7. Braunstein JB, Schulman SP, Powe NR. Effect of ethnicity on distrust toward medical researchers and willingness to join a cardiovascular drug prevention trial (abstr). J Am Coll Cardiol 2003;41 Suppl A:534A.
8. Alexander KP, Harding T, Coombs L, Peterson E. Are patients properly informed prior to revascularization decisions (abstr)? J Am Coll Cardiol 2003;41 Suppl A:535A.

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Noninvasive Imaging

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The abstract highlights for noninvasive imaging include submissions related to echocardiography, nuclear cardiology, magnetic resonance, and computer tomography. The research presented at the 2003 American College of Cardiology (ACC) Annual Scientific Sessions covered a broad range of subjects and spanned the hierarchy of evaluation of imaging methods, including demonstrations of technical capacity and subsequent diagnostic performance, as well as the impact on diagnostic and prognostic thinking, therapeutic outcome, and health-related outcomes. The primary theme of the highlighted abstracts is expanded technical capacity, both in the clinical arena as well as significant extensions of noninvasive imaging methods to the cellular and subcellular levels. A secondary theme is the impact of established methods on diagnostic and prognostic thinking.

ECHOCARDIOGRAPHY

Research presented at this meeting included important advances in the field of targeted microbubbles, the principles of which are represented schematically in Figure 1. Echo contrast bubbles have the following properties: first, they move as red cells through the vascular bed; second, the interface between the shell and the contained gas is very echogenic, and the bubbles are easily imaged with ultrasound techniques; third, bubbles can be selectively destroyed with exposure to ultrasound, typically of high intensity and/or prolonged duration. These properties can be harnessed by attaching ligands to, or incorporating compounds into, contrast bubbles to achieve imaging or therapeutic end points.

Selective *imaging* is achieved by using a ligand with specific affinity for cell types or biochemical compounds that are markers of particular types of biologic activity. The bubble-ligand complex can then be used as a probe because the ligand directs the complex to the specified activity and the bubble permits it to be imaged with ultrasound. Targeted *therapy* can be achieved when a ligand with therapeutic properties is selectively released at a target site by directing ultrasound to that site, thereby destroying the bubble-ligand complex.

Two animal studies which used imaging applications of targeted microbubbles were presented by Leong-Poi et al. Both studies used bubbles targeted to markers of angiogenesis (α_v integrins expressed in neovessels). In the first study, angiogenesis was demonstrated in a rat model of hind limb ischemia (1). When compared with control limbs, the chronically ischemic hind limb demonstrated clear evidence of angiogenesis. The same group used a similar approach to demonstrate angiogenesis in both primary and metastatic glioblastoma in a rat model (2).

Several studies reported the use of targeted bubbles for therapeutic applications. Using a porcine model, Porter et al. (3) demonstrated that formation of the c-myc protooncogene, a mediator of intimal hyperplasia, was suppressed at the site of stent and balloon injury by intravenous delivery of anti-c-myc (antisense to the c-myc protooncogene) bound to microbubbles. A long-term goal of this work is the use of targeted microbubbles to reduce post-intervention restenosis. In related work, Bekeredjian et al. (4) demonstrated the feasibility of selective intravenous gene delivery to the heart, brain, and pancreas. They incorporated recombinant adenoviruses or plasmids containing expression constructs of beta-galactosidase and luciferase into contrast bubbles and then released them at target sites with directed ultrasound-mediated bubble destruction.

An understanding of the impact of bubble destruction on local tissue is important to ensure that therapeutic applications minimize adverse events and to optimize the time course of ligand delivery to the perivascular space. Work presented by Vancraeynest et al. (5) built on earlier studies from the same group which had demonstrated time- and energy-dependent functional and structural myocardial alterations in rats exposed to myocardial contrast echocardiography. Their hypothesis that these alterations might have an ischemic origin was supported by the current study, which demonstrated time- and energy-dependent "ischemic-like" ST-T changes in this model. The greatest ST-T elevation occurred in the setting of the most prolonged and the highest powered myocardial echocardiographic ultrasound exposure.

