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History of Echocardiographic Contrast Agents

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Summary: Since its experimental introduction over 30 years ago, the use of cardiac ultrasound has expanded expeditiously, particularly in the last decade. The inception of managed care has fueled this expansion because ultrasound technology has the potential to enhance cost-effective diagnosis and medical care. Another important factor driving the growth of cardiac ultrasound has been the recent and rapid development of contrast echocardiography (CE). This diagnostic technique, involving the injection of a contrast agent to enhance ultrasound imaging, provides a safe, noninvasive means of directly assessing myocardial perfusion and a host of other aspects of cardiovascular health and integrity.

Key words: history, contrast agents, perflenapent emulsion, EchoGen®, contrast echocardiography, Doppler, imaging

Development of Contrast Echocardiography Agents

The concept of ultrasound contrast agents is widely acknowledged to have emerged in 1968, when Gramiak and Shah observed a "cloud" of echoes from the aortic root after injecting saline through an intra-aortic catheter.[1] Since then, many contrast agents have been used to enhance echocardiography.

The first contrast solutions were injected into the venous circulation to make gross anatomic abnormalities visible. Additional applications have included detecting valvular regurgitation, identifying and distinguishing atrial and ventricular septal defects, assessing congenital heart disease, measuring cardiac output, and evaluating surgical repair of valves or congenital abnormalities intraoperatively.[2–10] The most common application of contrast echocardiography (CE) is to assess left-right shunting.[11,12]

Commercial development of contrast media began during the 1980s. Early agents contained air-filled microbubbles of saline, indocyanine green, sonicated dextrose, or other substances. These short-lived agents contained bubbles too large to pass through the pulmonary circulation and did not opacify the left heart. Later products made use of high-molecular-weight gases, which are less diffusable than air, cross the pulmonary capillary bed, and provide Doppler and gray-scale enhancement.[13] Newer contrast agents, either currently available or under development, can traverse the pulmonary capillaries and be seen in the left side of the heart.

First-Generation Agents

First-generation agents include agitated saline, indocyanine green, sonicated solutions of dextrose, and renograffin, among others. These early agents proved less than ideal as contrast media, because the microbubbles they generated were too large to pass through the lungs and opacify the left ventricle and systemic arteries after a peripheral intravenous injection.[14] In addition, these agents had half-lives of only a few seconds. As a result, the enhancement they provided was too transient for practical use.[15]

Echovist®

SHU-454, (Echovist®, Schering AG, Berlin, Germany) is a first-generation contrast agent stabilized with D-galactose, commercially available in Germany and awaiting approval in the U.S.[16] It cannot pass the lung capillary bed and therefore cannot opacify the left heart.[13,16]

Recent research indicates that Echovist is safe and provides adequate clinical information regarding the right heart comparable to that of first-pass radionuclide ventriculography in healthy subjects, including obese patients.[17] No biological changes in heart rate, blood pressure, or arterial blood gases have been found with Echovist in dogs.[18]

Albunex®

Sonicated albumin, (Albunex®, Molecular Biosystems Inc., San Diego, Calif.) was the first echocardiographic contrast

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agent able to pass through the pulmonary capillaries that the FDA approved for general sale to the clinical market. The substance is an isotonic dispersion of air-filled microspheres of human serum albumin.[19] Studies have found that Albunex increases the reflectivity of blood in the left atrium and ventricle, thereby improving the definition of left-ventricular endocardial borders and regional wall-motion analysis.[20] In addition, venous injection of Albunex opacifies the left-ventricular cavity in 63% of patients given up to 0.12 ml/kg; however, venous injection rarely opacifies the myocardium adequately and may cause arterial oxygen desaturation at doses of 0.5 ml/kg or more.[21] In addition, Albunex has been found to be pressure-dependent and to last < 30 s in the left ventricle.[13]

Although Albunex can pass through the pulmonary vasculature, resulting in left-sided cavity contrast after intravenous injection, several problems must be resolved before the assessment of myocardial perfusion is attempted intravenously with this agent.[22] The contrast appearing in the left-side cavities and, even more so, in the myocardium after an intravenous injection is inconsistent. In addition, contrast disappears from the left ventricular cavity during systole, possibly limiting the amount of contrast that goes to the myocardium.

