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Impact of Contrast Echocardiography on Diagnostic Algorithms: Pharmacoeconomic Implications

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Summary: The major goal of medicine in the era of managed care is to control escalating costs and to attain a high level of quality health care. Capitation has limited access to expensive and unnecessary testing, placing an emphasis on the prudent use of available technology. A vast armamentarium of available diagnostic screening tests are available within cardiology. Routine two-dimensional (2-D) echocardiography is a high-quality, low-cost test that provides enhanced portability and real-time test interpretation over other noninvasive test modalities. The echocardiogram may cost up to 50% less than competitive nuclear single-photon emission computed tomography (SPECT) imaging. However, on average 10% of routine and 33% of stress echocardiograms are suboptimal (disproportionately affecting obese patients and those with lung disease). Myocardial contrast echocardiography has been shown to provide enhanced endocardial border delineation and left ventricular opacification, to enhance Doppler signal, and to provide information on myocardial perfusion. In several recent phase II and III studies, the use of a contrast agent has been shown to improve the diagnostic accuracy of echocardiography substantially. Improvements in the diagnostic capabilities of echocardiography have been shown to (1) impact upon downstream repetitive testing in patients with an initially nondiagnostic echocardiogram, (2) potentially increase laboratory throughput, and (3) reduce the rate of false-positive and negative tests as a result of improved image quality. As clinical and cost-effectiveness parallel one another, the use of myocardial contrast echocardiography in selected patient cohorts will result in improved diagnostic accuracy and a cost-effective pattern of care.

Key words: economics, diagnostic algorithms, cost effectiveness, patient outcomes, disease management, EchoGen®, contrast echocardiography

Pharmacoeconomic Considerations: Cost-Effectiveness and Patient Outcomes

Managed care has augmented the need for clinically and cost-effective diagnostic tests.[1] Ultrasound, a relatively inexpensive, multipurpose technology, may have a critical role in the future of health care because it combines low cost and wide availability; it may, in fact, become a "diagnostic gatekeeper."[2] This prospect is made more likely given the ability of newer, second-generation ultrasound contrast-enhancing agents to reduce the number of patients referred for higher-priced procedures, as well as their ability to augment disease management through early diagnosis, rapid triage, and management. With low cost but highly accurate ultrasound, the patient may be able to proceed directly to therapeutic options rather than being delayed and burdened by the additional expense of further diagnostic testing.

Myocardial contrast echocardiography (MCE) with contrast administered in the cardiologist's office should be very cost-effective. One researcher estimated the costs (Table I) of four common diagnostic tests for coronary artery disease (CAD): exercise electrocardiography, $300; single-photon emission computed tomography (SPECT), $1,200; positron emission tomography (PET), $1,800; angiography, $4,800. The cost of myocardial contrast echocardiography is estimated to be similar to exercise electrocardiography.[3]

Because of its relatively low cost and the potential to provide definitive information, high-quality echocardiography should be a major asset in cost-conscious environments.[4] Definitive echocardiographic studies should obviate the need for more expensive, more invasive examinations in a large proportion of patients and improve the likelihood of cost-effective patient care.

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TABLE I Estimated costs of common diagnostic tests for coronary artery disease

Procedure	Estimated cost
Myocardial contrast echocardiography	$300
Exercise electrocardiography	$300
Single-photon emission computed tomography (SPECT)	$1,200
Positron emission tomography (PET)	$1,800
Angiography	$4,800

Source: From Ref. No. 3 with permission.

The field of contrast echocardiography is advancing with the introduction of contrast agents that traverse the capillaries, enabling left ventricular (LV) opacification via intravenous (IV) injection. Advances in ultrasonic hardware and software are also occurring. Harmonic imaging with ultrasound contrast agents yields images closely related to those obtained with radiopharmaceuticals.[2] In both modalities, interference from background tissues is minimal. Early clinical data suggest that the combination of harmonic and transient imaging methods may profoundly expand future applications of ultrasound contrast media by requiring lower doses of contrast agents and by increasing diagnostic contrast. The result would be fewer nondiagnostic CAD examinations, fewer unnecessary invasive examinations, better patient care, and lowered costs.

Impact of New Contrast Agents on Myocardial Contrast Echocardiography

Without contrast agents, echocardiography provides, at best, gross anatomic data. In the 1970s, M-mode echocardiography evolved into a valuable tool for the quantification of LV mass. Still, M-mode echocardiography provides limited information.[5] By the 1980s, two-dimensional (2-D) echocardiography had progressed so that volumetric chamber quantitation had become feasible. However, it was limited by poor image quality and the need for digital acquisition and storage.