In related studies, Li et al. (6) used a rat model in which extravasation of Evans blue was used as a marker of coronary microvascular leakage. They demonstrated that the degree of microvascular leakage was directly related to ultrasound transmit energy. In this study, the duration of exposure was not varied. In a second study using ultrasound of high power (7), extravasation of Evans blue was demonstrated immedi-

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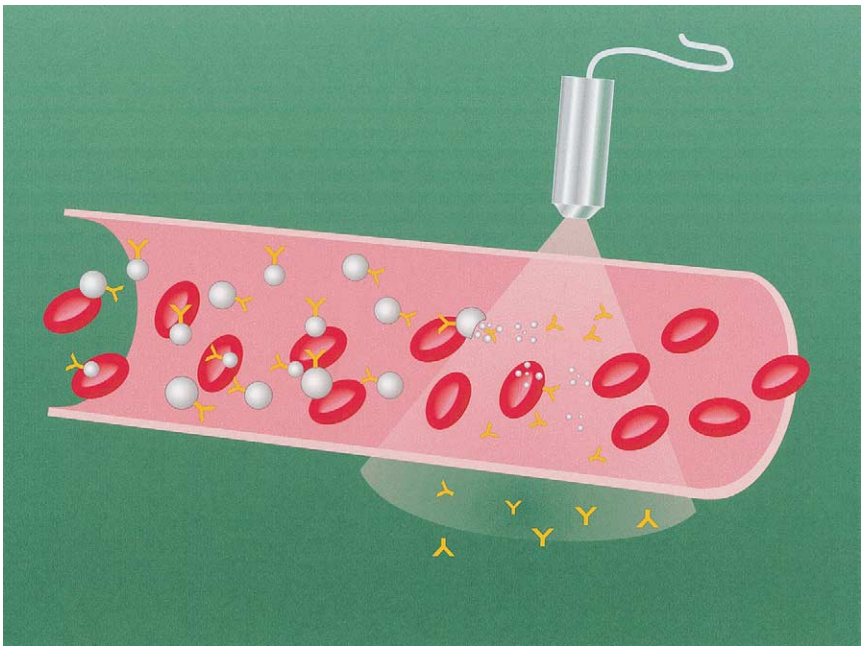

Figure 1. Schematic representation of method in which targeted microbubbles may be used for imaging and therapeutic applications. **White spheres** = microbubbles; **yellow tags** = ligands.

ately after contrast echocardiography. However, this rapidly diminished over time with evidence of return of microvascular integrity by 20 min. This suggests that the time window for delivery of therapeutic agents into the interstitium may be narrow although potentially manipulated by changing the duration and energy of ultrasound exposure.

In the clinical arena, two studies (8,9) presented preliminary work with real-time three-dimensional ultrasound echocardiography. This methodology, currently limited to imaging, allows real-time acquisition and display of three-dimensional images and creates an archive that can be easily and rapidly sliced and rotated to display cardiac anatomy and function from different vantage points. The preliminary experience presented at this meeting suggests that major

