Contrast Echocardiography

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ABSTRACT

Ultrasound contrast agents are widely used in clinical practice for left ventricle opacification in sub-optimal echocardiograms. Recently, significant research has focused on the use of contrast echocardiography as a non-invasive means to evaluate myocardial perfusion. Advances in contrast agents as well as ultrasound technology have enabled investigations into myocardial contrast echocardiography as a possible alternative to nuclear imaging studies. This review will focus on the development and current uses of contrast echocardiography, as well as future indications, including myocardial perfusion and risk stratification following myocardial infarction.

INTRODUCTION

Echocardiography has become a standard tool in the evaluation and diagnosis of a wide range of cardiac conditions. In addition to the determination of cardiac size and function, echocardiography is widely used for the assessment of left ventricular wall motion, systolic and diastolic function, valvular structure and function, as well as imaging of the great vessels. The use of agitated saline as an intravenous ultrasound contrast agent to enhance images has been well described and is currently in use for evaluating right to left shunts. However, the large size and short half-life of saline bubbles prevent their passage through the pulmonary circulation and thus precludes their use as an intravenous agent for enhancement of the left ventricle. Recent advances in microbubble technology, along with improved ultrasound transducer technology, have enabled the wide-spread use of intravenous contrast for left ventricular opacification. However, it has not historically been possible to assess myocardial perfusion, that is, the functional state of the coronary vasculature, using echocardiography. Expanding on the technology of ventricular opacification, much research has focused on the use of echocardiography with intravenous contrast to evaluate myocardial perfusion. This review of contrast echocardiography will discuss the development and current indications for contrast echocardiography, as well as possible future uses of the technology.

CONTRAST AGENTS

The ability to opacify vascular structures on echocardiograms by injecting agitated saline solution has been well recognized for more than thirty years (Gramiak and Shah, 1968). Early contrast agents were produced by manually agitating solutions such as saline, yielding bubbles that provided brief ultrasound contrast by scattering the incoming ultrasound energy before dissolving rapidly in blood. These hand-agitated intravenous solutions have been shown to be safe and are still used clinically to provide brief contrast during echocardiograms for evaluating cardiac shunts and patent foramen ovale (Bommer et al., 1984). Hand-agitated intravenous solutions, however, cannot be used to evaluate left-sided cardiac chambers because the bubbles have neither a small enough size nor the stability to cross the pulmonary vasculature. (Table 1)

<table>
<thead>
<tr>
<th>TABLE 1 PROPERTIES OF AN IDEAL ECHOCARDIOGRAPHIC CONTRAST AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High echogenicity (scattering)</td>
</tr>
<tr>
<td>• Minimal diffusion of gas outside the microbubble</td>
</tr>
<tr>
<td>• Small size to transverse pulmonary circulation</td>
</tr>
<tr>
<td>• Stability during pulmonary passage</td>
</tr>
<tr>
<td>• Confinement to the intravascular compartment</td>
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</table>

Sonication, or the exposure of a solution to ultrasound energy leading to the formation of stable microbubbles, was originally described by Feinstein (Feinstein et al., 1984). The first commercially available contrast agent, Albunex, consisted of sonicated albumin microbubbles containing air, and was approved by the Food and Drug Administration (FDA) in 1992 as an intravenous injection for left ventricular opacification in sub-optimal echocardiograms. The air within Albunex bubbles diffused rapidly into the circulation following peripheral injection, causing the bubbles to become progressively smaller. Because the ability to detect a microbubble by ultrasound is a function of the sixth power of the radius of the bubble, these first-generation microbubbles such as Albunex began to lose their echogenicity in a relatively short time as air diffused out into the circulation (Cheng, et al., 1998). In low output states, with increased contact time between the microbubbles and blood, Albunex did not reliably lead to cavity opacification. Gandhok et
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Recently, second-generation contrast agents have been developed using poorly soluble gases such as high-molecular-weight perfluorcarbons. The resulting microbubbles have an increased longevity compared to first-generation agents, and maintain their echogenicity for several minutes following peripheral injection, providing sufficient time to obtain the desired opacification (Skyba and Kaul, 2001). Several second-generation agents have been granted FDA approval for ventricular opacification in sub-optimal studies and are now widely used in clinical practice for left ventricular opacification (Table 2).

