Contrast-enhanced ultrasound for myocardial perfusion imaging

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Chapter 2

Abstract

Ultrasound contrast agents are gas-filled microbubbles that enhance visualization of cardiac structures, function and blood flow during contrast-enhanced ultrasound (CEUS). An interesting cardiovascular application of CEUS is myocardial contrast echocardiography, which allows real-time myocardial perfusion imaging. The intraoperative use of this technically challenging imaging method is limited at present, although several studies have examined its clinical utility during cardiac surgery in the past. In the present review we provide general information on the basic principles of CEUS and discuss the methodology and technical aspects of myocardial perfusion imaging.
Introduction

Diagnostic ultrasound provides clinicians with a powerful noninvasive tool that is associated with minimal adverse side effects. The addition of contrast agents during ultrasound imaging further enhances the diagnostic capacity of this technique. Ultrasound contrast agents consist of gas-filled, encapsulated microbubbles that enhance the blood compartment in ultrasound images by their behavior in the acoustic field.\(^1\)

Contrast-enhanced echocardiography is at present limited to transthoracic imaging and routinely used by cardiologists. The application of contrast-enhanced echocardiography may, however, also be of interest to anesthesiologists, in particular for improvement of left ventricular opacification and real-time myocardial perfusion imaging.

This review aims to provide general information on ultrasound contrast agents and the basic principles of contrast-enhanced ultrasound (CEUS) in the perioperative environment. In addition, technical considerations for myocardial perfusion measurements and previous intraoperative experience with this technique will be discussed.

Background and principles of CEUS

**Microbubbles and Ultrasound**

The use of microbubbles in ultrasound imaging is based on their behavior in an acoustic field. When exposed to ultrasound, microbubbles start oscillating under the influence of the compression and rarefaction phase of the ultrasound wave resulting in the generation and emission of an acoustic signal, with a fundamental frequency. The fundamental frequency of available contrast agents lies between 1.5 to 3 MHz, which approximates transducer frequencies used in transthoracic echocardiography (TTE). The degree of microbubble oscillation, and thus the frequency of the emitted signal, depends on microbubble size, shell composition, and transducer frequency.\(^1\), \(^2\) Microbubble oscillatory behavior differs in response to weak or strong ultrasound. Very-low-intensity ultrasound (mechanical index <0.05)\(^a\) induces linear oscillations of microbubbles (Figure 1). At a low-intensity level (0.05 < MI < 0.5) microbubbles expand and compress nonlinearly, which results in emission of signals comprising fundamental frequencies and its multiples, which are called harmonics. On the other hand, tissue responses at this intensity level are primarily linear. High-intensity ultrasound (MI >0.5), as used for conventional diagnostic ultrasound methods, causes unrestrained oscillations, eventually destroying the microbubbles.\(^3\) CEUS imaging techniques selectively detect the nonlinear behavior of microbubbles and suppress linear tissue signals.\(^4\) These low MI imaging techniques (MI ~0.1) minimize the microbubble destruction, thereby allowing real-time imaging of the microbubble-emitted frequencies.

\(^a\) The acoustic intensity of an ultrasound beam to which tissue or microbubbles are exposed is estimated by the mechanical index (MI). The MI is defined as the peak negative ultrasound pressure divided by the square root of the frequency of the transmitted ultrasound wave.
Figure 1. Microbubble oscillation (indicated by the four arrows) in an ultrasound field. Depending on the mechanical index (MI), the microbubble-emitted signal contains only the fundamental frequency ($f_0$, similar to the transmitted frequency), or also multiples (harmonics) of $f_0$: A, linear microbubble oscillation in response to very low-intensity ultrasound resulting in generation of echo at $f_0$; B, nonlinear microbubble oscillation (expansion larger than compression) generating $f_0$ and second harmonic frequencies ($2f_0$); C, microbubble destruction due to high-intensity ultrasound; upon destruction a brief signal is generated, rich in harmonic signals.