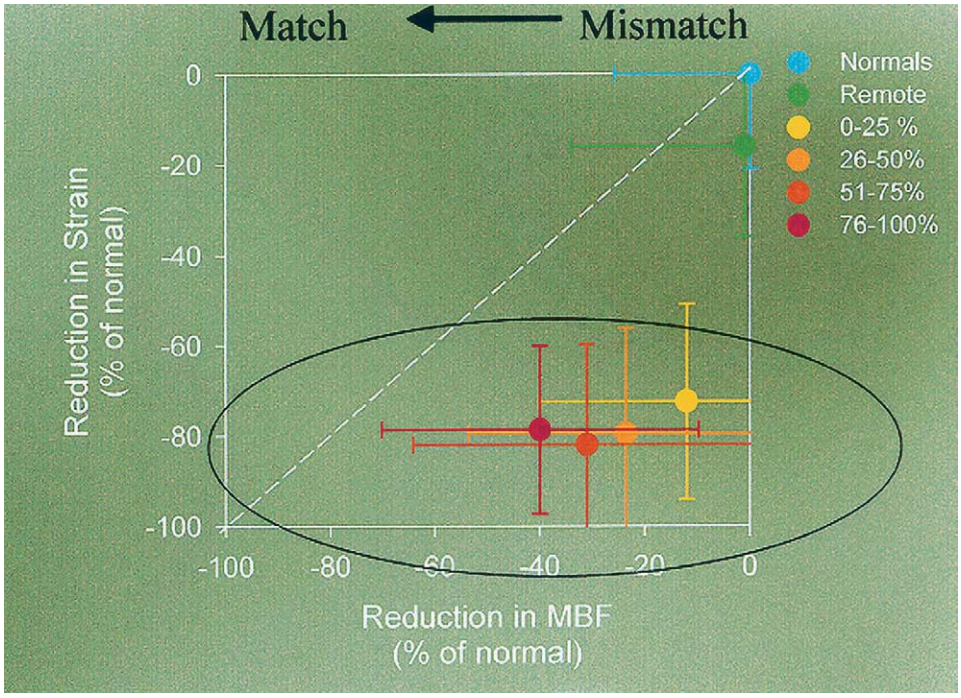

Figure 2. Reduction in left ventricular systolic function (measured with magnetic resonance strain methods) versus reduction in myocardial blood flow. Subjects are grouped according to the transmural extent of necrosis and **color coded**. Data points represent mean ± SD values. See text for details. Modified and reprinted with permission of the authors.

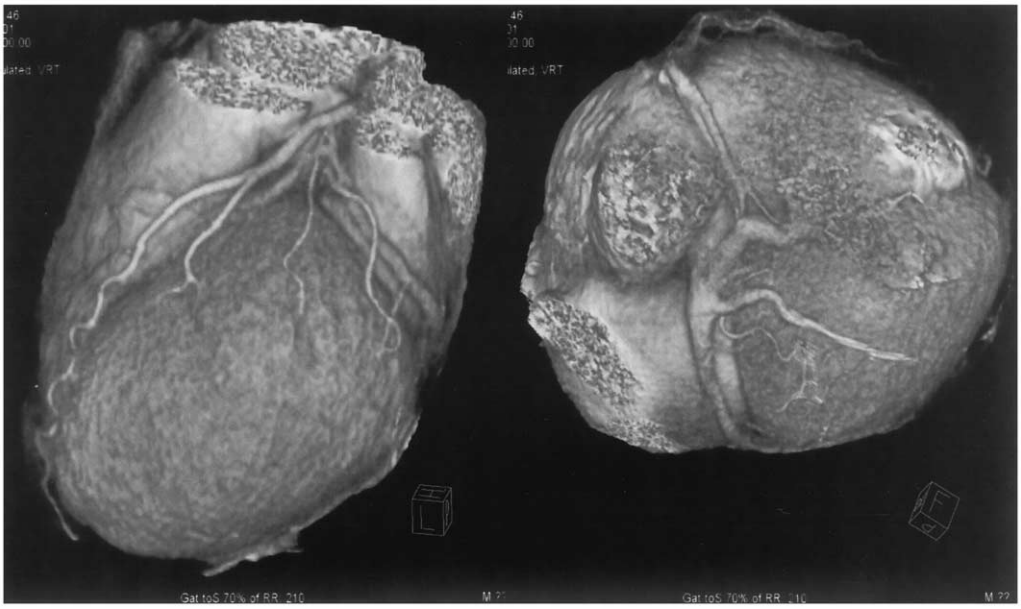

Figure 3. Representative coronary angiograms obtained with 16-slice computed tomography. Provided by Dr. S. Schroeder (17).

applications are likely to be the assessment of valvular and ventricular structure and function.

NUCLEAR CARDIOLOGY

The potential of extending nuclear imaging methods to the cellular and subcellular level was also demonstrated at ACC 2003. ^{99m}Tc-annexin V has a high affinity for phosphatidylserine that is exteriorized on apoptotic cells surfaces. Johnson et al. (10) and Hartung et al. (11) both used this agent in animal models to demonstrate the feasibility of imaging vascular plaque apoptosis associated with vulnerable plaque. The study by Hofstra et al. (12) suggested that phosphatidylserine that is exteriorized during ischemia may subsequently be re-interiorized after perfusion. These authors suggest, therefore, that imaging with annexin V may provide a novel approach to define ischemic memory.