The limitations of ultrasonographic studies are increasingly evident as physicians demand more information from B-mode and Doppler examinations. The necessity of contrast agents to increase the efficacy of ultrasound and Doppler examinations has grown over the last 20 years.[6] Contrast-enhanced color-Doppler and/or spectral-Doppler echocardiography could improve diagnoses of valvular blood flow abnormalities, including regurgitation. Detection of atrial or septal shunts as well as hemodynamic deficiencies of the pulmonary artery or vein could be simplified. Thus, the addition of a contrast agent improves the utility of echocardiography in a number of ways. Sensitivity is improved, allowing the clinician to assess smaller areas and observe disease processes in earlier stages. Recently developed contrast agents permit more accurate imaging of organs, tissues, and disease states where imaging was suboptimal and nondiagnostic or impossible. Specificity is improved, permitting greater differentiation between normal and abnormal features. Enhanced image quality reduces the rate of false-positive, indeterminate, or equivocal studies, thus enhancing the diagnostic yield of the echocardiogram and refining posttest referral patterns to higher-risk patients in need of treatment and/or intervention. As a result of early and effective treatment, improved survival may be the result of enhanced image quality. This may be particularly apparent in higher-risk cohorts of patients where the echo is currently used to decide and track disease processes as well as therapeutic effectiveness (e.g., congestive heart failure, valvular disease).

Myocardial Contrast Echocardiography as a Diagnostic Tool for Coronary Artery Disease

Coronary artery disease is the most widespread, debilitating, and potentially lethal disease in the Western world. In the United States alone, CAD is responsible for approximately 750,000 deaths each year.[2,7] Because CAD is often asymptomatic or symptoms are often nonspecific, clinicians value diagnostic tools and techniques that offer prompt, early detection of the disease and aid in the management of patients already diagnosed with CAD.[8,9] A low-cost, highly accurate, diagnostic tool that could be readily available in most cardiologists' offices obviously would be invaluable. Ideally, patients presenting with symptoms such as chest pain or shortness of breath could be examined quickly and more accurately. Such a tool might be incorporated into the general examination of persons at risk for CAD.

Among the cardiologist's current armamentarium of diagnostic tools is the exercise electrocardiogram (ECG), which costs approximately $300. Although the ECG is a low-cost diagnostic technique, it also is plagued by substantially lower sensitivity and specificity leading to higher rates of false-positive and negative examinations. A high rate of false-positive tests will lead to higher rates of more expensive imaging or invasive coronary angiograms—with fees of $1,500 to $4,800.[3] The treadmill test has an average sensitivity of 65% for the detection of coronary disease.[10] For risk stratification, the positive predictive value of the exercise ECG in patients post-MI is ≤10%.[11] This diminished accuracy of the exercise ECG has led many researchers to advocate additional imaging in patients with an indeterminate or intermediate risk treadmill test; this includes ≤60% of the population.[12,13] Furthermore, the addition of an imaging modality is the test of choice in patients with resting ECG abnormalities or in women.[13,14]

Although the treadmill test may be adequate in lower-risk populations, cost efficiency with enhanced diagnostic accuracy may be achieved by the use of echocardiography with the use of contrast agents (where appropriate) in intermediate risk patients. In patients who are not treadmill test candidates, contrast echocardiography has been shown to reduce the rate of equivocal results by 30 to 50%.[15]

A competitive but more expensive technique to echocardiography is the use of nuclear imaging with thallium-201

(^{201}Tl) or technetium-99m (^{99m}Tc). During the 1980s, a number of software, hardware, and radionuclide agent developments significantly improved the accuracy of this technique. Despite those improvements, certain patient cohorts are prone to a suboptimal image due to attenuation artifacts; this includes obese patients and women (about 30% of the population). The use of ^{99m}Tc agents has resulted in higher count rates, improved image quality, and a lower rate of breast artifact or diaphragmatic attenuation, although these ^{99m}Tc–based agents cost approximately \$130–\$160 per dose. The current standard methods for this imaging technique, including tomographic imaging and quantitation, have vastly increased the price of this technique and limited portability.

Radionuclide scintigraphy involves the injection of a radioactive isotope (^{201}Tl or ^{99m}Tc). Developments in this area have allowed for the addition of an ejection fraction during imaging as well as quantitative perfusion defects. However, with the new improvements the routine cost of this technique has also increased from \$300 to \$850. The cost of single-photon emission computed tomography (SPECT) imaging is additive due to the use of tomographic cameras, technetium-based agents (80% of use), image correction software, gating software, radiation safety, and handling costs, as well as of the need for specialized personnel [i.e., radiopharmacy, certified nuclear medicine technologist (CNMT)]. An additional limitation of SPECT imaging is the time required for the patient to remain in the facility; depending upon the protocol, this averages 3 to 4 h.