Available Ultrasound Contrast Agents
The earliest report on contrast agents in ultrasound imaging dates back to 1968.(5) The first investigations used air-filled microbubbles, which were highly unstable, and significant amounts were filtered by the lungs because of their large diameter (>10 µm).(6, 7) Second-generation contrast agents were developed to overcome these limitations. Using an inert gas encapsulated in a lipid or albumin shell, gas solubility and diffusibility decreased, thereby improving microbubble stability.(8) These second-generation microbubbles remain intact in the systemic circulation and effectively pass the pulmonary circulation because of their small diameter.
Table 1. Examples of Ultrasound Contrast Agents Approved for Left Ventricular Opacification and Endocardial Border Delineation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Manufacturer</th>
<th>Gas</th>
<th>Shell</th>
<th>Mean Size</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definity</td>
<td>Lantheus Medical Imaging</td>
<td>Octafluoropropene</td>
<td>Lipids</td>
<td>1.1 to 3.3 µm</td>
<td>FDA/EMEA</td>
</tr>
<tr>
<td>Optison</td>
<td>GE Healthcare</td>
<td>Octafluoropropene</td>
<td>Albumin</td>
<td>2.0 to 4.5 µm</td>
<td>FDA/EMEA</td>
</tr>
<tr>
<td>Sonovue</td>
<td>Bracco Imaging</td>
<td>Sulphur hexafluoride</td>
<td>Lipids</td>
<td>2.0 to 3.0 µm</td>
<td>EMEA</td>
</tr>
</tbody>
</table>

FDA = U.S. Food and Drug Administration; EMEA = European Medicines Agency

**Indications for CEUS**

Table 1 shows commonly used contrast agents. With respect to cardiovascular applications, contrast agents are approved for left ventricular opacification and endocardial border delineation in cases where poor-quality images by conventional transthoracic ultrasound impede assessment of left ventricular structure and function. After reports of CEUS-related adverse events, regulatory approval was postponed in the United States and Europe but a direct relation between these events and microbubble use has not been demonstrated. Approval was regained after retrospective studies showed the safety and added value of CEUS.(9, 10) There is still an active Food and Drug Administration safety alert for contrast agents stating that cardiopulmonary reactions may occur and monitoring is necessary.\(^b\) Ultrasound contrast agents are not yet approved for myocardial perfusion imaging, although the benefit of this application is increasingly recognized. As per American Society of Echocardiography consensus statement, contrast agents are recommended when 2 or more consecutive myocardial segments cannot be visualized by conventional ultrasound.(11) In addition, CEUS should be considered for exclusion of hypertrophic cardiomyopathy and intracardiac tumors or thrombi. Finally, enhancement of Doppler signals is advised for assessment of diastolic or valvular function when conventional signals are suboptimal.

**Technical considerations for myocardial perfusion imaging**

**Physiology of Myocardial Perfusion**

Myocardial perfusion is regulated by metabolic and neural factors, matching myocardial blood flow (MBF) to oxygen demand. Under resting conditions, the level of myocardial oxygen extraction is already high due to the high capillary density (3000 to 4000 capillaries mm\(^2\)).(12)

Therefore, an increase in myocardial oxygen demand during stress is followed by an increase in MBF, up to 4 times the resting level. Coronary resistance and perfusion pressure are the main determinants of myocardial perfusion. If metabolic demand is kept constant, autoregulation maintains perfusion over a wide pressure range. During pharmacologically induced maximal coronary vasodilation (hyperemia), autoregulation is absent and MBF becomes more or less linearly related to perfusion pressure. The ratio of MBF during maximal vasodilation to flow at resting conditions, the coronary flow reserve, is a useful variable in the evaluation of coronary artery disease (CAD) and for functional assessment of the coronary microcirculation. Myocardial contrast echocardiography (MCE) allows assessment of the blood volume and flow through the myocardium. Second-generation contrast agents have characteristics similar to that of erythrocytes in terms of size, distribution, and rheology. After IV injection, microbubbles remain intravascular for several minutes before their shell is metabolized to free fatty acids and the gas is eliminated via the pulmonary route. Therefore, assessment of microbubble passage through the myocardium can be used for qualitative and quantitative assessment of myocardial perfusion.

Qualitative Assessment of Perfusion

Wei et al. described that during continuous microbubble infusion, homogenous opacification of the myocardium is reached, reflecting the steady-state concentration of microbubbles in the blood. Myocardial perfusion is assessed by visual inspection of a destruction-replenishment cycle. Using a short pulse of high-intensity ultrasound (MI > 0.5), virtually all microbubbles within the ultrasound beam are destroyed. Subsequently, during low MI imaging (MI ~ 0.1) microbubbles will reappear in the myocardium. Assessment is focused on the uniformity of contrast appearance and the homogeneity of opacification. In case of diminished myocardial perfusion, the rate of contrast appearance will be delayed and homogenous opacification is decreased in the affected region (Figure 2).

