SPECIAL REPORT

A Suggested Roadmap for Cardiovascular Ultrasound Research for the Future

Sanjiv Kaul, MD, FASE,* James G. Miller, PhD,* Paul A. Grayburn, MD, Shinichi Hashimoto, Mark Hibberd, MD, PhD, Mark R. Holland, PhD, FASE, Hélène C. Houle, BA, RDMS, RDCS, RVT, FASE, Allan L. Klein, MD, FASE, Peg Knoll, RDCS, FASE, Roberto M. Lang, MD, FASE, Jonathan R. Lindner, MD, FASE, Marti L. McCulloch, RDCS, FASE, Stephen Metz, PhD, Victor Mor-Avi, PhD, FASE, Alan S. Pearlman, MD, FASE, Patricia A. Pellikka, MD, FASE, Nancy DeMars Plambeck, BS, RDMS, RDCS, RVT, David Prater, MS, Thomas R. Porter, MD, FASE, David J. Sahn, MD, FASE, James D. Thomas, MD, FASE, Kai E. Thomenius, PhD, and Neil J. Weissman, MD, FASE

INTRODUCTION

The leadership at the American Society of Echocardiography (ASE) decided on a proactive role in defining selected areas of research necessary in this decade that will meet our future clinical needs. Consequently, ASE sponsored a Technology and Research Summit in the fall of 2010 in conjunction with the American Heart Association Scientific Sessions in Chicago. In addition to the ASE executive committee, in attendance were the editor, deputy editor, and one of the associate editors of the *Journal of the American Society of Echocardiography*. Also invited were physician-scientists active in the field of cardiovascular ultrasound, respected ultrasound physicists, and senior engineers from the various ultrasound companies.

The agenda for the full-day meeting covered a selected range of subjects including the assessment of global and regional left ventricular function, regional myocardial perfusion, molecular imaging, therapeutic ultrasound, and peripheral vascular imaging. Also addressed were research necessary to determine the broad clinical utility of hand held ultrasound devices and the impact of future technological developments on the field of cardiovascular imaging.

Because of time constraints, other important and worthy areas of research were not discussed. There was an hour devoted to the discussion of each subject that was initiated by the chairs and panelists assigned to each of the topics. The discussion was robust, and at the end, the chairs and panelists for each topic were requested to submit in writing a short synopsis of the discussion. These have been compiled into a document that we believe will serve as a roadmap for cardiovascular ultrasound research for this decade. At the end of each section a short list of references for selected reading is provided.

Although we have defined the areas that are ripe for future research, we also strongly believe that we have to train the future scientists who will implement this research agenda. ASE has historically awarded one or two fellowship training grants a year and also an award for research training of a sonographer. At some institutions fellows have also received training grants from the local American Heart Association, and very occasionally a training grant (F32) from the National Institutes of Health. However, this is not enough. We need more institutional training grants from the National Institutes of Health in order to train an adequate number of MD and PhD scientists in cardiovascular imaging. To our knowledge there are currently only a handful of such training grants in the country, which is woefully inadequate. We believe that we need at least 20–25 such training grants devoted to the general field of cardiovascular imaging so that within a decade there will be enough physicians trained in scientific methods and clinical research to address the subjects that have been discussed in this report.

The field of cardiovascular ultrasound is very broad, ranging from clinical validation of new technology to studies requiring knowledge of physics, mathematics, organic chemistry, physiology, pharmacology, molecular and vascular biology, genetics, clinical trials, and outcome research. Cross-training of individuals in one or more of these fields is essential for cardiovascular ultrasound to thrive and succeed. Our hope is that this report will encourage young people to realize the scope of cardiac ultrasound research and make a career in this dynamic field.

The following authors reported no actual or potential conflicts of interest in relation to this document: Mark R. Holland, PhD, FASE; Sanjiv Kaul, MD, FASE; Allan L. Klein, MD, FASE; Peg Knoll, RDCS, FASE; Roberto M. Lang, MD, FASE; Jonathan R. Lindner, MD, FASE; Victor Mor-Avi, PhD, FASE; Alan S. Pearlman, MD, FASE; James D. Thomas, MD, FASE; and Neil J. Weissman, MD, FASE.

The following authors reported a relationship with one or more commercial interests: Paul A. Grayburn, MD, receives research support from Abbott Vascular, Medtronic, General Electric, and Guided Delivery Systems. Shinichi Hashimoto is an employee of Toshiba Medical Systems Corporation. Mark Hibberd, MD, PhD, is an employee of Lantheus Medical Imaging. Hélène C. Houle, BA, RDMS, RDCS, RVT, FASE, is an employee of Siemens Healthcare. Marti L. McCulloch, RDCS, FASE, is a speaker for Lantheus Medical Imaging, and is an advisor and consultant for General Electric and Siemens. Stephen Metz, PhD is an employee of Philips Healthcare. James G. Miller, PhD, receives research support from Volcano, Inc. Patricia A. Pellikka, MD, FASE, served as a consultant for Novartis. Nancy DeMars Plambeck, BS, RDMS, RDCS, RVT, is an employee of Toshiba America Medical Solutions. Thomas R. Porter, MD, FASE, receives research support from Astrellas Pharma Inc., Lantheus Medical Imaging, and NuVox Pharma, and also serves as a consultant to Astrellas Pharma Inc. and Lantheus Medical Imaging. David Prater, MS, is an employee of Philips Medical Systems. David J. Sahn, MD, FASE, is a consultant for General Electric, Philips, and Siemens. Kai E. Thomenius, PhD, is an employee of General Electric Global Research.

Reprint requests: American Society of Echocardiography, 2100 Gateway Centre Boulevard, Suite 310, Morrisville, NC, 27560 (E-mail:*ase@asecho.org*).

*Co-chairs with rest of the panelists listed in alphabetical order. See Appendix for institutional affiliations

0894-7317/$36.00

doi:10.1016/j.echo.2011.02.017

Selected Reading

1 Dorsey ER, Thompson JP, Carrasco M, de Roulet J, Vitticore P, Nicholson S, Johnston et al. Financing of US biomedical research and new drug approvals across therapeutic areas. PLoS ONE 2009;4:e7015.

Abbreviations

ASE = American Society of Echocardiography

CAD = Coronary artery disease

CEU = Contrast enhanced ultrasound

DICOM = Digital Imaging and Communications in Medicine

HIFU = High intensity focused ultrasound

ICE = Intracardiac echocardiography

MCE = Myocardial contrast echocardiography

PAD = Peripheral arterial disease

TEE = Transesophageal echocardiography

tPA = Tissue plasminogen activator

VV = Vasa vasorum

2D = Two-dimensional

3D = Three-dimensional

ASSESSMENT OF GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION

Global and regional function assessments are key to the clinical management of patients with cardiovascular diseases. Currently, these are usually performed qualitatively because most current quantitative methods for assessing them are not robust and are not automated. Recently, however, new methods have been introduced for quantifying cardiac function from estimates of myocardial deformation (myocardial strain and strain rate) and torsion (spatial variation of cardiac rotation) based on analyses of ultrasonic myocardial speckle patterns over the cardiac cycle. While these methods show great promise for assessing alterations in global and segmental myocardial performance, they currently exhibit a wide variation in the reported values with a significant dependence on the imaging system used as well as the image quality. Hence, there is a need to standardize the measurements among the echocardiographic systems employed. Additionally, for these measurements to be clinically useful, their precision, accuracy, and reproducibility must be significantly improved. Furthermore, the current standards are not optimized to permit the efficient storage and transfer of three-dimensional (3D) echocardiographic cineloops and related information.