ULTRASOUND TECHNOLOGY

Along with advances in microbubble technology, significant progress has been made in ultrasound imaging. The ability of an ultrasound wave to detect microbubbles depends on the degree of physical change that the bubble undergoes. At progressively higher diagnostic ultrasound intensity, which can be monitored by the mechanical index, the bubbles oscillate with increasing intensity, eventually breaking apart and yielding a maximum signal. Mechanical index is directly proportional to the power output of the ultrasound transducer and inversely proportional to the square root of the transducer frequency. This means that a high intensity, low frequency signal generates a maximal signal from the microbubble (Kaul, 2001). The goal in using contrast agents is to increase the signal from the tissue or cavity that contains the contrast while simultaneously minimizing the signal from surrounding tissues. In opacifying the left ventricle, blood within the cavity contains maximum amount of contrast, which generates a more intense signal compared to the myocardium which contains comparatively few microbubbles. Soft tissues scatter the incoming ultrasound wave in a linear fashion, while microbubbles have the ability to scatter a given frequency at multiples of the original frequency, termed harmonics (Porter et al., 1996). By filtering out the fundamental frequency and processing only the harmonics, the technology described as harmonic imaging has enhanced the differentiation between contrast and surrounding tissue.

In numerous clinical trials, harmonic imaging echocardiography with intravenous contrast has improved the quality and diagnostic yield compared to echocardiograms without contrast. The impaired transmission of ultrasound energy caused by body habitus, lung disease, hyperventilation, or tachycardia can result in non-diagnostic images in up to 30% of patients referred for echocardiogram (Marwick et al., 1992). Contrast offers the potential to convert many of these non-diagnostic studies into diagnostic images by improving the ability to visualize the endocardial border and myocardial thickening (Figures 1 & 2). Cohen et al. (1998) studied 203 patients with initial sub-optimal non-contrast echocardiograms and found that the use of Optison, a second-generation contrast agent consisting of an albumen shell filled with octafluoropropane, achieved 100% left ventricular opacification in 89 out of 102 (87%) patients. In addition, Optison increased the amount of well-visualized left ventricular endocardium by as much as 7.6 cm at the highest dose used. This study by Cohen et al. (1998) compared Optison to Albunex, a first-generation, air-

### TABLE 2 INTRAVENOUS CONTRAST AGENTS (partial list)

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Shell Composition</th>
<th>Gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albunex *</td>
<td>Molecular Biosystems</td>
<td>Albumin</td>
<td>Air</td>
</tr>
<tr>
<td>(no longer available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optison *</td>
<td>Mallinckrodt Medical</td>
<td>Albumin</td>
<td>Octafluoropropane</td>
</tr>
<tr>
<td>Definity *</td>
<td>Dupont Pharmaceuticals</td>
<td>Lipid</td>
<td>Octafluoropropane</td>
</tr>
<tr>
<td>(approved in Europe)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levovist</td>
<td>Schering</td>
<td>Galactose/Palmitate</td>
<td>Air</td>
</tr>
<tr>
<td>Imagent</td>
<td>Schering</td>
<td>Surfactant/powder</td>
<td>Perflexane</td>
</tr>
<tr>
<td>SonoVue</td>
<td>Bracco Imaging</td>
<td>Phospholipid</td>
<td>Sulfur-hexafluoride</td>
</tr>
<tr>
<td>PB-127</td>
<td>Point-Biomedical</td>
<td>Albumin/Polylactide</td>
<td>Nitrogen</td>
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*approved by FDA

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al.,(1997) found that only 44% of selected patients with ≥1 of the following conditions (moderate-to-severe systolic dysfunction, moderate-to-severe mitral or tricuspid regurgitation, pulmonary hypertension, or atrial fibrillation) achieved significant left ventricular opacification with Albunex, compared to 88% of patients without these conditions. In view of the large percentage of patients referred for echocardiography with these conditions, Albunex achieved less than ideal opacification in a significant number of patients.
filled contrast agent and found that in all clinical endpoints, including the degree of left ventricular opacification, the length of visualized endocardium, and the duration of contrast enhancement, the second generation agent yielded significantly superior results. Specifically, 63 out of 85 patients (74%) with non-diagnostic baseline studies were converted to diagnostic studies with Optison, compared to only 22 out of 85 patients (26%) with Albunex. In a follow-up study by Shaw et al. (1998), the improvement in image quality using Optison resulted in a greater ability to answer the primary referral question in as many as 50% of patients. In terms of cost-savings, Thanigaraj et al. (2001) estimate that the regular use of contrast during stress echocardiography in patients with sub-optimal images would yield a savings of $238 per patient, primarily by reducing the number of patients that require a follow-up nuclear stress study because the initial non-enhanced stress echocardiograph was sub-optimal in quality.