Although there are other modalities [e.g., PET, magnetic resonance imaging (MRI), ultrafast computed tomography (CT)], those discussed represent the most commonly used for screening of ischemic heart disease in this country. For example, PET has the highest reported accuracy due to a true representation of the distribution of blood flow, but it is one of the most expensive noninvasive tests and is available at only 83 centers in this country.[16] The standard of reference for diagnosis is obviously coronary angiography. From the coronary angiogram, a tremendous amount of prognostic information is also available (e.g., ejection fraction, extent of coronary disease) upon which subsequent risk-reducing medical and surgical interventions are often based.[17] However, this diagnostic technique is also invasive and expensive.

In the U.S., approximately 600 diagnostic cardiac catheterizations per 100,000 patients are performed annually. About 40% of patients are referred as a result of evidence of myocardial ischemia.[18] On average, 20 to 30% of patients who undergo coronary angiography have no significant stenosis; the rate reaches 50% in the female population. The optimization of current noninvasive modalities may enrich the diagnostic yield of angiography by limiting referral to cardiac catheterization only to patients whose post-noninvasive test risk of disease is high.[19] In a recent multicenter registry of stable angina patients, the rate of cardiac catheterization could be reduced by about 20% by limiting referral to those with evidence of ischemia on their initial stress test. When referral to cardiac catheterization is limited only to highest-risk patients, the rate of referral to angiography may be further reduced.[20]

When comparing all available diagnostic modalities, stress echocardiography is inexpensive, portable (i.e., it can be performed in the cardiologist's office), and provides enhanced diagnostic capabilities over the less expensive exercise ECG. Despite the improved accuracy of stress echocardiography, in an estimated one third of patients, a suboptimal image occurs due to movement, hyperventilation, and tachycardia.[21, 22] In the stress laboratory, myocardial contrast echocardiography offers numerous advantages in diagnosis and evaluation of CAD. Using contrast agents provides enhanced endocardial border delineation, LV opacification, and increases the Doppler signal. Thus, determination of exercise-induced dyssynergy may improve with addition of a contrast agent. One exciting development in diagnostic testing will be the determination of myocardial perfusion with contrast agents that measure both microvascular blood flow and blood volume.[23]

One may envision a number of applications for the use of MCE perfusion imaging, including the evaluation of myocardial perfusion defects, area at risk, myocardial blood flow including collateral flow, and coronary flow reserve.[24] However, currently available echocardiographic contrast agents require intra-aortic or intracoronary injection, thus restricting use to the operating room or catheterization laboratory. Recently developed contrast agents and ultrasound technology have demonstrated myocardial perfusion imaging after venous injection. This advance may prove to be the most valued in contrast echocardiography.[25]

Unlike coronary angiography, contrast echocardiography is noninvasive and can be performed at the patient's bedside or in the clinician's office with minimal or no patient discomfort. Absence of adverse effects and patient discomfort means that the echocardiographic procedures can be repeated as often as clinically indicated.[26] Of particular concern to patients, contrast echocardiography also does not involve ionizing radiation.

In outcomes research, MCE provides a unique opportunity to improve the diagnostic capabilities of current techniques while adding minimal cost to the diagnostic "work-up." Newer MCE agents have been shown to be substantially more accurate than the current agent, sonicated albumin (Albunex®, Molecular Biosystems, San Diego, Calif.). The initial upfront cost of an agent may be minimized by several factors: (1) less imaging time for difficult-to-view patients (e.g., obese patients or those with lung disease); (2) a reduction in downstream, duplicate testing due to improved diagnostic accuracy; (3) a lower rate of false-positive and negative tests resulting from enhanced border delineation, and the integration of myocardial perfusion into the test interpretation. When contrast agent technology develops to enable myocardial opacification via IV injection, clinical applications for MCE will increase to include clinical and cost-effective alternatives to nuclear imaging for many patients evaluated annually in this country.[27]

Finally, in the diagnosis of CAD in office-based settings or by general internists or family practitioners, a recent study evaluated the accuracy of echocardiographic imaging by fellowship-trained physicians versus the accuracy of general internists. There was a substantial difference in the ability to classify LV ejection fraction between the two groups.[28] Thus,

diagnostic evaluations performed by less experienced physicians may be disproportionately improved with the addition of myocardial contrast.

Implications of Contrast Echocardiography in Patient Populations

The use of echocardiography enhanced by a contrast agent may benefit selected subsets of the population. A brief synopsis follows of several patient cohorts who would be aided by the improved cost efficiency with MCE.