The formation of echocardiographic images and associated measurements based on analyses of speckle pattern data depend upon the processing and detailed characterization of received backscattered ultrasonic signals from the myocardium, which are dependent upon the intrinsic ultrasonic scattering and attenuation properties of the myocardium, the frequency-dependent attenuation properties of overlying tissues (e.g., chest wall), and the specific features of individual imaging systems. The specific characteristics of each type of imaging system have a profound impact on the detailed nature of the received backscattered signals and subsequent speckle patterns observed and include transmit and receive beam profiles, line density, frequency bandwidths, and pulse lengths. Because each manufacturer implements uniquely different choices of system-dependent characteristics, the received signals and features of resultant speckle patterns can give rise to system-dependent variations in measured values. In addition, manufacturers often choose to measure and report slightly different realizations of myocardial strain parameters. This makes the data acquired and analyzed using different echocardiographic imaging systems difficult to compare.

In addition to the technical issues associated with the nature of backscattered signals and characteristics of echocardiographic imaging systems that can have a significant impact on measurements, the effects of image acquisition and user analysis (e.g., the placement of the region-of-interest) also impact the variability of measured values. Although it is generally accepted that poor or non-standard echocardiographic windows can affect results of measurements, the degree of this effect is unknown. The effect of region-of-interest placement on measurement variability has not been systematically investigated. It is expected that precision will be adversely impacted as regions-of-interest grow smaller.

Utilization of myocardial deformation and torsion measurements will require knowledge of the range of normal values. The mean values and associated variations of these parameters for specific cohorts of normal subjects need to be firmly established before routine clinical adoption of myocardial deformation and torsion measurements can be implemented. Variability can take several forms. The easiest to achieve consistency should be with the same cardiac cycle data being analyzed by the same software. To the extent that this is fully automated, the same results should be achieved each time. If there is manual intervention, there may be variability based on precise placement of regions-of-interest, but such variability should be small. Analysis of the same acquisition by a second software package might also be considered; this may yield either random or systematic deviation from the first result depending on whether the two packages use the same mathematical algorithm to estimate strain. Even this simple test is often impossible to do, since most of the vendors store their data in proprietary scan line format, which can only be analyzed by their own software package. Additionally, analysis of successive beats within the same study should be assessed, using either the same software package or a different one. Finally, the ultimate test of variability is the test-retest assessment whereby the patient is scanned twice (with either the same or, more relevantly, another scanner), and the data are analyzed independently.

Standard methods for characterizing images and measurements obtained with ultrasonic imaging systems are available from a number of sources including the International Electrotechnical Commission, the American Institute of Ultrasound in Medicine, and the American Association of Physicists in Medicine. These approaches typically utilize images of commercially available tissue-mimicking phantoms and are largely designed to assess properties such as spatial and contrast resolution, sensitivity and dynamic range, and geometric measurement accuracy on static images. In addition, there are somewhat more limited approaches described for characterizing Doppler measurements using special "flow" phantoms. However, to date, there are no standard methods or commercially available tissue-mimicking phantoms designed to assess echocardiographic-specific measurements of myocardial deformation and rotation. The only such standards to date have been short lifetime models, ones utilizing ex-vivo porcine hearts with implanted sonomicrometry crystals and gel-based models that can be compressed, but unfortunately degrade within days. The development of standard characterization methods and specialized, well-characterized phantoms would provide an objective approach to estimate the limiting uncertainties of these echocardiographic image based measurements.

Image data archiving standards and formats are not currently optimized to handle all the types and large amounts of data associated with volumetric echocardiographic imaging and advanced image analysis features. For example, the current Digital Imaging and Communications in Medicine (DICOM) standard for two-dimensional (2D) echocardiographic images only accepts pixels in a Cartesian, raster-based orientation. Unfortunately, speckle tracking for most of the major vendors is performed on proprietary formats based on individual scan-lines. Full interoperability in speckle tracking will require collaboration to harmonize formats. There are three

possible approaches to this: (1) the DICOM committee (and appropriate companies) could agree upon a single scan-line format, which all vendors would support. In the past, there has been little enthusiasm for this from either the vendor community or the DICOM parent committee, which is loath to produce complex standards that are applicable only to ultrasound. (2) The vendors in question could release details of their format standards, allowing others to develop programs to analyze the data. (3) Finally, it is desired that emerging analysis packages based on the raster DICOM format will yield results that are equivalent to those obtained from the proprietary formats and analysis packages. Given the challenges of the DICOM process, it is likely that interoperability will emerge most quickly from a combination of (2) and (3).

The situation is even more challenging in 3D, where storage requirements can quickly overwhelm a network. A typical scan-line based format stores (for example) a 90 x 90 pyramid of scan lines, each with 512 8-bit data samples, requiring more than 4MB per volume or about 120MB for one second's storage of 30 volumes/sec of 3D data. Storage requirements are even more onerous with the recently-approved DICOM 3D standard, which mandates Cartesian rather than scan-line storage. Assuming isotropic sampling at the original data rate (512 samples/scan line), a single 512 x 512 x 512 x 8 bit volume requires 134MB in storage or $>$ 4GB for a single second of 3D imaging! While lossless run-length-encoding can reduce this by a factor of 3 or more, it is noteworthy that to date, none of the major ultrasound vendors are exporting data in the approved 3D DICOM format. One significant deterrent is the lack of an approved lossy compression technique for 3D echo, similar to the $\sim$15:1 JPEG compression allowed in the 2D standard. Prior work on first-generation real-time ultrasound data showed that 3D wavelet compression as great as 100:1 could be applied without significant image degradation. Whether such compression would impact 3D speckle tracking is unknown, but it certainly seems to be a fruitful area of investigation and possible adoption by the DICOM committee.

Recommendations

To increase confidence in the precision and accuracy of speckle-based measurements of myocardial deformation and torsion (across all vendors), quantifying the uncertainties associated with the measurements, and standardizing 2D and 3D data archiving formats and reported values among different echocardiographic imaging systems, specific recommendations are offered in the following key areas:

1 *Encourage vendor interoperability to allow better workflow in advanced echo mechanics:*
- Provide a setting, perhaps under the auspices of echocardiographic societies, where vendors can work together to improve interoperability without antitrust concerns. ASE and the European Association of Echocardiography have already established a task force for this purpose.
- Encourage all vendors to release details of the algorithms used to measure strain within their software packages. This is essential since "strain" can be defined in various acceptable ways, which yield discrepant values from the same deformation map.
- Encourage all vendors to place in the public domain (or, less ideally, via cross licensing agreements) the details of their individual scan-line formats.
- Explore with DICOM the possibility of a multidimensional scan-line format specific to ultrasound.
- Encourage the development and validation of analysis packages based on raster-based DICOM images.