Quantitative Assessment of Perfusion

After ultrasound-induced destruction, myocardial microbubble replenishment is characterized by a time-intensity curve with a specific shape (Figure 3, green curve). The slope of the curve (β) represents the reappearance rate of microbubbles and has been interpreted as myocardial microbubble velocity. The plateau intensity (A) is a measure of myocardial blood volume. The product of β and A provides a quantitative estimate of MBF. For determination of these variables, a destruction-replenishment cycle should be recorded using low-MI imaging (see Supplemental Digital Content 1, Video 1, http://links.lww.com/AA/A364, and Supplemental Digital Content 2, Video 2, http://links.lww.com/AA/A365; see Appendix for video legends). With manufacturer-specific or
custom-designed software, pixel intensities are measured offline by drawing regions of interest in the myocardial wall in the end-systolic frame of each cardiac cycle (Figure 4). The obtained intensity data are used for quantification of MBF. Depending on the quality of the acoustic window, several myocardial segments can be analyzed from a single recording. Vogel et al. further studied microbubble replenishment kinetics in conjunction with low MI imaging and validated a model enabling absolute quantification of MBF in mL per minute per gram myocardium. (15) This model uses signal intensities from the myocardial wall and the adjacent left ventricular cavity for calculation of a normalized plateau intensity, also referred to as the relative blood volume. Together with the reappearance rate of the microbubbles (β) and the tissue density, the relative blood volume can be used to calculate absolute MBF.

**Figure 2.** Contrast-enhanced transthoracic apical 2-chamber view, zoomed in on left ventricle. After microbubble destruction, replenishment of contrast is visible in all myocardial segments except in the apical/mid inferior region, indicating a perfusion defect. Green arrow points toward normal replenishment, black arrows toward the perfusion defect. M = myocardium; LV = left ventricle.

**Validation**

Several studies showed the accuracy of MCE for assessment of myocardial perfusion. In healthy subjects, MCE was validated against positron emission tomography by comparing MBF measurements at baseline and during hyperemia. (15, 16) Using a similar protocol in patients with CAD, MCE was compared to invasive hemodynamic studies during coronary angiography. (17) Furthermore, a meta-analysis confirmed the ability of MCE to differentiate between patients with and without stable CAD. (18)
Pitfalls and limitations of MCE

**Transesophageal Echocardiography**

MCE has developed as a refined application for TTE, whereas technical factors limit the use of contrast-enhanced transesophageal echocardiography (TEE). Transesophageal transducer frequency is suboptimal to instigate microbubble oscillations and contrast-specific imaging features still need to be optimized for these transducers. Furthermore, attenuation artifacts occur more frequently due to the presence of left atrial contrast. Also, MBF quantification algorithms are not optimized for TEE, limiting quantification of MBF to TTE. Further technical developments are necessary before contrast-enhanced TEE can be recommended for routine use.

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**Figure 3.** Typical example of time-intensity curve reflecting myocardial microbubble replenishment at rest (○) and during adenosine-induced hyperemia (■). Note that during hyperemia, plateau intensity A is reached faster and variables β and A are increased compared to resting conditions, resulting in an increase in myocardial perfusion. β = reappearance rate of microbubbles in the region of interest; A = plateau intensity or myocardial blood volume; MBF = myocardial blood flow.

**Figure 4.** Typical example of an destruction-replenishment cycle obtained by myocardial contrast echocardiography. Transthoracic apical 4-chamber view at rest, zoomed in on left ventricle, only end-systolic frames: steady state image (A), burst of high-intensity for complete myocardial microbubble destruction (B) and subsequent replenishment of myocardial contrast (C to F). Image A contains examples of myocardial (red) and ventricular (green) region of interest.
Image Acquisition
Ultrasound systems require contrast-specific imaging software for MCE. Available techniques use different types of acoustic transmitting modes to enhance perfusion imaging. Furthermore, for obtaining images suitable for MBF quantification certain variables have to be considered. First, a linear relationship is required between microbubble concentration and the signal intensity measured in the images. However, all ultrasound scanners logarithmically compress acoustic signals for better image presentation. This transformation must be reversed for reliable MBF quantification. To minimize the distortion of the original input values, the dynamic range of the ultrasound system should generally be at least 50 dB with linear postprocessing settings. Second, infusion rate and power are critical settings and should be carefully adjusted. The initial infusion rate is altered by visual evaluation of contrast agent distribution and myocardial signal intensity. After a steady and homogeneous distribution of myocardial contrast is reached, the power of the scanner system should be adjusted based on visual inspection of signal intensity in the left ventricular cavity. Figure 5 shows examples of infusion rate and power settings. Finally, because acoustic processing differs for each ultrasound system, it is important to check the manufacturer’s presets for optimal perfusion imaging.