Patients with Stable Coronary Artery Disease

There are approximately 7.5 million patients evaluated annually for chest pain symptoms in this country,[29] with an average of 4 million patients referred for stress nuclear test scans or echocardiography. Research reveals that patients with stable chest pain symptoms at intermediate risk for coronary disease benefit greatly (in the form of diagnostic and prognostic stratification) from diagnoses based upon the results of an echocardiogram or nuclear scan.[12–14, 30] A recent meta-analysis of 49 published reports on the diagnostic accuracy of exercise echo revealed that the sensitivity and specificity for testing are 82 and 76%, respectively.[31] Similar meta-analyses of patients at risk of CAD have revealed parallels in prognostic stratification between stress echo and nuclear testing.[11] Thus, economically, the potential exists for equally efficacious tests while containing costs to ≤ 50% of the current nuclear testing techniques.

Achieving Cost Efficiency

A recent multicenter registry of patients with stable chest pain (i.e., the Economics of Noninvasive Diagnosis) examining the cost efficiency achieved by nuclear stress tests reveals a 35% cost savings when nuclear tests are the gatekeeper for cardiac catheterization compared with catheterization.[19] Given the similar accuracy of nuclear and echo imaging, an additional savings may be realized through the use of less expensive MCE when employing cost minimization analysis, and incorporating the assumption that the outcomes achieved or identified by the disease management strategy and the underlying risk in the comparative populations are similar. Cost minimization may be used to compare strategies in competitive methods. Therefore, two tests that are equally effective in expert hands (i.e., echo imaging and nuclear) will show echocardiography to be more advantageous due to lower cost. The additional advantage of nuclear testing as a result of information on stress perfusion imaging, is offset by the addition of MCE.

The most obvious merit of the use of MCE is that multiple tests may now be combined into a single, noninvasive test. The test will offer accuracy similar to others at a substantial reduction in cost (compared with nuclear, MRI, ultrafast CT, PET, and multiple modalities). Until the advent of IV contrast echocardiography, direct assessment of myocardial perfusion was unavailable in echocardiography. Multiple tests were often necessary to link anatomy with physiology. Stress echocardiography, for example, permits assessment of wall-motion abnormalities not present at rest, but their detection remains an indirect measurement of perfusion. Myocardial contrast echocardiography, on the other hand, is especially useful for characterizing regional distribution of coronary blood flow and measurement of myocardial perfusion as well as integrating information on regional and global ventricular function and valvular function.

From the perspective of judicious resource use, the rate of false-positive tests is a major limitation of any noninvasive test. False-positive tests lead to unnecessary diagnostic testing and higher costs of care. The overall rate of false-positive echocardiograms is approximately 26%.[31] In two recent studies, echocardiographic examinations were shown to be nondiagnostic in 20 to 35% of cases.[32, 33] Recent evidence from using MCE has suggested that the rate of equivocal or indeterminate studies will decrease by as much as 50% with MCE.[15, 34] In clinical trials, contrast echocardiography using newer contrast agents and current sonographic technologies has increased the number of diagnostically useful examinations.[35] Furthermore, the rate of true normal and abnormal studies will also increase, thus increasing the precision of the routine echocardiogram.[15, 34]

Two cohorts of patients who benefit greatly in terms of diagnostic accuracy from MCE include obese patients and those with lung disease. Myocardial contrast echocardiography significantly enhances border detection in even obese patients.[26] Contrast agents have more predictable reflectivity compared with saline injections with comparable image quality. Patients in whom calculation of right ventricular ejection fraction is important often have poor echo windows because of accompanying chronic obstructive pulmonary disease (COPD). Contrast echocardiography can produce superior images in those patients as well.[36] Prior to MCE, such patients often required lengthy imaging times or were referred to more expensive transesophageal echocardiography (TEE) testing. A high percentage of the TEE population with suboptimal images often then received redundant and unnecessary testing. Additional testing needed due to nondiagnostic results has been associated with a lower rate of patient satisfaction in a recent study conducted by Kangarloo *et al.* (1996).[37] Thus, these issues are crucial to member longevity in a health care system, managed care organization's perception of the test quality, and the overall confidence in the test. The initiation of prospective laboratory procedures for obese patients or those with lung disease may aid in substantially reducing diagnostic costs (as a result of a reduction in unnecessary downstream resource use). In a hypothetical evaluation of patient-care costs, the upfront cost of the contrast agent in obese patients or those with lung disease may be offset by reduced imaging time and increased laboratory throughput.