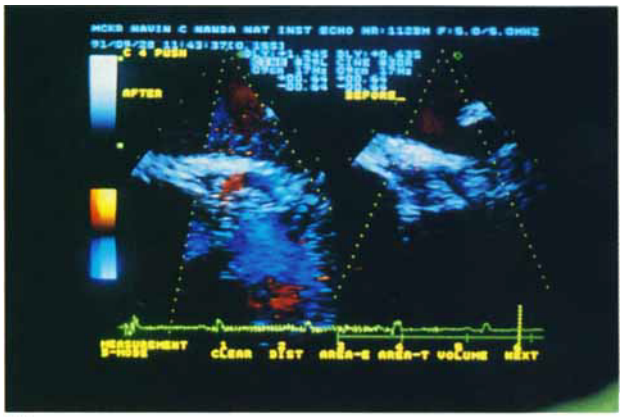
Like other contrast agents, intravenous Albunex may improve the definition of the Doppler spectral profile of both right- and left-sided regurgitant and stenotic velocities, which may be useful in the diagnosis of valvular heart disease. The demonstrated enhancement of color-flow Doppler signals may improve the evaluation of valvular lesions. Albunex is among the agents that have been used to confirm ventricular anatomy and to characterize blood flow dynamics in patients with congenital heart disease.[23] Among the clinical uses of Albunex are the evaluation of intracardiac shunts and valvular dysfunction, and the simple opacification of the cardiac chambers.[24]

Levovist®

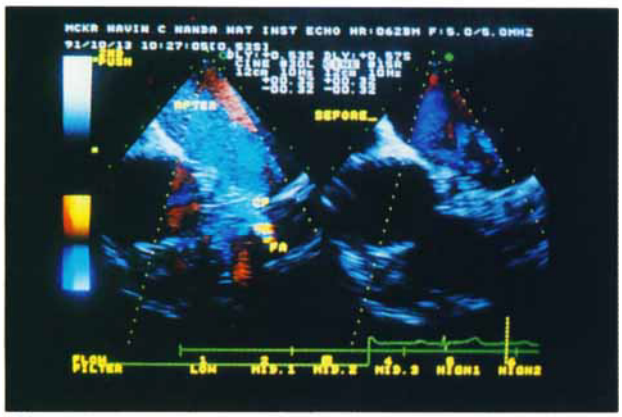
SHU-508A (Levovist®, Schering AG, Berlin, Germany), an Echovist derivative, is a suspension of galactose and a small amount of fatty acid that releases small air bubbles when mixed with sterile water. It causes left ventricular opacification after venous injection in all patients with normal pulmonary artery pressures; in patients with pulmonary hypertension, however, this effect is minimal or absent.[21] In a European multicenter trial of more than 1,200 patients with diagnostically insufficient Doppler signal intensity in routine imaging, Doppler signal enhancement was achieved in > 95% with at least one dose of Levovist, even in peripheral vessels.[16] Uses include cardiac B-mode and Doppler enhancement (Figs. 1, 2).[25–28] Levovist, which is available in Europe but awaiting approval in the U.S., also allows for left ventricular opacification, except in patients with pulmonary hypertension (Fig. 3).

Levovist and Echovist cause no serious or long-lasting side effects and are considered safe.[24] Schlief *et al.* found that Levovist caused no changes in heart rate, blood pressure, electrocardiogram, blood chemistry, hematology, or urinalysis.[29] In other studies, repeated intravenous injections of Levovist were well tolerated and no specific risks were found for patients in any disease group. Galactosemia is a contraindication for the application of galactose contrast agents, however.[16]

Although these first-generation agents are promising, none can be considered ideal as a nontoxic, ready-to-use formulation that is injectable intravenously, can cross the pulmonary capillary bed, is sufficiently stable, and provides both Doppler- and gray-scale enhancement.[13] A major limitation is that these agents contain air, which is highly diffusible and rapidly escapes from the bubbles when mixed with blood, resulting in a decrease in backscatter.