Methodological Limitations
The methodology of MBF quantification has some limitations. The clinical use is currently hampered by the time-consuming, offline analysis of perfusion sequences, which takes about 15 minutes per myocardial segment in experienced hands. Another limitation is that the feasibility depends highly on the quality of the acoustic window. Therefore not all patients will be suitable candidates for quantitative MCE. Finally, MCE is technically challenging and requires practical experience before images suitable for quantification can be obtained.

Intraoperative experience with MCE
At present, MCE is not part of routine intraoperative care most likely due to suboptimal imaging quality with TTE in general and unfamiliarity with the technique. However, several clinical studies investigated the use of CEUS with TEE during coronary artery bypass graft (CABG) surgery. In a retrospective study by Zaroff et al., the ability of MCE to assess cardioplegia distribution and thereby predict clinical outcome after CABG was investigated. The results showed that patients with an abnormal cardioplegia distribution by MCE were more likely to have a depressed left ventricular function postoperatively.
Figure 5. Transthoracic apical 4-chamber view, zoomed in on left ventricle. A, conventional image without contrast enhancement; B, contrast-enhanced image of left ventricle with adequate scanner settings and infusion rate; C, underdosing of contrast agent, reflected by weak contrast signals in the entire myocardium and some microbubbles in the left ventricle; D, microbubble overdosing results in left ventricular pixel saturation (black arrows) and in regions with attenuation (white arrows) in the basal myocardium and left ventricle; E, equal distribution of weak contrast signals in the ventricle and myocardium caused by underexposure of the image, which contains insufficient myocardial intensity information for reliable myocardial blood flow (MBF) quantification; F, overexposure of the images indicated by strong ventricular intensities; after a sufficient intensity threshold is reached (pixel intensity ~180), an increase in power leads to a nonlinear increase in intensity due to pixel saturation. This affects the measurement of the relative blood volumes and thus MBF.
Furthermore, a prospective study by Aronson et al. demonstrated that retrograde delivery of cardioplegia leads to adequate dispersion to all left ventricular segments. (21) Protection of the right ventricular myocardium was investigated with MCE in another prospective study. Winkelmann et al. showed that the right ventricular free wall was not reliably perfused with retrograde cardioplegia delivery. (22) Several studies have investigated methodological aspects of intraoperative MCE during CABG surgery, such as safety and optimal settings. (23-25) Furthermore, Aronson et al. successfully investigated the feasibility of intraoperative MCE for qualitative assessment of myocardial perfusion during CABG procedures. (26) More recently, Kitahata et al. used MCE before CABG to determine whether sevoflurane causes coronary steal, which could not be proven. (27) Although the results of these studies were promising, the methodologies were limited by technical factors. Still in its infancy, MCE was performed with conventional, i.e., not contrast-specific, 2-dimensional imaging, and bolus injections of first-generation contrast agents. This resulted in suboptimal imaging quality and impeded the recording of reliable destruction-replenishment cycles. The introduction of second-generation contrast agents and contrast-specific imaging techniques for TTE improved the quality and reliability of MCE. Currently, transthoracic quantitative MCE with second-generation contrast agents and recording of destruction-replenishment cycles is being used for research purposes by our group. In humans, evaluation of the effects of anesthetics on myocardial perfusion is difficult because of the invasive and nonportable character of most techniques for flow measurements. In our study, anesthesia-related alterations in myocardial perfusion will be investigated with MCE under different conditions.

**Future perspectives**

Developments in contrast agents and imaging techniques have broadened the spectrum of applications of CEUS. In radiology, the use of ultrasound contrast agents provides a significantly higher sensitivity and specificity for detection of malignant liver lesions compared to conventional B-mode imaging. (28) CEUS also has an added value in the follow-up of prostate cancer by detecting patterns and alterations in tumor perfusion. (29) Intraoperatively, CEUS is used during partial hepatectomy for localization of metastases. (30) A method similar to MCE is used in an experimental setting for quantifying microvascular blood flow in skeletal muscle. (31) Moreover, the added value of CEUS during neurosurgery is being explored for monitoring surgical resection of tumors or arteriovenous malformations. (32, 33) Other applications are being developed in the field of urology, gynecology, and vascular surgery.

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Conclusion
Ultrasound contrast agents significantly enhance the blood compartment in ultrasound images. During the last decade the use of contrast agents has expanded to various fields and CEUS has evolved from a research tool to a rapid and safe bedside technique with added clinical value. In cardiology, MCE has been introduced as an accurate method for qualitative and quantitative assessment of myocardial perfusion. In the perioperative setting, MCE may be a powerful, noninvasive tool for studying the effects of anesthesia, surgical procedures, and other perioperative factors on myocardial perfusion.
References