Disease Management Strategies

A growing field of research is the development of therapeutic disease management strategies. *Integrating diagnostic test-*

ing into existing therapeutic regimens is a current challenge. Recent use of dobutamine stress echocardiography to identify functional recovery of regional wall motion following coronary bypass surgery has shown promising results.[38] Current review of the accuracy of PET, SPECT, and echo has revealed similar outcomes.[39] However, one present limitation in the use of echo is lack of data on the functional significance of a given coronary stenosis. By boosting the echogenicity of the blood, MCE provides clinicians with direct information about myocardial structure and function.[2] Moreover, echocardiography, unlike nuclear imaging methods such as PET and SPECT, provides direct information on contractility at a substantial reduction in cost.

The prospective identification of potentially reversible ventricular dysfunction caused by stunned myocardium has significant clinical implications.[40,41] That wall-motion abnormalities at rest frequently improve after revascularization has aroused interest in diagnostic techniques that can predict such improvements. Myocardial contrast echocardiography may be particularly useful in determining the viability of stunned or hibernating myocardial tissue. As a means of differentiating between reversible and irreversible tissue damage—and the extent of the irreversible damage—MCE could help identify candidates for revascularization procedures. Researchers have shown that MCE can detect stunned but viable myocardium in humans and animals.[40,41]

Recent controversy exists concerning the added value of an ejection fraction over and above perfusion data.[42] In part, the limitation to current SPECT techniques for acquiring an ejection fraction in combination with the perfusion data is that it is collected approximately 15 min after stress. Thus, only those patients with marked ischemia will have evidence of global or regional LV dysfunction.[43] Furthermore, the ejection fraction acquired during SPECT imaging is gated and represents an average of beat-beat ventricular function. Therefore, echo offers some advantages in acquiring early, real-time data. The use of MCE will enhance early imaging as a result of increased echogenicity in patients whose stress-induced hyperventilation may have previously limited image acquisition.

Women

The evaluation of chest pain in women is difficult because of the atypical nature of their symptoms.[44,45] Despite the dissimilar presentation, near equal numbers of women and men die from CAD, with the overall death rate declining in white men. The decline in mortality in men has been attributed to more aggressive and earlier diagnosis of CAD. Some reports have noted an apparent gender bias in the use of noninvasive and invasive diagnostic options in women at risk compared with men.[46,47] A test that could identify CAD in women would prove invaluable to the clinician, thus enhancing the referral of women with CAD. Until such a test appears, current modalities in the evaluation of women are limited for several reasons. The presence of ECG ST depression on a treadmill test has a reported lower accuracy in women than in men.[48,49] Many now advocate the same routine use of imaging in women and in men.[13,50] In several recent reports on the use of exercise echocardiography, the overall sensitivity for detecting CAD in women was 80%.[13,31] Clinicians have found that SPECT imaging in women may result in technical difficulties due to breast or soft tissue attenuation, resulting in higher-than-expected rates of nondiagnostic examinations.[46] The use of more sensitive imaging tests has resulted in increased false-positive diagnoses of CAD in women, leading to a high rate of normal coronaries at catheterizations.[51] Thus, an inexpensive test that furnishes information on ventricular function and myocardial perfusion as well as valvular disease will be a versatile tool to evaluate symptomatic young women (at risk of mitral valve prolapse) and older women (at risk of congestive heart failure or CAD).

Acute Ischemic Syndromes

From the recent acute chest pain (ACP) guidelines for risk stratification of post-MI patients, early and continual risk stratification (in particular within the first 72 h) is crucial to effective intervention, management, and risk reduction.[52] There are two uses for MCE in acute ischemic syndromes: (1) emergency room (ER) imaging in acute cases, and (2) post-MI management. With regard to the former, both SPECT and echo imaging have been proposed as means to identify patients with ongoing ischemia presenting to the ER with chest pain (a large cohort of patients with a vast array of differential diagnoses). Although a multicenter trial has recently been completed using tetrofosmin SPECT imaging, showing an ability to differentiate among patients with normal versus abnormal perfusion defects,[53] SPECT imaging has not been uniformly implemented because of many logistic limitations. One major limitation in the use of SPECT imaging in the ER is the need for radioisotope injection close to the onset of symptoms;[54] this is possible only if in-house staff members are available throughout the day. Furthermore, echo imaging is portable—a distinct advantage in the ER. An additional advantage is that many ER physicians are becoming increasingly comfortable performing this type of ultrasound. These advantages coupled with improved image quality and function and perfusion information heighten the possibility of MCE becoming a test that physicians rely upon heavily in the ER. As stated in the recent Unstable Angina Guidelines, patients presenting without evidence of ventricular function or perfusion abnormalities during a rest study may then be discharged, with a stress test to be performed within 72 h to rule out stress-induced ischemia.[55] Although chest pain units have cut costs of evaluations by half, rapid diagnosis within the early hours of chest pain presentation and further testing in the outpatient setting could achieve additional cost savings.[56]