(A)



(B)

FIG. 1 (A) Transesophageal echocardiographic assessment of proximal coronary arteries after contrast enhancement. After contrast injection (left), prominent flow signals fill the lumen of the left main coronary artery and the proximal left anterior descending coronary vessel, which shows hardly any flow signals at baseline (right). (B) Transesophageal echocardiographic assessment of proximal coronary arteries after contrast enhancement. At baseline (right), virtually no flow signals are noted in the left main coronary artery. After contrast injection (left), prominent flow signals not only completely fill the lumen but also opacify an additional segment of the proximal left anterior descending coronary vessel that was not visualized at baseline. In addition, flow aliasing is noted more distally, and its site corresponds to an area of severe stenosis in the left anterior descending artery on the coronary angiogram. CF = the origin of the circumflex vessel. Reproduced from Ref. No. 25 with permission.

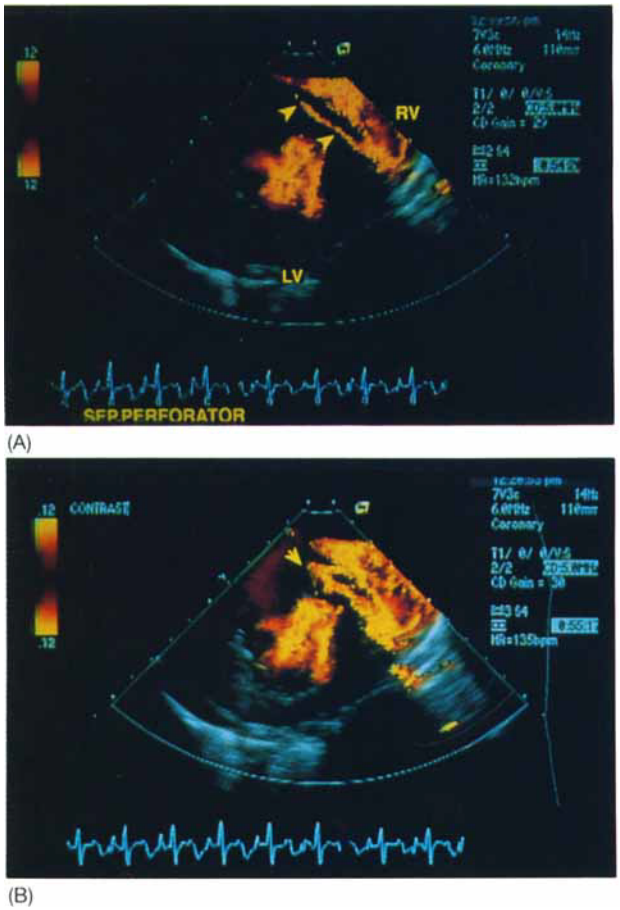


FIG. 2 (A) Color Doppler examination of intramyocardial coronary arteries. Baseline examination in a canine shows linear flow signals (arrows) within the anterior ventricular septum consistent with the septal perforator coronary artery. (B) Following injection of Levovist through a catheter placed in the left main coronary artery, the perforator artery not only becomes more prominent but also displays numerous branches (arrow). LV = left ventricle; RV = right ventricle. Reproduced from Ref. No. 27 with permission.