MYOCARDIAL PERFUSION

A large area of research has focused on the potential use of transthoracic echocardiography with intravenous contrast to assess myocardial perfusion. At least in theory, echocardiography has several potential advantages over nuclear imaging studies currently used to evaluate myocardial perfusion. In addition to its wide-spread availability and relatively low cost, echocardiography has very good spatial resolution (<1mm in the axial direction), which is superior to that offered by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (Kaul, 2001). In addition, contrast echocardiography offers the potential to image the coronary microcirculation because, unlike other imaging modalities, the microbubbles reside entirely in the microvasculature without entering the extravascular space (Keller et al., 1989). Myocardial contrast echocardiography (MCE) describes the use of transthoracic

![FIGURE 1 | Sub-Optimal Echocardiogram (without contrast)](image)

In this apical four-chamber view, the apex of the left ventricle is not visualized adequately, which prevents an accurate assessment of wall motion or wall thickening and making the evaluation of ejection fraction impossible.
echocardiography with intravenous contrast to evaluate perfusion of the myocardium. The underlying concept behind MCE is that the relative concentration of microbubbles detected by ultrasound in different portions of the microvasculature reflects the myocardial blood flow in those regions and thus the status of the coronary circulation.

Initial studies of MCE during experimental coronary artery occlusion reported a clear delineation between perfused and non-perfused myocardium, suggesting that MCE may be useful for determining specific regions of coronary stenosis (Wei et al., 1998; Cheng et al., 1998). Early clinical trials of MCE on patients with known coronary artery disease, however, yielded disappointing results. Marwick et al. (1998) compared MCE to SPECT nuclear imaging in evaluating coronary artery disease. In the study, 203 patients with a prior myocardial infarction during the preceding year received both a nuclear imaging study and MCE, performed with the use of a second generation intravenous contrast. Segmental analysis of the ultrasound images obtained from MCE resulted in a specificity of 93%, although with a poor sensitivity of 31% at the highest contrast dose. This study, one of the first direct comparisons of intravenous contrast MCE with nuclear imaging found that MCE had limited sensitivity for detecting moderate to severe perfusion defects.

**FUTURE DEVELOPMENTS AND APPLICATIONS**

Following the study by Marwick et al. (1998), significant advances in ultrasound technology have been realized, including the development of harmonic power Doppler imaging (HPDI). In power Doppler, the imaging system calculates the differences in amplitude between the initial

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**FIGURE 2** | Sub-Optimal Echocardiogram (with contrast)
This second image from the same patient using Optison, a second generation ultrasound contrast agent, to facilitate left ventricular opacification. A clear delineation between the myocardium and the ventricular cavity is observed. The apex (arrow), which was not visualized without contrast, is now clearly seen, and wall thickening can be assessed.
ultrasound pulse and the returning signal, in contrast to traditional color Doppler which analyzes only the change in frequency of the signal (Villanueva et al., 2001). When a microbubble is exposed to ultrasound energy, the return signal is scattered, or non-linear. Power Doppler technology averages the scattering and filters out the linear, or stationary components of the signal which originate from the myocardium. A second advance in ultrasound technology is dual-frame triggering, in which two ultrasound pulses are transmitted a fraction of a second apart. The first of the two pulses destroys the microbubbles present in the tissue and assigns a color based on the amplitude of the returning signal. Regions with more microbubbles will generate a stronger return signal because more microbubbles are destroyed by the initial ultrasound pulse. The second pulse, called the destruction frame, occurs 40 to 50 milliseconds later and yields a significantly less intense return signal, often appearing as black on the ultrasound color display since most of the microbubbles within the tissue have been destroyed by the first pulse. The purpose of the destruction frame is to confirm that the mechanical index of the initial pulse was high enough to destroy microbubbles present in the myocardium. With a continuous intravenous infusion of microbubbles, myocardial blood flow can be quantified by measuring the rate that new microbubbles enter the tissue between each dual-triggered pulse, usually separated by 3-5 seconds. During this pause, microbubbles which are in high concentration within the left ventricular cavity and have not been destroyed by the preceding pulses, enter the coronary microcirculation. By repeating the triggered pulses at a set interval, a pattern develops: the first frame demonstrates the high-amplitude signal from microbubble destruction and the second frame appears black, confirming that microbubbles were indeed destroyed. Stenosed vessels causing a defect in perfusion in a specific region of the myocardium will appear as a decreased signal, or more black, on the initial pulse (Figure 3).

FIGURE 3 | Myocardial Contrast Echocardiography
Harmonic power Doppler with trigger mode imaging. The perfusion image on the left demonstrates the presence of microbubbles in the ventricular septum. The destruction image on the right, a fraction of a second later, demonstrates that microbubbles within the septum have been destroyed, appearing black. A perfusion defect in the septal base is noted in the first image (arrow).
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Numerous studies have shown harmonic power Doppler imaging to yield superior opacification of the myocardium in detecting coronary stenosis compared to traditional color Doppler ultrasound (Masugata et al., 2000). Heinle et al. (2000) compared harmonic power Doppler MCE to SPECT nuclear imaging during rest and adenosine stress and found an overall concordance of 81%. For specific regions of stenosis, concordance was 81% for the LAD, 76% for the RCA, and 72% for the LCX. The Heinle et al. (2000) study demonstrates the ability of harmonic power Doppler MCE to detect myocardial perfusion with reasonably high concordance to nuclear imaging.