Within the first few days of an acute event, echo imaging plays a key role in identifying patients at risk of mechanical complications.[57] Current MCE research has revealed it to be a useful diagnostic tool in the aftermath of acute infarction.[58] Myocardial contrast echocardiography may allow the differentiation of infarcted from viable tissue in the acute post-ischemic state. Such differentiation allows early treatment

strategies based on the quantity of remaining viable myocardium. Quantitating the percentage of myocardial salvage with varying treatment regimens post MI has been posited as a valid use of SPECT imaging and could be equally applied with MCE.[59]

Recent guidelines of the American College of Physicians on risk stratification recommend determining LV function prior to discharge (preferably by Days 3 to 5) in all patients with MI. The role of echo imaging and myocardial contrast may be enhanced by the addition of perfusion data in subsets of patients with recurrent chest pain who may benefit from selective catheterization. With the addition of rapid triage and management, those patients identified as uncomplicated (without evidence of systolic dysfunction or ischemia) may be readied for discharge within the first 72 h. In MCE-tested patients who had no evidence of LV dysfunction or ischemia on a predischarge test, routine discharge may be by Day 5; thus, significant cost savings over average length of stay may be realized.

Furthermore, MCE offers clear advantages in the amount of information obtained and in the improved accuracy over the exercise ECG. In a recent meta-analysis of post-MI predischarge testing, Shaw *et al.*[11] reported the positive predictive value of stress myocardial perfusion imaging was ≤10% in identifying cardiac death or MI within 1 year of discharge. Thus, current guidelines have limited test recommendations to the exercise ECG, in large part due to the low cost and prognostic information obtained from a patient's functional capacity.[52] In sum, a low-cost MCE test that adds both ventricular function and myocardial perfusion data could prove successful in aiding post-MI management.

Valvular Disease and Patients with Congestive Heart Failure

In two patient populations echocardiography is the test of choice: patients with valvular disease or those evaluated for LV function. In the first patient group, the use of MCE that enhances the Doppler signal may provide increased diagnostic accuracy in patients at varying stages of their disease. Furthermore, in patients with heart failure or decreased cardiac output, the improved Doppler signal and enhanced endocardial border delineation in those with resting abnormalities may aid in effective and rapid identification and treatment.

Intraoperative Myocardial Contrast Echocardiography

Myocardial contrast echocardiography is being used intraoperatively to monitor myocardial perfusion and assess patency during coronary bypass grafting and percutaneous transluminal coronary angioplasty. It can be performed quickly and employs small, mobile equipment, yet can provide real-time imaging of myocardial blood flow and on-line assessment of graft bypass function. Current methods employ TEE to assess intraoperative ischemia. The addition of myocardial perfusion with wall thickening and segmental wall motion may aid in the evaluation of the "true positive" nature of new dyssynergy in this setting. The identification of patients with true ischemia will allow for rapid triage and management and the prevention of perioperative complications, including postoperative MI.

Patients with Vascular Surgery

Recent guidelines for the evaluation of patients with vascular surgery have been published by the American College of Cardiology/American Hospital Association, for despite the low risk of perioperative complications, patients who have vascular surgery have a high rate of CAD. Thus, many advocate the use of stress nuclear and echocardiography for the preoperative evaluation of vascular surgical candidates.[60,61] In a recent meta-analysis, the use of dobutamine stress echo showed similar accuracy to stress nuclear imaging.[61] However, many physicians still rely upon evidence of flow limitations in perfusion as a rate-limiting step in the referral of patients with vascular disease to cardiac catheterization and revascularization (where appropriate). With the addition of MCE-determined myocardial perfusion, this test may provide estimates of global ventricular function, regional wall motion, and myocardial perfusion—all of the components of risk stratification needed for subsequent clinical decision making.[11,52] A recently conducted decision analysis, applied to selective preoperative risk stratification in high-risk patients, was able to achieve significant cost savings vis-à-vis reductions in perioperative events, prophylactic coronary revascularization, and surgery cancellation.[62] This analysis included the cost of stress nuclear techniques; a lower cost test that is equally effective in risk stratification would achieve additional cost savings with MCE.

Pharmacoeconomic Studies of Contrast Agents

In one trial, the responses from two blinded readers were assessed to compare the attributes of sonicated albumin (Albunex®, Molecular Biosystems, San Diego, Calif.) with those of perflenapent emulsion (EchoGen®, SONUS Pharmaceuticals, Bothell, Wash.) (Data on file, SONUS Pharmaceuticals.)