2 *Identify sources of error and uncertainty in speckle-tracking based estimates of myocardial deformation and torsion (error mechanisms) and identify methods for enhancing the precision and accuracy of measurements:*
- Develop a better understanding of the underlying physical mechanisms that influence the measured segmental and global values. How do regional intrinsic ultrasonic properties of myocardium (scattering, attenuation) affect measurements? How can the effects of overlying tissue affect measurements?
- Identify the impact of imaging system dependent characteristics on measurements and develop methods for the compensation and reduction of these effects on reported results.
- Identify the impact of variability in image acquisition and (user) analysis methods on measured values. Establish image acquisition and data analysis protocols designed to reduce variability of measurements.

3 *Develop methods for quantifying the uncertainties associated with speckle-tracking based estimates of myocardial deformation and torsion and verifying results:*
- Establish a set of standard echocardiographic images/data sets to be used to verify analyses among different manufacturers. These might be derived from animal experiments where sonomicrometry provides a reference standard.
- Develop specialized, stable tissue-mimicking phantoms to be used to verify measurements. The use of phantoms with known, well-controlled properties will provide estimates of the limiting uncertainties of measurements.
- Encourage additional studies designed to establish the mean and standard variation of myocardial strain and rotation measurements for specific normal subject populations (e.g., age, gender, etc.). Perform these studies with multiple machines and analysis approaches to determine intervendor reproducibility.

4 *Develop methods for standardizing the reported myocardial deformation and torsion values among different echocardiographic imaging systems and enhance formats for archiving and sharing 3D and enhanced 2D image data sets:*
- Develop a two-tiered approach for reporting myocardial deformation and torsion measurements: a set of standardized measurements and other measurements unique to each manufacturer. Establishing a set of standard measurements will permit comparison of results of data acquired with different echocardiographic imaging systems. Measurements unique to each manufacturer will continue to encourage innovation among developers. Over time, some vendor specific measurements may enter the standardized list.
- Establish optimal data formats and enhance image and data archiving standards (e.g., an enhanced DICOM standard) to permit the efficient storage and transfer of 3D and four-dimensional echocardiographic images and associated data.
- Investigate the impact of lossy 3D data compression on image quality, volumetric measurements, and speckle tracking. If acceptable, strongly urge the DICOM committee to develop a standardized method of compressing 3D data.
- Identify and define standard universal formats of 2D and 3D data for archiving relatively unprocessed image data permitting subsequent analyses of the data sets beyond standard image processing methods.

Selected Readings

1 Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005;45:2034-41.
2 Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, et al. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. Circulation. 2006;113:2524-33.
3 Opdahl A, Helle-Valle T, Remme EW, Vartdal T, Pettersen E, Lunde K, et al. Apical rotation by speckle tracking echocardiography: a simplified bedside index of left ventricular twist. J Am Soc Echocardiogr 2008;21:1121-8.

4 Seo Y, Ishizu T, Enomoto Y, Sugimori H, Yamamoto M, Machino T, et al. Validation of 3-dimensional speckle tracking imaging to quantify regional myocardial deformation. Circulation Cardiovascular Imaging 2009;2:451-9.
5 Ashraf M, Myronenko A, Nguyen T, Inage A, Smith W, Lowe RI, et al. Defining left ventricular apex-to-base twist mechanics computed from high-resolution 3D echocardiography: validation against sonomicrometry. JACC: Cardiovascular Imaging 2010;3:227-34.
6 Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-93.
7 Hang X, Greenberg NL, Zheng YF, Thomas JD. Compression of 3-D echocardiographic images using a modified 3-D set-partitioning-in-hierarchical-trees algorithm based on a 3-D wavelet packet transform. J Electron Imaging Apr–Jun 2006;15:023016-1.

ASSESSMENT OF REGIONAL PERFUSION

Many of the patients we see and assess by echocardiography have coronary artery disease (CAD) for which abnormal regional function-perfusion relation at rest and/or stress is the hallmark. In this regard, echocardiography has some worthy competitors in nuclear and magnetic resonance imaging as well as computed tomography. The latter also offers the advantage of a direct look at the coronary arteries. For echocardiography to remain competitive for CAD assessment, it has to provide robust measurements of regional function and perfusion. The previous section deals in detail with the technical challenges and potential research in regional function assessment. This section will deal with regional perfusion assessment with myocardial contrast echocardiography (MCE). Issues regarding DICOM standards and image storage and analysis capability are similar to that of regional function analysis.

MCE has been validated in animal models more than any other imaging method for CAD assessment and yet its clinical penetration is marginal for several reasons. First, there is no ultrasound contrast agent that has been approved for clinical perfusion assessment by the US Food and Drug Administration. Second, most echocardiography laboratories are averse to routine intravenous line placement. Third, in its current form, MCE is difficult to perform and interpret. Fourth, there is no reimbursement for it.

MCE utilizes gas-filled microbubbles that have an intravascular rheology similar to that of erythrocytes. These microbubbles remain entirely within the intravascular space and therefore as flow tracers they are superior to all other contrast agents used in other imaging modalities. MCE is the only method that can provide an independent assessment of both myocardial blood volume and blood flow velocity. Despite this enormous advantage, its clinical use is limited only to a few medical centers.

Because MCE at both rest and stress is fast to perform, does not use radiation, can be performed at the bedside, and can be coupled to any form of stress, it should be preferable to other imaging techniques. However, we need to train individuals in its use and provide them with tools that give them confidence in interpretation.

MCE can permit the assessment of myocardial perfusion during a continuous infusion of commercially available microbubbles. Both high mechanical index and low mechanical index real-time perfusion techniques have been utilized to assess myocardial perfusion during rest and stress echocardiography. Because high mechanical index techniques will destroy the microbubbles, these techniques must be triggered to the end-systolic frame on the electrocardiogram and image, one or more R-R intervals after the initial destruction pulse, to allow for replenishment of microbubbles. Low mechanical index techniques are less destructive, and can therefore be performed in real-time (>20 Hertz). Ultrasound system manufacturers have developed very sensitive low mechanical index imaging modalities that permit perfusion to be detected in real time with their current commercial scanners. When microbubbles are administered as a continuous infusion, intermittent high mechanical index impulses can be delivered that clear the myocardial contrast and allow the analysis of myocardial contrast replenishment. The reappearance of bubbles in the myocardium allows the analysis of mean microbubble velocity, while the plateau (or peak) myocardial signal intensity is an index of capillary blood volume. Multiplying these two variables together, one can quantify myocardial blood flow changes.

These imaging techniques have been applied in three specific clinically relevant areas, where the addition of perfusion imaging adds incremental value to patient care, both in terms of improved detection of CAD as well as prediction of patient outcome. During dobutamine stress echocardiography, MCE has been shown to improve test sensitivity and accuracy. MCE during vasodilator stress has similarly been shown to detect CAD in a manner that is either equivalent to or superior to nuclear perfusion imaging. Quantitative studies, examining myocardial blood flow changes with MCE, have shown the incremental value over visual analysis of perfusion in detecting CAD during vasodilator stress in both normal subjects and patients with unexplained cardiomyopathy. The assessment of microvascular perfusion with triggered or real time MCE has proven to have incremental value in predicting functional recovery after treated ST segment elevation myocardial infarction and in patients with ischemic cardiomyopathy. Finally, the evaluation of perfusion with contrast echocardiography adds incremental value to clinical variables and regional wall motion in predicting outcome in patients presenting at the emergency department with chest pain and a non-diagnostic electrocardiogram.

