Potential Bioeffects of Ultrasonic Destruction of Microbubble Contrast Agents*

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It is well known that microbubble destruction can occur during contrast echocardiography, primarily by acoustic cavitation (1). The propensity of microbubbles to undergo this process when exposed to ultrasound depends on physical properties of both the bubbles themselves and the ultrasound beam. Higher rarefractional peak amplitude (a measure of ultrasonic acoustic power) and lower frequencies cause greater microbubble destruction (1–3). Thickness, compressibility, and elasticity of the microbubble shell are important factors in their susceptibility to ultrasound-mediated destruction (4). The ability to destroy microbubbles has useful clinical applications, allowing the quantification of myocardial perfusion using replenishment geometry (5). Also, we and others (6) have begun to investigate this attribute of microbubbles as a method for targeting gene or drug delivery.

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It also has been suggested that the destruction of microbubbles may have adverse effects, such as induction of ventricular ectopy (7), increased vascular permeability (8,9), and even cell death within the exposed organ or tissue (10). In this issue of the Journal, Miller et al. (11) advance our knowledge of this important area by carefully examining the effects of destruction of a commercially available contrast agent (Definity, Bristol Myers-Squibb, Billerica, Massachusetts) using a clinical ultrasound machine (Vingmed System V, General Electric, Cincinnati, Ohio) and standard ultrasonic acoustic power settings in a dog model. This choice of model is relevant because most previous studies of the bioeffects of microbubble destruction have been performed using rodents (8–10,12–14) or isolated, perfused rabbit hearts (15).

Miller et al. (11) found leakage of Evans Blue dye, an accepted marker of vascular permeability, along the short-axis scan plane of the left ventricle. This increased vascular permeability was present mainly in a transmural pattern across the anterior wall, which is not surprising, because the posterior wall is likely to be protected by attenuation of the ultrasound beam by the intervening bubbles in the ventricular chamber. Moreover, the Evans blue dye content was greatest for the highest acoustic power (−2.2 MPA vs. −1.2 MPA) setting in open chest dogs. There was, nonetheless, some evidence of increased vascular permeability in closed chest dogs as well, with no evidence of Evans blue dye extravasation in sham-treated dogs. Although this evidence demonstrates that microbubble destruction, using the contrast agent and ultrasound settings used in this study, causes increased vascular permeability, it is not clear how long this effect lasts. It is possible that this vascular permeability is completely reversible. Moreover, transient increased vascular permeability may be an important factor in gene or drug delivery by ultrasound-targeted microbubble destruction. Further studies are needed to assess the physiological results and persistence of this phenomenon.

Of greater concern is the finding that increased propidium iodide staining was present in all six open-chest dogs that received bubbles and cardiac ultrasound. This stain is moderately specific for cell death because propidium is excluded from living cells. Although the histologic methods used did not allow distinction between endothelial cells, cardiomyocytes, or fibroblasts, it is clear that substantially more propidium iodide-stained cells were present within the scan plane (27.5 ± 16.5/mm² vs. 2.3 ± 2.0/mm²). A previous study showing a mild troponin leak in closed-chest rats after ultrasonic microbubble destruction suggests that at least some of these cells were cardiomyocytes (12). Unfortunately, the present study did not measure propidium iodide staining in the closed chest model, nor did it measure biomarkers specific for cardiomyocyte injury. Thus, we do not know whether similar damage would occur in the more clinically pertinent situation of the closed chest model. A previous small study in human subjects did not find evidence of myocardial injury as evidenced by myocardial enzymes, such as creatine kinase-MB or troponin I (16).

Finally, the authors showed no evidence of ventricular ectopy in sham treatment or the lower power setting (−1.2 MPA) but a substantial increase in premature ventricular contractions with higher acoustic power (−2.2 MPA) in the open chest model. It is probable that the ventricular ectopy is related to the relatively high power delivered directly to the exposed heart; ventricular ectopy was observed primarily in the open-chest dogs in the present study. It also is possible that ectopy was related to the specific microbubble used in this study. A recent large clinical trial using a non-perfluorocarbon gas microbubble showed no evidence of ventricular ectopy in humans (17). An additional explanation for this discordance, suggested by the authors, is that prolonged microbubble destruction (10 min) within the...
same scan plane is unlikely in human studies of myocardial perfusion, wherein the scan plane is frequently changed to evaluate multiple myocardial regions.

The investigation of bioeffects of microbubble destruction is a complex area of investigation because of a large number of involved variables. Some of the important ultrasound variables are acoustic power, frequency, duration, beam profile, and attenuation. Microbubble variables include shell composition, encapsulated gas, dose, concentration, and duration of infusion. Patient variables have not been studied but should include body habitus (which affects attenuation), cardiac output or transmural flow (which might affect microbubble dose and concentration), and perhaps underlying diseases. It seems likely that electrolyte concentrations and ischemia, as examples, might influence vulnerability to potential toxic effects of microbubble destruction. To date, animal studies have focused on bioeffects in normal hearts. It also seems likely that each organ could have a distinct spectrum of potential bioeffects, which could be related to blood flow, and structural characteristics that determine the response to increased vascular permeability or cellular damage.

It seems to us that the bioeffects of microbubble destruction resemble in many respects the side effects of pharmaceutical agents. Medical school pharmacology emphasizes the therapeutic window that exists for almost every useful drug. However, this is not merely a simple matter of knowing the upper and lower limits of dosing. Other variables that produce idiosyncratic variation in pharmacodynamics will influence both efficacy and vulnerability to side effects. Similarly, it is likely that the bioeffects of ultrasound-mediated microbubble destruction will prove to be complex and variable. Nevertheless, the potential risk(s) of this increasingly valuable clinical tool are an important and timely topic. The authors are to be congratulated for reminding us, with these initial observations, of the need for caution with any new technique. Clearly, much remains to be learned.

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