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Microbubble Dynamics Visualized in the Intact Capillary Circulation

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The potential for the use of contrast echocardiography to study myocardial perfusion has generated efforts to develop standardized echo contrast agents. The two methods used in this laboratory to generate microbubbles in solutions serving as contrast agents included the widely used hand-agitation method and the newer ultrasonic microcavitation (sonication) method. The latter has been demonstrated to generate smaller and more uniform microbubbles in an in vitro system.

The present study was designed to observe, by direct microscopic examination of a cat mesentery preparation, the behavior and fate of the microbubbles in an in vivo system. The in vivo mesentery observations confirm the critical role of microbubble size in its unhindered passage through the capillary vasculature. The smaller and more uniform sonicated microbubbles passed rapidly through the microcirculation along with the red blood cells, whereas the larger microbubbles were observed to coalesce and interrupt the flow of blood and subsequently collapse or shrink.

Existing techniques for two-dimensional contrast echocardiographic imaging of myocardial tissue (1–5), chambers (6), shunts (7) and valvular abnormalities (8) rely on the introduction of contrast agent solutions containing microbubbles of air, which alter the acoustic impedance and produce differential echo enhancement. Kremkau et al. (9) and Meltzer et al. (10) have shown that the source of the echo contrast effect is gaseous microbubbles. Initial studies used hand-agitation techniques to generate the microbubbles in various solutions. However, the hand-agitated microbubbles were subject to significant variability in size and stability (11), thus limiting their reliability in quantitative echo contrast studies.

To minimize the variability, we have used ultrasonic cavitation (sonication) to generate small, relatively uniform and more stable microbubbles. This new method of producing microbubbles has been applied during in vitro screening studies of echo contrast agents (12).

The present study was designed to observe, within a living system, the comparative behavior of hand-agitated and sonicated contrast agent solutions containing microbubbles of different sizes. The cat mesentery preparation was used as the in vivo model, because prior investigations (13) of the microcirculation have also used the cat model. The present observations confirm our earlier postulate, based on in vitro studies, that the smaller and more uniform microbubbles resulting from sonication are capable of transcapillary passage.

Methods

The mesentery preparation and methods used in this study were similar to those used in an earlier study (14) and will be described briefly.

Intravital microscope. The intravital microscope apparatus consisted of the animal stage, microscope, xenon light source, both cine and videotape recording capabilities, TV monitor and camera. The telescopic microscope was equipped with 10× (UM10), 32× (UMK32) and 50× (UMK50) objectives with a long working distance (Leitz). Twenty percent of the beam was directed into a low light level TV monitor that was connected to a video recorder, and 80% was directed into a cine camera. A 16 mm Milliken camera (DBM 54, Teledyne Camera System) synchronized

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