Recommendations for Research and Development

It is evident from single center studies that if MCE were utilized more often in the evaluation of patients with CAD and its complications, patient care would be enhanced. A concerted effort is needed to develop automated data acquisition and display, especially with the advent of 3D echocardiography, as well as software that would permit the robust analysis of myocardial contrast replenishment curves from within the myocardium as well as acoustic intensity from the adjacent left ventricular cavity for the quantification of myocardial blood flow. This software should not be vendor-specific, but rather should allow quantification of myocardial blood flow on or from all commercially available scanners.

Multi-center studies should be planned to evaluate both the quantitative and qualitative assessments of myocardial perfusion during dobutamine, bicycle, and vasodilator stress echocardiography. These studies should be designed not only to assess the predictive value of MCE for CAD detection but also predicting patient outcome. In the emergency setting, multi-center studies are also needed to determine the incremental value of qualitative and quantitative assessments of myocardial perfusion in predicting outcome of patients with chest pain and non-diagnostic electrocardiograms. Finally, the quantification of myocardial blood flow needs to be examined in patients with acute and chronic left ventricular dysfunction and known coronary artery disease, to determine the incremental role of

myocardial blood flow assessment in predicting outcomes and recovery of regional function following revascularization.

Another area where MCE has a unique role is in studying microvascular disease and function, whether it be in Syndrome X, hypertension, hypertrophic cardiomyopathy, or diabetes mellitus. Multicenter studies should be designed in these specific patient sets to determine the value of MCE in determining outcome.

Selected Readings

1 Kaul S. Myocardial Contrast Echocardiography: A 25 year retrospective. Circulation 2008;118:291-308.
2 Wei K, Jayaweera AR Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97:473-83.
3 Elhendy A, O'Leary EL, Xie F, McGrain AC, Anderson JR, Porter TR. Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. J Am Coll Cardiol 2004;44:2185-91.
4 Tsutsui JM, Elhendy A, Anderson JR, Xie F, McGrain AC, Porter TR. Prognostic value of dobutamine stress myocardial contrast perfusion echocardiography. Circulation 2005;112:1444-50.
5 Kaul S. Evaluating the 'no reflow' phenomenon with myocardial contrast echocardiography. Basic Res Cardiol 2006;10:391-9.
6 Wei K, Peters D, Belcik TJ, Kalvitis S, Womak L, Rinkevich D, et al. A predictive instrument l using contrast echocardiography in patients presenting to the emergency department with chest pain and without st-segment elevation. J Am Soc Echocardiogr 2010;23;636-42.

MOLECULAR IMAGING

The term, molecular imaging, has been broadly applied to describe non-invasive imaging techniques that have been developed to assess processes such as protein expression, metabolic status, intracellular molecular trafficking, gene transcription, enzyme activity, and pH, to name only a few. The most common approach for molecular imaging involves the application of targeted contrast probes that are bioengineered to identify a specific molecular process.

Molecular imaging with contrast enhanced ultrasound (CEU) relies on the selective targeting and retention of a contrast agent at sites of disease. Due to the confinement of ultrasound contrast agents to the intravascular compartment, CEU molecular imaging can only target microbubbles to antigens that are expressed within the vascular compartment.

Targeting of ultrasound agents has been accomplished by one of two strategies. A simple approach has been to select certain microbubble shell constituents that facilitate their attachment to cells in regions of disease. Common examples of this strategy include the complement-mediated attachment of anionic lipid microbubbles to activated leukocytes, or the attachment of lipid or albumin-shelled microbubbles to the endothelium. A second and more specific strategy has been to attach specific ligands such as monoclonal antibodies, recombinant proteins, or small peptides to the microbubble shell surface that will facilitate their attachment to disease-related ligands. Generally, this approach has involved the conjugation of the ligand at the end of a polyethylene glycol spacer "arm" resulting in a surface density of several thousand ligands per μm^2. Detection of these agents in vivo is based on imaging backscatter from microbubbles retained in tissue after most of the freely circulating bubbles have cleared from the blood pool. Algorithms have been developed to calculate retention fraction of microbubbles from time-intensity curves, which minimizes the influences of contrast dose and tissue perfusion.

Potential Clinical Applications of CEU Molecular Imaging

A key issue for molecular imaging with CEU is that, for the most part, only intravascular processes can be targeted. Accordingly, CEU has been used to evaluate endothelial phenotype, leukocyte or platelet activation/adhesion, and thrombus formation. When considering potential clinical applications, it is reasonable to assume that CEU could be used in situations where there are clear advantages of using ultrasound rather than another imaging modality because of portability, speed of acquisition, high-throughput capability, sensitivity, and low cost. These advantages make CEU an attractive approach for disease screening such as early detection of aggressive atherosclerotic disease or transplant rejection. It is promising as a tool for the detection of active or recent myocardial ischemia in patients with chest pain (ischemic memory imaging) with microbubbles targeted to selectins. The opportunity to pair this information with wall motion and perfusion may be of particular benefit, especially in separating wall motion abnormality caused by a new versus an old event. Similarly, the ability to image cardiovascular anatomy with relatively high resolution makes ultrasound targeted imaging of thrombus a reasonable option. It is also possible that some of the therapeutic effects of bubbles for applications such as sonothrombolysis or ultrasound-mediated gene delivery may also be amplified by targeting. This idea has not been fully explored.

Challenges and Future Directions

A major hurdle in the development of a targeted ultrasound contrast agent for clinical use is safety. Strategies for ligand conjugation that are neither toxic nor immunogenic must be developed and tested. Additionally, the ligands must be safe for human use while not losing their biological activity when conjugated to a bubble. Another hurdle is the costs for the development, pharmacology-toxicology testing, and clinical trials. These costs will probably be justified only if molecular imaging provides unique information that will substantially change patient care in a sufficiently large population to allow the investment to be recouped.

Another complex issue is that, for any specific application, the ideal contrast agent formulation needs to be established. Conditional variables for different diseases include vascular environment (e.g., hydrodynamic forces, glycocalyx, etc.), the density of the molecular target, endogenous competitive inhibitors, and the stoichiometry of the target molecule. Bubble design can and should be modified in order to control the circulation time which may need to be varied according to the disease process. Even optimal dosing is currently unknown.

Finally, better imaging methods are required. Currently, the technique relies on the detection of agent that is "retained" due to target-specific attachment. New methods for specifically detecting signals for attached microbubbles may be advantageous, especially when imaging structures directly adjacent to a blood pool (such as the vascular endothelial surface) where even a few freely circulating microbubbles can confound signals. For certain diseases (atherosclerosis, thrombosis) there may be a need to display fused images by overlaying a high-frequency high-resolution B-mode image with contrast-specific imaging modes which are generally low spatial resolution. Deformation imaging should be highly complementary to

perfusion imaging, but the presence of microbubbles in the myocardium appears to confound speckle tracking. Strategies must be developed to allow these techniques to be used together optimally. Finally, we need to determine whether CEU molecular imaging provides quantitative information.

