Myocardial Perfusion Imaging: Contrast Echocardiography Today and Tomorrow*

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The clinical need to evaluate myocardial perfusion is not satisfied by conventional imaging techniques (1). Angiography is frequently used to provide qualitative anatomic data, but it lacks a physiologic basis for assessing regional blood flow and is an unreliable predictor of it (2,3). Recent technical advances in contrast echocardiography permit direct perfusion assessment and promise to provide a safe, convenient and economical alternative to more invasive and costly imaging techniques.

Clinical Applications of Contrast Echocardiography

The recent development of small, stable sonicated microbubble contrast agents permits myocardial blood flow assessment in patients undergoing cardiac catheterization, angioplasty and thrombolytic revascularization procedures (4,5). Now the effects of therapeutic interventions can be monitored on the basis of direct, real-time, tomographic data.

Early microbubble contrast agents were created by hand agitation (6). Virtually all noninvasive laboratories use hand-agitated microbubbles for right heart contrast echocardiographic studies of valve regurgitation (6-9), cavity dimension (10,11) and shunt detection (12). In addition, several laboratories use hand-agitated microbubbles to assess perfusion during cardiac catheterization or open heart surgery (13,14); however, dynamic physiologic assessments of blood flow have been limited because of the relatively large size and instability of the microbubbles. Nevertheless, the relative safety of hand-agitated microbubbles has been acknowledged (15) and their hemodynamic and histologic effects have been studied (16).

We have developed sonicated microbubbles that are smaller than hand-agitated microbubbles and, in fact, are smaller than red blood cells (17). This enables them to flow with the red blood cells through the microvasculature (18) at physiologic transit times. Sonicated microbubbles are excellent ultrasound reflectors because of the acoustic impedance of the liquid-gas interface. They are produced by applying ultrasound energy to a nontoxic solution and generating first generation cavitation bubbles that ultimately collapse and produce the second generation "by-product" bubbles used as contrast material. Their small size and reproducibility have been confirmed by light microscopy (17) and in situ laser and Coulter counter analyses (19). In addition, we have used electromagnetic flowmeters to correlate arterial blood flow patterns with sonicated microbubble flow patterns measured by videodensitometry during perfusion studies of the dog heart (20) and kidney (21). A decrease in arterial blood flow consistently resulted in a prolonged videodensitometric signal.

Our laboratory has used sonicated Renografin-76 microbubbles without complication in more than 60 patients undergoing cardiac catheterization (4). Direct intracoronary injections were performed through a catheter, using 1.5 to 2 ml of the sonicated solution. Microbubbles measured 3.8 ± 2.1 μ in diameter, using laser analysis. The contrast echocardiographic portion of the procedure added only minimally to the entire time required. Results included blood flow information not otherwise available.

In our contrast echocardiographic perfusion studies, transient 15 second hemodynamic or electrocardiographic changes, or both, were observed. These transient effects were likely a consequence of the properties of the carrier solution, rather than the presence of the microbubbles; studies analyzing left ventricular contractility during perfusion...
of tissue with sonicated microbubbles indicated that the agent and the volume delivered, as opposed to the presence of the microbubbles, were the dominant factors affecting the heart rate, blood pressure, electrocardiogram and epicardial blood flow (22).

Future Applications: Intravenous Screening Procedure

Perfusion screening studies outside the catheterization laboratory and operating room will require the development of a contrast agent capable of transpulmonary transit from a peripheral venous injection site. Intravenous perfusion screening would present several advantages over current imaging techniques. No arterial invasion or X-ray exposure would be required. Ultrasound equipment is economical, widely available and relatively simple to operate. In addition, serial and follow-up studies would be feasible. An intravenous procedure could potentially be performed in a physician’s office, outpatient clinic, emergency room or cardiac care unit. This would markedly broaden the information available in both routine and emergency situations.

Our laboratory (23) recently found that sonicated albumin microspheres pass intact from a peripheral venous injection site in sufficient numbers to permit real-time myocardial perfusion imaging in the monkey, dog and pig. The albumin microspheres are 2 to 4 μ in diameter, and traverse the capillary vasculature in a manner physiologically similar to that of red blood cells. They also are isometric to human serum, biodegradable and stable and echogenic for days.

Quantitation of Blood Flow

Measuring blood flow within tissue depends in part on understanding the mathematic relation between microbubble size and concentration and reflected ultrasound energy. We have used direct radiofrequency analysis in vitro to demonstrate the mathematic relation between known concentrations and diameters of sonicated microbubbles and reflected energy (24,25). These calculations serve as a basis for quantitating blood flow by ultrasound.

In addition, current commercial ultrasound equipment needs to be redesigned to permit direct access of the entire cardiac blood flow (22).

Conclusion

Contrast echocardiography promises to satisfy the clinical need for direct images of regional blood flow, linking coronary anatomy and physiology. The development of small, stable and reproducible sonicated microbubbles currently permits perfusion imaging during cardiac catheterization, angioplasty and surgery. In addition, with further development and validation of intravenous contrast agents, contrast echocardiography may in the future be used in non-invasive imaging procedures yielding quantitative regional perfusion data. Clinical trials will be designed to monitor the efficacy of therapies used in patient management. Ultimately, whether used alone as a screening or follow-up procedure, or in combination with interventional therapy, contrast echocardiography would affect the management of ischemic heart disease by providing perfusion data in a manner that is relatively simple, safe and widely available.

References