Two clinical studies used nuclear methods to address the issue of the prevalence of myocardial perfusion abnormalities in asymptomatic diabetics. In a follow-up to a previous study which had shown a high prevalence of abnormal scans in asymptomatic diabetics referred for screening stress single photon emission computed tomography (SPECT), Rajagopalan et al. (13) compared the results in community-based versus referral subgroups. They demonstrated no significant difference between the two groups in terms of the prevalence of positive and high-risk scans, arguing that the initial results did not reflect a referral bias of sending only the highest risk patients for screening. In a related study, the Detection of Ischemia in Asymptomatic type II Diabetics (DIAD) investigators (14) reported abnormal adenosine SPECT studies in 22% of subjects between the ages of 50 and 75 years (16% had perfusion abnormalities). It is important to note that neither of these studies was truly a population survey. However, both speak to the high prevalence of abnormal perfusion scans and, by extrapolation, asymptomatic coronary disease in diabetics and support the concept that these patients should be screened.

MAGNETIC RESONANCE

In an elegant human study, Gerber et al. (15) used a variety of magnetic resonance methods to explore flow-function and transmurality of necrosis relationships in patients with chronic ischemic dysfunction. In the clinical assessment of myocardial viability, it is generally thought that myocardial stunning is characterized by perfusion-function mismatch, whereas hibernating myocardium is typically associated with perfusion-function match. The authors of this study measured myocardial blood flow, left ventricular function (myocardial tagging strain methodology), and the transmural extent of necrosis (based on the extent of hyperenhancement). Ammonia positron emission tomography scans provided a secondary index of perfusion. The results are summarized in Figure 2. The line of identity represents the situation in which there would be a perfect flow-function match. The data points circled in the lower right corner demonstrate flow-function relationships for differing degrees of transmural necrosis. With progressive increases in the degree of transmural necrosis, there is a transition from the greatest flow-function mismatch towards improved flow-function matching. This suggests that dysfunctional myocardium demonstrating perfusion-function match is associated with significant degrees of necrosis.

In another clinical magnetic resonance study, Hirsch et al. (16) used magnetic resonance measures of infarct size, left ventricular volume, and sphericity to determine the degree of left ventricular remodeling as a function of myocardial infarction size and patient age. They demonstrated that remodeling (based on end-systolic volumes) was

greatest in patients with the largest infarcts. Further, patients older than 60 years of age had a much greater tendency to remodel than younger patients.

COMPUTED TOMOGRAPHY

Noninvasive coronary angiography has long been one of the holy grails of non-invasive imaging. Two studies (17,18) reported the initial experience with coronary angiography obtained with 16-slice computed tomography and demonstrated the feasibility of delineating stenosis in vessels as small as 1.5 mm. Using conventional cineangiography as a gold standard, both groups demonstrated sensitivities of 88% to 90% and specificities of 90% to 95%. A representative image provided by Dr. Schroeder (17) is shown in Figure 3.