Recommendations for Research and Development

1 Develop targeted microbubbles that are safe in humans.
2 Selection of a common but important condition, such as inflammation, where a targeted bubble could find clinical application in multiple fields.
3 Clinical trials demonstrating incremental value of molecular imaging to standard assessment in specific disease conditions.

Selected Readings

1 Chadderdon S, Kaul S: Molecular imaging with contrast-enhanced ultrasound. J Nucl Card 2010;17:667-77.
2 Weller GER, Lu E, Csikari MM, Klibanov AL, Fischer D, Wagner WR, Villanueva FS. Ultrasound imaging of acute cardiac transplant rejection with microbubbles targeted to intercellular adhesion molecule-1. Circulation 2003;108:218-24.
3 Villanueva FS, Lu E, Bowry S, Kilic S, Tom E, Wang J, et al. Myocardial ischemic memory imaging with molecular echocardiography. Circulation 2007;115:345-35.
4 Kaufmann B, Lewis C, Xie A, Mirza-Mohd A, Lindner JR. Detection of recent myocardial ischaemia by molecular imaging of P-selectin with targeted contrast echocardiography. Eur Heart J 2007;28:2011-7.
5 Kaufmann BA, Sanders JM, Davis C, Xie A, Aldred P, Sarembock IJ, et al. Molecular imaging of inflammation in atherosclerosis with targeted ultrasound detection of vascular cell adhesion molecule-1. Circulation 2007;116:276-84.
6 Anderson DR, Tsutsui JM, Xie F, Radio SJ, Porter TR. The role of complement in the adherence of microbubbles to dysfunctional arterial endothelium and atherosclerotic plaque. Cardiovasc Res 2007;73:597-606.
7 Thomas JD, Mills G. In Defense of Structure, Function, and Perfusion: The case against molecular imaging. J Am Coll Cardiol Imaging 2011. (Epub ahead of print)

THERAPEUTIC ULTRASOUND

Whereas many imaging modalities can be used to define phenotype and monitor the effects of therapy, ultrasound is unique in that it also offers enormous potential as a treatment modality. This discussion focuses on the most relevant aspects of ultrasound as a therapeutic modality in cardiovascular medicine – sonothrombolysis, gene and drug delivery, and high intensity focused ultrasound (HIFU) for tissue ablation.

Sonothrombolysis

Work in animal models has demonstrated that ultrasound, alone and in combination with microbubbles, enhances the activity of thrombolytic agents. Ultrasound and microbubbles alone (in the absence of thrombolytic agents) have also been shown to dissolve intravascular thrombi. However, relatively few clinical trials have been done to translate this work into clinical practice. To date, only one randomized study has been done in humans with acute myocardial infarction (MI): the Percutaneous Low Frequency Ultrasound (PLUS) trial. This study used low frequency ultrasound (<100 Kilohertz) without microbubbles, and did not show a benefit of ultrasound and tissue plasminogen activator (tPA) on thrombosis in MI flow grade, compared to tPA alone, despite evidence of better ST segment elevation resolution. Pre-clinical studies in animals have also demonstrated the potential for diagnostic ultrasound and microbubbles to reduce infarct size, even in the absence of epicardial recanalization.

There are more clinical studies of sonothrombolysis in stroke than in acute MI. The Combined Lysis of Thrombosis in Brain Ischemia with Transcranial Ultrasound in Brain Ischemia (CLOTBUST) trial showed a higher patency rate with continuous transcranial Doppler and tPA, compared to tPA alone. Several smaller trials have shown similar results, and pilot studies of sonothrombolysis with microbubbles have demonstrated even greater efficacy. When used with tPA, ultrasound with or without microbubbles also has the potential to increase intracranial hemorrhage. The European Stroke Network is currently using ultrasound and microbubbles in multicenter trials as an adjunct therapy (without tPA) for stroke treatment.

Several important questions remain to be answered. What is/are the mechanism(s) of thrombus dissolution? Are we causing downstream embolization with sonothrombolysis which may cause additional diffuse tissue destruction? Can sonothrombolysis achieve recanalization without any anti-coagulants or with lower, potentially safer doses of thrombolytic agents? What is the mechanism of reduced infarct size with ultrasound even in the presence of total coronary occlusion? Is this due to nitric oxide production, prevention of microemboli, or both, or some other mechanism? Would image-guided sonothrombolysis work more effectively, particularly with 3D imaging? Can we enhance sonothrombolysis by targeting microbubbles to thrombus? Should such a strategy differentiate between platelet-clots and thrombin clots?

Research goals need to focus on clinical trials to demonstrate the efficacy of sonothrombolysis in acute MI, particularly in hospitals that do not have access to prompt catheter-based coronary reperfusion. Stroke trials have already demonstrated the benefit of ultrasound, and clinical trials using microbubbles are underway, especially in Europe.

Gene and Drug Delivery

So far, gene therapy using ultrasonic microbubble destruction has been performed only in rodents, in both the heart and pancreas. Cardiomyocytes are difficult to transfect in vitro, and the candidate genes and therapeutic targets are not fully understood. Sarcoplasmic reticulum Ca++ ATPase 2a has been shown to prevent left ventricular remodeling in acute MI. Vascular endothelial growth factor and stem cell factor have been shown to induce angiogenesis in mice after experimental MI using ultrasound-targeted microbubble destruction. Preliminary work has been done to increase high-density lipoprotein levels by gene delivery of Apo-A1 to the liver.

Greater success with ultrasound targeted microbubble destruction has been achieved in diabetic rats, where multiple genes involved in the embryologic development of the endocrine pancreas have been delivered with ultrasound targeted microbubble destruction, and shown to cause islet regeneration and cure of diabetes. Preliminary studies have also shown potential to deliver anti-angiogenic genes or cytotoxic genes to a murine model of human pancreatic cancer.

Microbubbles can also be used to target drug delivery to the heart. In theory, this would only be useful if the delivered drug has systemic side effects that could be avoided while getting the beneficial effects on the target organ. Amiodarone is an ideal candidate because of its long half-life in cardiac tissue, its efficacy, and its propensity to cause multiple systemic side effects. For atrial fibrillation, it would be ideal to deliver amiodarone to the atria, but this might be complicated by low

blood flow to the atria, and the difficulty of getting stable, efficient loading of amiodarone into microbubbles.

The primary research goal for gene/drug delivery is to move from rodents to primates. This is a critical step in the translation of this work to humans. However, it introduces several potential challenges. Ultrasound attenuation could be a problem. Current transducers are designed for imaging, not gene therapy. Therefore, therapy probes must be developed. Primate studies are also costly. Finally, much work remains to be done in elucidating the mechanisms of gene transfection through microbubbles, and thus optimizing the acoustic and biologic parameters for gene therapy using microbubbles.