Overall, perflenapent provided sufficient diagnostic information to affect patient care in 65% of the patients, compared with 22% in patients receiving sonicated albumin (Fig. 1). One blinded reader reported that perflenapent precluded the need for further tests in 67% of the cases, compared with 38% for sonicated albumin. Another blinded reader noted that perflenapent facilitated diagnoses by disclosing findings not apparent on the unenhanced scan in 73% of the cases, compared with 19% for sonicated albumin. Additional data are shown in Table II.

In the same study, perflenapent proved useful in improving suboptimal echocardiograms. The echocardiographic examination improved from suboptimal to diagnostically useful in 48, 52, and 50% of cases documented by the principal investigators and two blinded observers, respectively. The corresponding figures for sonicated albumin were 9, 10, and 15%. Such improvements in image quality can assist in the

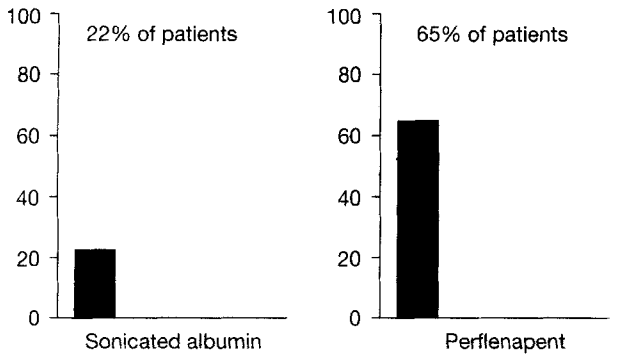

FIG. 1 Comparison trial of patient management attributes: Sonicated albumin and perflenapent. The imaging qualities of the contrast agent provided sufficient diagnostic information to assist in or change the management of the patient. *Source:* Data on file, SONUS Pharmaceuticals.

determination of ejection fractions and the assessment of wall motion. (Data on file, SONUS Pharmaceuticals.)

The overall advancements in image quality must have a positive impact upon the diagnostic costs of care. A theoretical analysis of a patient cohort determined that perflenapent has a positive cost impact (18%) in patients who have inconclusive stress echocardiograms without contrast agents.[63] The pharmacoeconomic implications of those findings should be clear: Expenditures are reduced when fewer tests are required to secure diagnostic results; tests that increase the manifold of diagnostic information can improve patient care and patient management. Quite often, clinical effectiveness and cost-effectiveness are highly correlative.[64, 65] As a result, use of MCE in targeted populations with a known improvement in diagnostic capabilities over routine 2-D echocardiography should prove to be both clinically and cost effective.

A pharmacoeconomic analysis of patient care in a phase III study of an ultrasound contrast agent evaluated cost of care related to initial patient condition for the ultrasound study, including baseline and follow-up tests.[66] Cardiologists performing the tests determined whether follow-up tests were required after contrast and noncontrast studies. Hospital and physician costs for such tests were derived from hospital cost accounting systems and Medicare fee schedules.

The analysis demonstrated a diagnostic yield of 86.7% after application of a contrast agent, compared with 49.3% following noncontrast studies (Fig. 2). This resulted in a need for follow-up testing in only 12.3% of patients receiving the contrast agent, compared with 41.9% of patients following noncontrast studies (Fig. 3). The follow-up studies included transesophageal echocardiograms, nuclear studies, and cardiac catheterizations. The difference in diagnostic costs between noncontrast and contrast-agent studies was 18.3% after including cost of the contrast agent. The savings per patient were calculated to be $119. Contrast agents producing even higher yields of diagnostic as opposed to nondiagnostic tests should result in even greater savings.

Extrapolation of these preliminary data to the Medicare population shows that, in any given year, 12 to 15 million Medicare patients undergo echocardiograms; of those tests, 10 to 15% are suboptimal.[67] Applying standard Medicare reimbursements yields a cost-waste figure of $200 million per year.[68] In addition, suboptimal examinations will result in additional extraneous resource use of $150 million per year. If contrast agents and echocardiography can achieve a reduction in suboptimal examinations and, accordingly, reductions in subsequent resource utilization, potential savings in the realm of $85 million to $125 million per year could be realized.

