitation in prosthetic heart valves. *ASIAO J*., **42** (5), M550--M554.

[45] Zapanta, C.M., Stinebring, D.R., Deutsch, S., Geselowitz, D.B., and Tarbell, J.M. (1998). A comparison of the cavitation potential of prosthetic heart valves based on valve closing dynamics. *J. Heart Valve Dis*., **7**, No.6, 655--667.

[46] Rambod, E., Beizaie, M., Shusser, M., Milo, S. and Gharib, M. (1999). A physical model describing the mechanism for formation of gas microbubbles in patients with mitral mechanical heart valves. *Ann. Biomed. Eng*., **27**, 774--792.

[47] Maines, B.H. and Brennen, C.E. (2002). Applicability of fluid transient test methods for mechanical heart valve cavitation scaling. *Sixth Annual Hilton Head Workshop sponsored by the Parker Institute for Bioengineering and Bioscience. Prosthetic Heart Valves: Past, Present and Future.*

[48] Chambers, S.D., Bartlett, R.H. and Ceccio, S.L. (2000). Hemolytic potential of hydrodynamic cavitation. *ASME J. Biomech. Eng.*, **122**, No.4, 321--326.

[49] Goldsmith, W. (2001). The state of head injury biomechanics: past, present and future: part 1. *Crit. Rev. Biomed. Eng*., **29** (5 & 6), 441--600.

[50] Goldsmith, W. (1972). Biomechanics of head injury. Chap.23, 585—634, in *Biomechanics, Its Foundations and Objectives*, eds: Y.C.Fung, N.Perrone and M.Anliker, Prentice-Hall.

[51] Lubock, P. and Goldsmith, W. (1980). Experimental cavitation studies in a model head-neck system. *J. Biomech*., **13**, 1041--1052.

[52] Benedict, J.V., Harris, E.H. and von Rosenberg, D.U. (1970). An analytical investigation of the cavitation hypothesis of brain damage. *ASME J. Basic Eng*., Sept.1970, 597--603.

[53] Knapp, R.T., Daily, J.W. and Hammitt, F.G. (1970). *Cavitation*. McGraw-Hill.

[54] Brennen, C.E. (2002). Micro-nucleation in supersaturated oxygen solution injection. *Proc. JSME Mech. Eng. Congr*., 18--19.

[55] Creech, J., Divino, V., Patterson, W., Zalesky, P.J. and Brennen, C.E. (2002). Injection of highly supersaturated oxygen solutions without nucleation. *ASME J. Biomed*. Eng., **124**, No.6, 676--683.