HIFU

HIFU is currently used for ablation of uterine fibroids, prostate tumors, and other soft tissue lesions that are easily accessible by ultrasound. Early enthusiasm for using HIFU for pulmonary vein isolation in atrial fibrillation was subsequently abandoned because of a high complication rate in clinical trials. Another potential cardiac target is septal ablation in hypertrophic obstructive cardiomyopathy. Theoretically, one could use microbubbles to highlight the portion of the septum that is causing obstruction to help target HIFU ablation. Catheter-based HIFU approaches could also be beneficial. However, the adverse results with atrial fibrillation ablation in the heart warrant caution because of potential adverse effects. For example, HIFU might not be able to ablate the septum without conduction system damage that also occurs with alcohol ablation or septal myectomy. Animal models of atrial fibrillation have been created, which could be utilized to test the resolution of HIFU to create focal lesions in the beating heart. Since HIFU's effects are not related to cavitation, it is unclear what effect microbubbles would have in potentiating the effects of HIFU.

Selected Readings

1 Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, et al. Ultrasoundenhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170-78.
2 Siegel RJ, Suchkova VN, Miyamoto T, Luo H, Baggs RB, Neuman Y, et al. Ultrasound energy improves myocardial perfusion in the presence of coronary occlusion. J Am Coll Cardiol 2004;44:1454-58.
3 Xie F, Lof J, Matsnaga T, Zutshi R, Porter TR. Diagnostic ultrasound combined with glycoprotein IIb/IIIa–targeted microbubbles improves microvascular recovery after acute coronary thrombotic occlusions. Circulation 2009;119:1378-85.
4 Shohet RV, Chen S, Zhou YT, Wang Z, Meidell RS, Unger RH. Echocardiographic destruction of albumin microbubbles directs gene delivery to the myocardium. Circulation 2000;101:2554-6.
5 Christiansen JP, French BA, Klibanov AL, Kaul S, Lindner JR. Targeted tissue transfection with ultrasound destruction of plasmid-bearing cationic microbubbles. Ultrasound Med & Biol 2003;29:1759-67.
6 Klinkenberg TJ, Ahmed S, Ten Hagen A, Wiesfeld AC, Tan ES, Zijlstra F, Van Gelder IC. Feasibility and outcome of epicardial pulmonary vein isolation for lone atrial fibrillation using minimal invasive surgery and high intensity focused ultrasound. Europace 2009;11:1624-31.

PERIPHERAL ARTERIAL DISEASE

Current Problems in Peripheral Arterial Disease (PAD) Assessment

In current practice, non-invasive methods commonly used for diagnosing and assessing the severity of PAD rely on the detection of a pressure gradient or decreased pulse volume caused by a stenosis. There are well-recognized limitations of these methods. Because flow through the limb inflow arteries normally increases 10-20 fold during exercise, the flow-diameter relationship at rest is relatively flat. Hence, significant pressure gradients do not develop at rest until inflow vessel stenosis becomes relatively severe. Quantitative perfusion imaging of the limb could potentially be used in PAD to detect moderate disease, to evaluate the adequacy of collateral flow, detect diffuse small vessel disease, and assess regional flow responses to exercise.

Potential Role of Contrast Enhanced Ultrasound for PAD Assessment

CEU has been developed to quantify perfusion in limb skeletal muscle. Although transit rate data after intravenous bolus injection of microbubbles has been used for this purpose, methods similar to myocardial perfusion imaging using continuous contrast infusion and analyzing time-intensity plots after a destructive pulse sequence is more optimal because it is not influenced by the rate of bolus injection or the cardiac output. This approach is also optimal for rapidly assessing multiple different imaging planes in both limbs. Limb skeletal muscle rest-stress perfusion imaging has been shown in animal and/or human trials to detect and quantify PAD, to assess microvascular abnormalities associated with diabetes mellitus, and to quantify the responses to angiogenic therapy.

Because of the ubiquitous presence of ultrasound in vascular labs and because multilevel rest-stress perfusion imaging of the lower extremities can be performed in minutes, CEU perfusion imaging is a very promising approach for evaluating perfusion in PAD. However, there are major steps needed for integration of CEU imaging in the vascular ultrasound laboratory.

Foremost is the approval by regulatory agencies for an ultrasound contrast agent for tissue perfusion imaging. Targeting PAD as a primary indication for perfusion imaging with microbubbles may be an effective approach because, unlike the case for myocardial perfusion imaging, there are no existing competing technologies that can be used to assess perfusion in PAD. Second, because tissue flow at rest in skeletal muscle is very low (0.05-0.20 mL/min/g) ultrasensitive contrast-specific imaging techniques must be used. Currently, intermittent high-power multipulse decorrelation techniques are most sensitive for contrast detection, yet for PAD imaging it will be necessary to use continuous low-power imaging in order to assess multiple different planes in each limb. Third, the ideal ultrasound frequency for any contrast-specific imaging method must be established for optimizing the balance between penetration, resolution, and contrast sensitivity.

Optimum probe shape for limb imaging should also be examined with an eye towards adjustable circumferential, wrap-able, or ring arrays that can adapt to differences in limb dimension according to imaging plane and patient morphology, so as to allow simultaneous imaging in multiple planes in order to develop a 3D perfusion map. Integrated with Doppler, this could also provide 3D flow maps in the larger vessels. Finally, methods for stress imaging should be fully explored in order to quantify the severity of disease. Exercise stress works well because even with the very low levels of exercise that patients with severe PAD symptoms can perform, limb skeletal muscle flow is markedly increased. However, the need to assess multiple different muscle groups in the proximal and distal limb should prompt further exploration of vasodilator stress which has been shown to be feasible in animal models.

Contrast-Enhanced Ultrasound for Vasa Vasorum (VV) Imaging

Expansion of the VV and plaque neovascularization (growth of vessels that penetrate the external elastic lamina) contributes to the progression and instability of atherosclerotic disease. Neovessels promote instability by: (1) serving as a site for leukocyte migration; (2) hemorrhage and leakage of proatherogenic molecules that promote a pro-inflammatory state; and (3) the production of endothelial-derived proteases that are expressed during vascular remodeling. The presence of plaque neovessels has been shown to be associated with atherothrombotic events and plaque growth.

CEU is well-suited to the evaluation of plaque neovascularization because of practical issues such as cost and availability; and technical issues such as the balance between sensitivity and spatial resolution. The technique has been applied to evaluate VV proliferation and plaque neovessels in humans and animal models of disease. Transition to routine clinical practice will depend on both technologic advances and clinical trials demonstrating that CEU provides important prognostic information that can be used to guide patient management.

Among the most important advances in technology will be the ability to acquire and/or display vascular CEU information in 3D. Even though in certain arteries, such as the carotid, there are predictable sites where disease is most likely to be severe, a circumferential evaluation of plaque morphology and associated neovascularization will be ideal.