Controlling costs and selecting the most cost-efficient diagnostic modalities for CAD are not solely the province of managed care. As risk is downstreamed from managed-care plans

TABLE II Patient management attributes of two contrast agents

	Perflenapent emulsion (%)	Sonicated albumin (%)	p Values
Improved study from suboptimal to diagnostic			
Blinded reader A	54	9	<0.001
Blinded reader B	50	16	<0.001
Improved endocardial border detection			
Blinded reader A	86.5	57.8	<0.001
Blinded reader B	82.9	61.8	<0.001
Improved diagnoses by showing findings not seen on unenhanced scan			
Blinded reader A	73	19	<0.001
Blinded reader B	80	55	<0.001
Prevented additional tests or patient referrals			
Blinded reader A	66	8	<0.001
Blinded reader B	67	38	<0.001
Gave sufficient information to assist in or change patient management			
Blinded reader A	68	10	<0.001
Blinded reader B	59	27	<0.001

Source: Data on file, SONUS Pharmaceuticals.

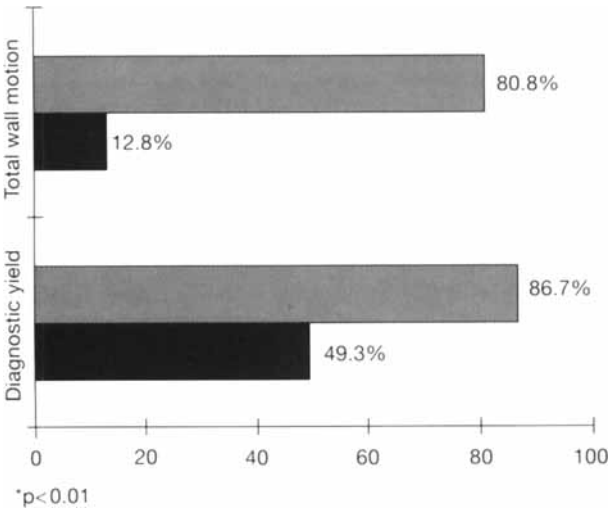

FIG. 2 Improvement in diagnostic accuracy using contrast. ■ = Noncontrast, ■ = contrast.

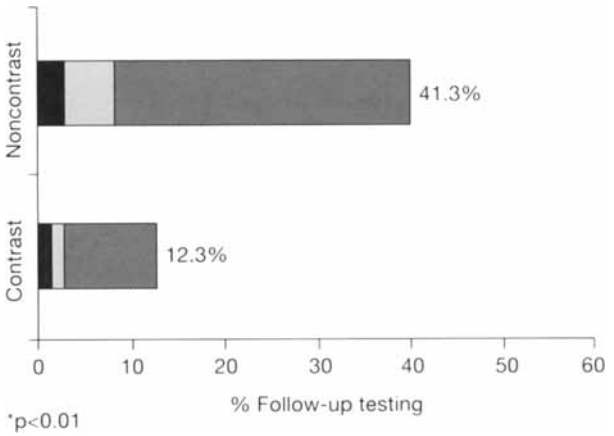

FIG. 3 Gatekeeper referral pattern. Only 12.3% of patients receiving a contrast agent needed follow-up testing, compared with 41.9% of patients who were studied using noncontrast methods. ■ = Catheterization, ▨ = transesophageal echocardiography, ■ = nuclear.

to providers via capitated reimbursements, bottom-line considerations will mandate that cardiologists select prudently from among available diagnostic modalities. Researchers found that California indemnity insurers—even those paying discounted fee for service to radiologists—were still spending between $8 and $10 per member per month for imaging. However, the trend is away from higher-paying indemnity plans and toward extremely low capitated per-member per-month fees. Radiologists in southern California were typically offered between $2.50 and $3.50 per member per month to cover all imaging services. Researchers noted that capitation will motivate providers to contain costs and adopt new technologies selectively, focusing on those that improve efficiencies and demonstrate cost-effectiveness. Cardiologists can expect to experience similar incentives and discouragements.

Conclusion

Myocardial contrast echocardiography is a readily available and low-cost diagnostic method that demonstrates many advantages over other diagnostic modalities. It provides high levels of diagnostic information—particularly with regard to CAD diagnosis and the development of treatment plans for patients with acute myocardial infarction. Improved contrast agents enhance the cardiologist's ability to use echocardiography to study myocardial perfusion and cardiac function simultaneously, in real time, in the office.

Myocardial contrast echocardiography delivers a high degree of specificity and selectivity, and is noninvasive. Research that identifies improved efficacy with MCE will also be the key to uncovering new ways to achieve cost effectiveness of cardiovascular diagnostic testing. Clinical effectiveness and cost effectiveness parallel each other. Using inductive reasoning, if improved diagnostic accuracy is achieved with MCE, the results will be lowered diagnostic costs in selected patient populations. Furthermore, if contrast agents yield more effective diagnostic tests clinically, almost certainly those tests will be more cost-effective.

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