Comment on "Ultrasound-induced lung hemorrhage is not caused by inertial cavitation" [J. Acoust. Soc. Am. 108, 1290–1297 (2000)]

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(Received 21 April 2001; accepted for publication 13 July 2001)

This contribution summarizes the reasons for disagreeing with a conclusion by O'Brien *et al.* [J. Acoust. Soc. Am. **108**, 1290–1297 (2000)] that ultrasound-induced lung hemorrhage is not caused by inertial cavitation. An argument is provided that illustrates how cavitation inception conditions in the lungs of animals are not altered significantly if the hydrostatic pressure is increased by increasing the pressure of air that is being breathed by the animal. © *2001 Acoustical Society of America.* [DOI: 10.1121/1.1401758]

PACS numbers: 43.80.Gx [FD]

The authors of an otherwise excellent paper by O'Brien *et al.*,[1] which reports on comprehensive tests of lung hemorrhage in adult rats exposed to ultrasound, have misinterpreted their own data. They report on the effects of hydrostatic pressure on lung hemorrhage and find that ''No effect of hydrostatic pressure on the probability of hemorrhage was observed.'' It then goes on to conclude that ''If inertial cavitation were responsible for lung hemorrhage, then elevated hydrostatic pressure should have resulted in less rather than more tissue damage at each ultrasonic pressure level.''

The problem stems from a clear understanding of the conditions for the onset of cavitation. An unstable mechanical equilibrium of a bubble is achieved when the following equation holds:

$$P_0 + 2\sigma/R + P_A \sin \omega t = P_g + P_v ,$$

where P_0 is the externally applied static pressure, the second term is the inward stress due to surface tension for a bubble of radius, R, the third term is the time-varying acoustic pressure (which is a tension in the negative part of the acoustical cycle), P_g is the equilibrium gas tension, and P_v is the constant vapor pressure.

When an animal is exposed to an increased ambient pressure due to an increase in the gas pressure that the animal is breathing, two things happen. P_0 increases immediately, and P_g increases more slowly. The very first tissues to equilibrate with the applied increased gas pressure are the lung tissues, and this occurs on a time scale of seconds to minutes. That is, the increase of P_0 is eventually just balanced by the increase in P_g. Thus if one were to measure the acoustic cavitation threshold amplitude P_A for producing cavitation in the lungs before increasing the hydrostatic pressure, and then were to apply gas pressure and repeat that measurement, it would be surprising to see much of a difference in the threshold (as shown in the paper's Fig. 1).

This equilibration effect on thresholds for cavitation is well known for decompression sickness (''the bends''), but in small animals (and especially mice that have a much higher respiration and perfusion rate) the equilibration rate can be very rapid not only for lung tissues but other tissues in proximity to the circulation system.[2]

The authors comment that for increased hydrostatic pressure, the severity of the lesions increased. This too is not unexpected. If the same acoustic threshold pressures produce lesions of about the same size while the animal is under pressure, then it is expected that once the chamber is decompressed and the mice are removed, the bubbles in the hydrostatically compressed group will grow.

The only information given about time scales for compression and decompression are given on p. 1292 of the article. The 6 min allocated for compression is certainly adequate for saturating the lung tissues even for the reduced respiration rates of the anesthetized animals. The 4 min for decompression to atmospheric pressure will be sufficient for much of the gas to diffuse out, especially that which is in immediate contact with the capillary circulation system. Gas trapped in bubbles may take longer to give up their extra gas.

The comments made herein point to a conclusion that is the opposite to that inferred by the title of the paper and its conclusions. By no means, therefore, does the paper prove in any conclusive way that ''Ultrasound-induced lung hemorrhage is not caused by inertial cavitation.'' To the contrary, the results remain consistent with inertial cavitation, if by this term it is meant bubble motion driven primarily by the inertia of the material surrounding the bubble induced by the tension phase of the acoustic cycle.

It should be noted that quite often ''inertial cavitation'' refers to the effects of the collapse of nearly spherical bubbles. In situations where *in vivo* cavitation is possible, it will often be likely that the bubble motions will not be symmetrical. Rather, the inward imploding motion of bubbles near free interfaces will produce asymmetric collapse and high shear velocities in the immediate vicinity of the bubble. Such motions may be responsible for lesions and are properly called inertial cavitation, because it is the growth and collapse of the bubble in relatively few cycles that has produced the high shear effects.

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[1] William D. O'Brien, Jr., Leon A. Frizzell, Ronald M. Weigel, and James F. Zachary, ''Ultrasound-induced lung hemorrhage is not caused by inertial cavitation,'' J. Acoust. Soc. Am. **108**, 1290–1297 (2000).

[2] Robert E. Forster, ''Exchange of gas between alveolar air and pulmonary capillary blood,'' Physiol. Rev. **37**, 391–452 (1957), and conversation with the author, a physiologist, Dr. Robert E. Forster (Cell Biology and Physiology Faculty, University of Pennsylvania Health System).