A second major advance will be the development of new tools to quantify VV proliferation. Conventional methods for microvascular flow quantification have been proposed. However, these techniques are not well-suited to 3D acquisition, will be affected in the far-field by luminal shadowing, and may be ill-suited for quantifying the low flow rates in the mural microvessels. An alternative approach, which has been shown to provide robust data on VV proliferation, is the use of maximum intensity projection processing to measure vascular density rather than perfusion. Each microbubble leaves a "trail" of enhancement during transition through a vessel, thereby increasing the efficiency of signal generation. Importantly, the evaluation of VV density with this technique has been shown to be relatively independent of the dose of microbubble contrast over a wide range of clinically relevant blood pool concentrations.

Recommendations for Research and Development

1 Development of customized transducers for assessing limb perfusion at multiple levels simultaneously.
2 Trials designed to validate ultrasound contrast agents for measuring skeletal muscle perfusion.
3 Development of algorithms to quantify VV perfusion.
4 Design of outcome studies to evaluate the incremental diagnostic and prognostic value of perfusion imaging compared to other routinely performed studies to assess PAD.

Selected Readings

1 Lindner JR, Womack L, Barrett EJ, Feltman J, Price W, Harthun NL, Patrie JT. Assessment of peripheral vascular disease by lower extremity contrast ultrasound perfusion imaging. J Am Coll Cardiol Img 2008;1:343-50.
2 Bragadeesh T, Sari I, Pascotto M, Micari A, Kaul S, Lindner JR. Detection of peripheral vascular stenosis by assessing skeletal muscle flow reserve. J Am Coll Cardiol 2005;45:780-5.
3 Duerschmied D, Olson L, Olschewski M, Rossknecht A, Freund G, Bode C, Hehrlein C. Contrast ultrasound perfusion imagng of lower extremeties in peripheral arterial disease: a novel diagnostic method. Eur Heart J 2006;27:310-5.
4 Staub D, Patel MB, Tibrewala A, Ludden D, Johnson M, Espinosa P, et al. Vasa vasorum and plaque neovascularization on contrast-enhanced carotid ultrasound imaging correlates with cardiovascular disease and past cardiovascular events. Stroke 2010;41:41-7.

HAND HELD ULTRASOUND SYSTEMS

Echocardiography has become a mature and widely utilized technology for the assessment of patients with known or suspected heart disease. Recent miniaturization of ultrasound machines has resulted in small, relatively inexpensive hand held systems. Under what circumstances should these systems be used and who should use them? What training is required? Are these devices cost-effective? Can their judicious use improve patient outcomes?

Battery-operated, pocket size ultrasound devices currently do not provide the full spectrum of features available on the large full-service ultrasound systems, but offer diagnostic quality two-dimensional and color Doppler imaging using a 1.7-3.8 MHz phased array transducer. Although limited storage of data is also available on the devices that can be transferred to a personal computer using a docking station, the system is not DICOM compatible, thereby preventing large scale archiving of data. Only simple measurements can be made and no report is generated. However, the findings may be described by the examiner as an extension of the physical examination and may provide important additive information to the clinician. These small devices are inexpensive compared to the larger systems, and could be afforded by individual physicians. However, currently the device is considerably more expensive than a stethoscope. In its current form, it does not have the capability of providing an audio signal, for example, for auscultation of the lungs since the value of ultrasound imaging of the lungs (comets) for mild or chronic pulmonary edema is not known.

Hand held ultrasound devices may be used in a wide variety of clinical settings as part of a focused examination. They can also be used as an extension of the physical examination. They may be used in the intensive care unit or emergency department, or in the medical school classroom as part of the physical diagnosis curriculum. They could potentially be used in less conventional settings, such as on an ambulance, or prior to transfer to a hospital, or in an underserved area in which echocardiography equipment is unavailable.

A variety of medical personnel may find these devices useful. Currently, not only cardiologists, but also emergency department physicians and anesthesiologists require ultrasound training. Cardiologists may appreciate the convenience of the portable device when examining patients. Medical students, house-staff, internists, and other physicians may find them useful to improve accuracy of the physical examination or even replace the physical examination, especially if the system also allows auscultation. Nurses and other paramedical personnel may also use it in selected situations. Moreover, patients may appreciate the immediate information that can be provided with the device at the time of their medical evaluation.

Potential specific applications of these devices are diverse. The etiology of cardiac murmurs can usually be determined, although quantitative assessment of valve areas, gradients and regurgitant volumes would require a more comprehensive examination. If minor disease is found that is consistent with the clinical findings, the need for

a regular echo examination may be circumvented. In the patient presenting with dyspnea, recognition of left ventricular dysfunction or enlargement of the right ventricle may suggest a specific underlying etiology. In a patient with cardiovascular collapse, the assessment of left and right ventricular systolic function and inferior vena cava size can provide important clues regarding the diagnosis. In other situations, estimation of cardiac chamber sizes and systolic function may allow recognition of hypertrophic or dilated cardiomyopathy, whereas quantitative assessment of systolic and diastolic function and left ventricular mass would not be feasible with current hand held devices and would require an examination best performed in the echocardiography laboratory.

In the intensive care or hemodialysis unit or the emergency department, inferior vena cava size and collapsibility may be readily evaluated to assess a patient's volume status. The presence and size of a pericardial effusion can be determined; this may be important in the acute situation in the cardiac catheterization or electrophysiology laboratories where echocardiography-guided pericardiocentesis may be considered. The device may be used to guide cannulation of the internal jugular or subclavian veins. Other potential roles include its use in athletic screening or screening for heart disease in symptomatic or at risk populations in underserved areas. Depending in part on the experience and skill of the examiner, as well as further refinements in device technology, these devices may have even broader applications.

Recommendations for Training and Research

Adequate training with these hand held devices is essential. Training programs for use of these devices should be developed and evaluated. ASE should take a lead in this endeavor so as to ensure quality. It will be necessary to determine how many examinations must be performed and interpreted by the new user to develop confidence in accuracy in interpretation. These training programs should be tailored to the users and to the expected cardiovascular applications of the device. Methodology for maintaining adequate quality control must be established. Interobserver and intraobserver variability must be characterized, and its relationship to the system, the imager, and the diagnosis determined.

Recommendations for the optimum features of these devices should be determined, including which measurements and calculations should be included, and whether pulsed or continuous wave Doppler is needed. The role of these devices as an extension of or an alternative to the physical examination appears promising but requires further evaluation. Additional information regarding the impact of these devices on the accuracy of the examination by examiners of varying experience level is needed.

Cost effectiveness of hand held echocardiography in delivery of care models must be assessed. Its effect on "downstream testing" should be evaluated. The potential role for these devices in patient triage and in determining in which patients a comprehensive echocardiographic examination is indicated should be determined. Hand held echocardiography appears promising for decreasing the number of unnecessary comprehensive echocardiograms and for permitting early discharge from the outpatient setting without further testing. More information regarding the situations in which use of these devices is appropriate is needed.

The role of these devices in improving patient outcomes should be evaluated in clinical trials. The use of these devices adds time to performance of the physical examination, and reimbursement issues concerning these devices should be explored, especially in the outpatient setting.