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REFERENCES

1. Leong-Poi H, Christiansen JP, Klibanov A, Kaul S, Lindner J. Noninvasive assessment of angiogenesis by contrast ultrasound imaging with microbubbles targeted to alpha-V integrins (abstr). J Am Coll Cardiol 2003;41 Suppl A:430a.
2. Leong-Poi H, Ellegala D, Carpenter J, et al. Site-specific imaging of tumor angiogenesis using contrast-enhanced ultrasound imaging with microbubbles targeted to alpha-V beta-3 (abstr). J Am Coll Cardiol 2003;41 Suppl A:431a.
3. Porter TR, Knapp D, Venneri L, et al. Increased suppression of intracoronary c-myc protein synthesis within the stent or balloon injury site using an intravenous microbubble delivery system containing antisense to c-myc: comparison with direct intracoronary injection (abstr). J Am Coll Cardiol 2003;41 Suppl A:431a.
4. Bekeredjian R, Chen S, Frenkel P, Grayburn P, Shohet R. Ultrasound targeted microbubble destruction can direct adenoviral or plasmid gene expression to the heart, pancreas, and brain (abstr). J Am Coll Cardiol 2003;41 Suppl A:431a.
5. Vancraeynest D, Pasquet A, Havaux X, Gerber BL, Giseullu G, Vanoverschelde J. Time- and energy-dependent ischemic-like ECG changes during myocardial contrast echocardiography in rats (abstr). J Am Coll Cardiol 2003;41 Suppl A:465a.
6. Li P, Cao L, Dou C, Armstrong WF, Miller DP. Myocardial capillary damage in myocardial contrast echocardiography: influence of ultrasound transmit energy (abstr). J Am Coll Cardiol 2003;41 Suppl A:465a.
7. Li P, Armstrong WF, Miller DL. Time course of microvascular leakage induced by myocardial contrast echocardiography (abstr). J Am Coll Cardiol 2003;41 Suppl A:465a.
8. Sugeng L, Weinert L, Katsnelson Y, et al. Utility of real-time 3-D transthoracic echocardiography in evaluation of mitral valve disease (abstr). J Am Coll Cardiol 2003;41 Suppl A:429a.
9. Hirata K, Miyake K, Sugioka K, Tullio MD, Homma S. Initial experience with a new real-time 3-D ultrasound imager: comparison with conventional echocardiographic methods (abstr). J Am Coll Cardiol 2003;41 Suppl A:430a.
10. Johnson L, Narula N, Schofield L, Chaves L, Narula J. TC-Annexin V imaging for detection of atherosclerotic lesions in porcine coronary artery (abstr). J Am Coll Cardiol 2003;41 Suppl A:445a–6a.
11. Hartung D, Petrov A, Kolodgie F, et al. Abrogation of apoptosis in atherosclerotic plaques: feasibility of noninvasive detection by radionuclide imaging with annexin-V (abstr). J Am Coll Cardiol 2003;41 Suppl A:445a.
12. Hofstra L, Dumont E, Petrov A, et al. Prolonged but reversible sarcolemmal phosphatidyl serine expression in myocardial ischemia represents ischemic memory and can be noninvasively detected by radiolabeled annexin-V imaging (abstr). J Am Coll Cardiol 2003;41 Suppl A:446a.
13. Rajagopalan N, Miller TD, Hodge DO, Gibbons R. Screening stress SPECT in a community-based population of asymptomatic diabetics (abstr). J Am Coll Cardiol 2003;41 Suppl A:409a.
14. Wackers FJ, Young LH, Inzucchi S, Chyun D, Davey J. Detection of ischemia in asymptomatic diabetics: preliminary results of the DIAD study (abstr). J Am Coll Cardiol 2003;41 Suppl A:409a.
15. Gerber BL, Pasquet A, Roelants V, Bol A, Vancraeynest D, Vanoverschelde J. Flow-function relationships in chronically dysfunctional myocardium revisited: impact of subendocardial perfusion and transmurality of myocardial necrosis (abstr). J Am Coll Cardiol 2003;41 Suppl A:469a.
16. Hirsch GA, Ingkanisorn WP, Aletras A, Kellman P, Arai AE. Infarct size needed to cause adverse left ventricular remodeling in humans: a magnetic resonance imaging study (abstr). J Am Coll Cardiol 2003;41 Suppl A:469a.
17. Schroeder S, Kopp A, Kuettner A, et al. Noninvasive coronary angiography with 16-slice detector computed tomography: initial experience (abstr). J Am Coll Cardiol 2003;41 Suppl A:467a–8a.
18. Ropers D, Baum U, Pohle K, et al. Noninvasive coronary angiograph by retrospectively electrocardiographically-gated, thin-slice multidetector-array computed tomography (abstr). J Am Coll Cardiol 2003;41 Suppl A:468a.

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Valvular Heart Disease

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Valvular heart disease was the focus of many exciting presentations at the American College of Cardiology Scientific Sessions in 2003. Traditional concepts related to "degenerative" native and prosthetic valve disease are being challenged, our surgical approaches are improving, and we are beginning to see over the horizon at the possibilities for percutaneous approaches to valve replacement and repair.

The role for cholesterol and inflammation in the development of calcific aortic stenosis (AS) continues to evolve. An estimated 2% to 9% of the elderly have calcific AS (1,2), and they share both similar risk factors with those suffering from atherosclerosis (3,4) and pathophysiologic mechanisms that result in calcification (5). Of the many abstracts investigating this, Fondard et al. (6) presented evidence for an increase in matrix metalloproteins in AS. Matrix metalloproteins are proteolytic enzymes that lead to the degradation of the extracellular matrix; overexpression has been associated with a variety of processes, most notably osteoarthritis (7). That tumor necrosis factor (TNF)-alpha may

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