Utilizing these advances in ultrasound technologies, a large number of clinical trials have sought FDA approval for the use of MCE to assess myocardial perfusion. Studies have attempted to determine whether the quantification of myocardial blood flow through MCE correlates to the degree of coronary stenosis. Wei et al. (2003) compared MCE to SPECT nuclear imaging in a phase II FDA trial using a continuous intravenous infusion of a second-generation microbubble contrast agent. In the trial, 54 patients with known or suspected coronary artery disease, who were referred for stress nuclear studies, received both the nuclear study and MCE with harmonic power Doppler. The study demonstrated concordance between the two methods in 84% of the patients, with MCE having a sensitivity and specificity of 96% and 63%. In 15 of the patients in the Wei et al. (2003) trial, cardiac catheterization was performed following the imaging studies, demonstrating severe stenosis in at least one coronary artery in all 15 patients. In this subset of patients that eventually required cardiac catheterization, the prior contrast echocardiography study had detected a perfusion defect in 15/15 cases (100%), whereas only 11/15 (73%) of the patients had lesions detected with nuclear imaging. Redefining the gold-standard as results on either SPECT or cardiac catheterization, the sensitivity and specificity of MCE improve to 97% and 83%. This study by Wei et al. (2003) demonstrates a significant improvement in the sensitivity and specificity compared to that of Marwick et al. (1998) several years earlier. One difference between the two trials is the use of harmonic power Doppler which was not available at the time of Marwick’s study. Currently, phase III trials of MCE are underway. FDA approval for the use of transthoracic echocardiography with intravenous contrast to assess myocardial perfusion is being sought and results are expected within the next 12-18 months.

Future applications of MCE may include predicting recovery following acute myocardial infarction. The accurate visualization of collateral perfusion is one area where MCE may offer superior results compared to traditional percutaneous coronary angiography. Because of the small size and intravascular location of the microbubbles, MCE allows the visualization of collateral circulation vessels which are smaller than the 100um limit of angiography (Kaul, 1997). Sabia et al. (1992) studied patients with recent myocardial infarctions and an occluded infarct-related artery by injecting microbubbles during catheterization directly into the left main and right coronary arteries just prior to intervention. After successful angioplasty, microbubbles were again directly injected to define the vascular bed and search for collaterals. Nearly 80% of the patients that exhibited adequate collateral perfusion by MCE within the infarct bed prior to intervention had a demonstrated improvement in regional systolic function one month after restoring blood flow. One significant finding in this study was that as long as collateral perfusion was present within the infarct zone, function improved after angioplasty even when anterograde flow was not established for days to weeks after the acute myocardial infarction. This study demonstrates that a direct intracoronary injection of microbubbles provides significant prognostic data and may one day be used to predict viability pre-coronary intervention.

Janardhanan et al. (2003) studied the use of MCE to differentiate necrotic from viable myocardium after reperfusion therapy in acute myocardial infarction. In this study, baseline echocardiography followed by MCE was performed 8 days after the infarction in 50 patients, all of whom had undergone coronary angiography. Echocardiography was repeated 12 weeks later to evaluate recovery. The study showed that functional recovery could be predicted based on the presence of myocardial perfusion as detected by MCE. While 85% of segments that achieved perfusion demonstrated functional improvement at 12 weeks, 150 segments (93%) with no demonstrated myocardial perfusion showed an absence of functional improvement at 3 months. One possible explanation for the results is that the detection of microbubbles at the capillary level acts as a marker of capillary integrity, and thus the degree of collateral circulation (Swinburn et al., 2001). These studies demonstrate that MCE offers significant prognostic data, which may be used in the future to assess viability following myocardial infarction. This technology may have the capability to risk-stratify patients following coronary catheterization to predict the potential for recovery of function.

CONCLUSION

Ultrasound contrast agents are widely used for ventricular opacification in patients with a technically sub-optimal echocardiogram, currently the only FDA approved use. Recent improvements in microbubble technology and harmonic power Doppler imaging have given impetus for the use of MCE to evaluate myocardial perfusion. Only when current phase III FDA trials are complete, which compare myocardial contrast echocardiography to nuclear imaging, will there be sufficient data to pre-
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dict the future role of MCE in clinical cardiology. Future use of MCE includes providing prognostic information following coronary catheterization and is an area which is currently being actively pursued in clinical research.

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REFERENCES


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