Selected Readings

1 Martin LD, Howell EE, Ziegelstein RC, Martire C, Whiting-O'Keefe QE, Shapiro EP. Hellmann DB. Hand-carried ultrasound performed by hospitalists: does it improve the cardiac physical examination? Am J Med 2009;122:35-41.
2 Ippisch HM, Kimball TR. The impact of evolving hand-carried echocardiographic technology on outpatient physical examination accuracy in pediatric cardiology. Congenital Heart Disease 2007;2:170-8.
3 Kobal SL, Trento L, Baharami S, Tolstrup K, Naqvi TZ, Cercek B, et al. Comparison of effectiveness of hand-carried ultrasound to bedside cardiovascular physical examination. Am J Cardiol 2005;96:1002-6.
4 Spencer KT, Anderson AS, Bhargava A, Bales AC, Sorrentino M, Furlong K, Lang RM. Physician-performed point-of-care echocardiography using a laptop platform compared with physical examination in the cardiovascular patient. J Am Coll Cardiol 2001;37:2013-8.

FUTURE TECHNOLOGY RELATED ISSUES THAT WILL INFLUENCE CARDIAC ULTRASOUND RESEARCH

The following is a summary of key technological changes that could influence cardiac ultrasound research in the future, and should be taken into consideration while planning protocols.

Sensor Technology. Advances in sensor technology are imminent and include new types of silicon based arrays and capacitive micromachined ultrasonic transducers, capable of fusing imaging and high intensity focused ultrasound therapy. Advances in piezoelectric ceramic arrays, such as single crystal or pure wave piezoelectric ceramics with better alignment of molecular structures, will have 2 to 3 times the sensitivity of the current piezoelectric crystals. The ability to withstand dicing into very high element count 3D arrays will result in manufacture of larger aperture and/or flexible blanket type arrays. Developments in 3D intracardiac echocardiography (ICE) and 3D transesophageal echocardiography (TEE) will lead to smaller probes (down to 12-13 mm for adults and down to about 7 mm for infants). For 3D ICE, sensors need to be forward-looking or side-looking. But these devices will be expensive to build and must be re-sterilizable to allow multiple uses.

Miniaturization. Miniaturization drives electronic innovation and results in more powerful systems—even hand-held and palmtops—capable of 2D and 3D cardiac ultrasound imaging. Hands-off controls and hands-off displays would obviously be quite helpful in interventions guided by ICE and/or TEE, requiring hands-off image acquisition and image manipulation. More intuitive types of imaging system control and/or image manipulation and measurement tools are required to broaden the applicability of these advanced technologies for defining 3D structure and function of cardiac chambers and valves.

3D graphics, some of which would come from the gaming industry (interactive manipulation of 3D objects, including 3D visualization and stereoscopic visualization) will help in acquiring a greater understanding and adaptation of advanced echo. Not only hands-off display but hands-off controls will be key to reducing manpower commitment for invasive ICE and/or TEE applications of advanced imaging with broadened application of advanced visualization technologies for defining 3D structure and function. Measurement tools must be developed with cross-branding to allow objective sophisticated manipulation, not only visualization of structure, mass and size, but for

quantification of chamber mechanics and cardiac function as well as visualization of valve structure and function.

Small Animal Imaging Systems. The industry as a whole needs to address the basic science community's need for small animal systems with sophisticated 2D/3D and cardiac mechanics features to overlap mainstream systems and add to the eclectic and limited number of vendors involved in developing small animal systems, while reducing costs of these systems.

With advances in molecular biology, epigenomics, and proteonomics, these small animal imaging systems will be vital not only to study phenotype but also physiology, something that is very much lacking in most basic science laboratories. Further training in use of these systems will be required.

Selected Readings

1 Huang Y, Sanli Ergun A, Hæggström E, Badi M. H, Khuri-Yakub BT. Fabricating capacitive micromachined ultrasonic transducers with wafer-bonding technology. J Microelectromech Syst 2003;12:128-37.
2 Park S, Shrout TR. Characteristics of relaxor-based pizoelectric single crystals for ultrasonic transducers. IEEE Transcactions on Ultrasonics, Ferroelectrics, and Frequency Control. 1997;44:1140-7.
3 Plas JL, Homer BD, Milne C, Jordan T, Kalyuga S, Kim M, Lee H. Design Factors for Effective Science Simulations. International Journal of Gaming and Computer Simulations 2009;1:16-35.

NOTICE AND DISCLAIMER

APPENDIX

The ASE Technology and Research Summit was held on November 13, 2010, at the Sheraton Hotel in Chicago. The participants are listed below:

Chairmen: Sanjiv Kaul, MD, FASE from Oregon Health & Science University, Portland, Oregon; and James G. Miller, PhD, from Washington University, St. Louis, Missouri.

ASE Executive Committee Members: James D. Thomas, MD, FASE, Cleveland Clinic, Cleveland, Ohio; Roberto M. Lang, MD, FASE, University of Chicago Medical Center, Chicago, Illinois; Patricia A. Pellikka, MD, FASE, Mayo Clinic, Rochester, Minnesota; Neil J. Weissman, MD, FASE, MedStar Health Research Institute at Washington Hospital Center, Washington, DC; Peg Knoll, RDCS, FASE, University of California Irvine Healthcare, Orange, California; and Marti L. McCulloch, RDCS, FASE, Methodist DeBakey Heart & Vascular Center, Houston, Texas.

Journal of the American Society of Echocardiography Editors: Alan S. Pearlman, MD, FASE, University of Washington School of Medicine, Seattle, Washington; Jonathan R. Lindner, MD, FASE, Oregon Health & Science University, Portland, Oregon; and Victor Mor-Avi, PhD, FASE, University of Chicago Medical Center, Chicago, Illinois.

Invited Cardiovascular and Ultrasound Scientists: Paul A. Grayburn, MD, Baylor University Medical Center, Dallas, Texas; Mark R. Holland, PhD, FASE, Washington University, St. Louis, Missouri; Allan L. Klein, MD, FASE, Cleveland Clinic, Cleveland, Ohio; Thomas R. Porter, MD, FASE, University of Nebraska Medical Center, Omaha, Nebraska; and David J. Sahn, MD, FASE, Oregon Health & Science University, Portland, Oregon.

Invited Ultrasound Engineers and Technology-Related Personnel: Shinichi Hashimoto, Toshiba Medical Systems Corporation, Tochigi, Japan; Mark Hibberd, MD, PhD, Lantheus Medical Imaging, North Billerica, Massachusetts; Hélène C. Houle, BA, RDMS, RDCS, RVT, FASE, Siemens Healthcare, Ultrasound Division, Mountain View, California; Stephen Metz, PhD, Philips Healthcare, Bothell, Washington; Nancy DeMars Plambeck, BS, RDMS, RDCS, RVT, Toshiba America Medical Solutions, Tustin, California; David Prater, MS, Philips Medical Systems, Andover, Massachusetts; and Kai E. Thomenius, PhD, GE Global Research, Niskayuna, New York.

ASE Staff in Attendance: Robin Wiegerink, MNPL; Hilary W. Lamb, MPA; Sherry Honey-Barrow, MPA; and Andrea M. Van Hoever *(coordinator of the event)*.

Guest Attendee: Denis Buxton, PhD, National Heart, Lung, and Blood Institute, Bethesda, Maryland.