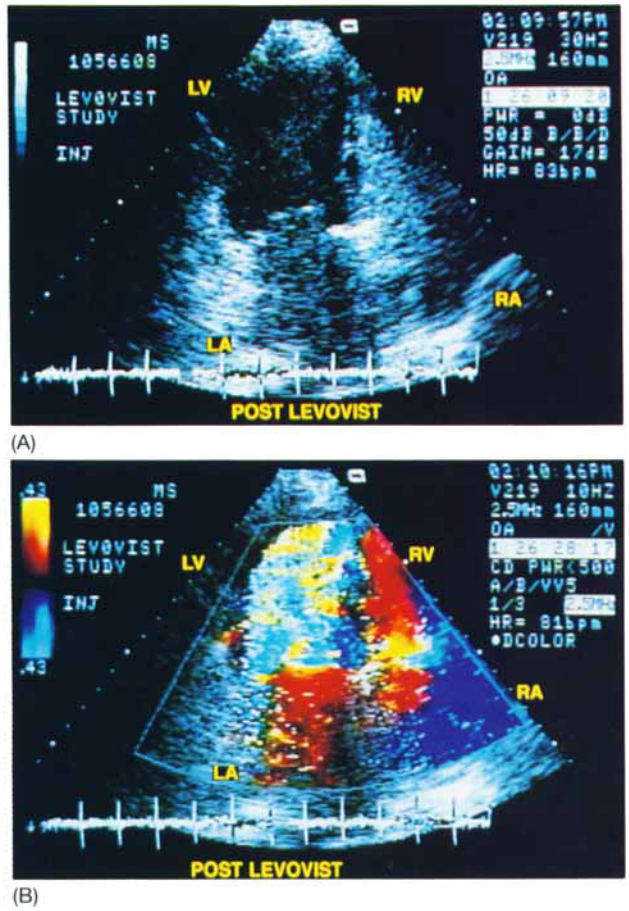


FIG. 3 Apical four-chamber view of a patient. Contrast-enhanced B-mode examination (A) shows incomplete filling of the LV cavity by contrast signals. However, when color Doppler was turned on (B), complete opacification of the LV cavity occurred. LV = left ventricle, RV = right ventricle, RA = right atrium. Reproduced from Ref. No. 41 with permission.

Second-Generation Agents

Research on second-generation agents (e.g., EchoGen®, Optison®, and BR-1) has focused on the size and stabilization of microbubbles, since these properties determine their effectiveness.[30] Various forms of stabilization have been added to increase longevity. These agents are detectable on B-mode as far as the left side of the heart, but once they have been diluted in the general systemic circulation, adequate visualization requires a more sensitive technique, such as Doppler imaging.[15]

Some second-generation contrast agents employ colloidal suspensions and emulsions, including collagen microspheres, perfluoro-octylbromide (Imagent®, Alliance Pharmaceutical Corp., San Diego, Calif.),[31] lipid emulsions,[32] and particles of iodipamide ethyl ester.[33]

Major limitations of the first-generation agents have been overcome by the use of high-molecular-weight gases, such as perfluorocarbons, which perfuse less readily. These agents have, in fact, been awarded a number of U.S. patents.[34] These newer, second-generation products, which are in development in the U.S., are less diffusible than air.[35] The substantially higher reflectivity provided by them permits enhancement to be detected in the peripheral circulation on the gray scale as well as with Doppler imaging.[15]

Optison®

FS069 (Optison®, Molecular Biosystems Inc, San Diego, Calif.) provides persistent contrast effect. Unlike Albunex, however, it gives no information about myocardial blood flow when injected into a coronary artery.[35]

In one study, FS069 produced higher levels of harmonic signals than Albunex. The researchers measured RMS amplitudes of the Doppler-shift spectra as a function of the concentration of the agents, frequency, and transmitted acoustic pressure.[36] Optison is awaiting FDA approval.

Overall, this agent provides persistent contrast with longer half-life than earlier agents. The agent has no effect on hemodynamics, myocardial blood flow, left ventricular wall thickening, or pulmonary gas exchanges. In addition, FS069 produces higher levels of first and second harmonic signals than Albunex.[36]

BR-1

BR-1 (Bracco Research SA, Geneva, Switzerland) is an aqueous suspension of stabilized sulfur hexafluoride microbubbles. Its developers identify BR-1 as a promising agent with high echogenicity, stability, and resistance to pressure changes. BR-1 injections in animals resulted in homogeneous, dose-dependent opacification of the left heart. The agent, now in the early stages of FDA review, was highly echogenic in an almost constant pattern over the entire medical frequency range of 1 to 10 MHz.[37]

EchoGen® Emulsion

Perflenapent emulsion (EchoGen®, SONUS Pharmaceuticals, Bothell, Wash.) was the first fluorocarbon microbubble contrast agent to be developed and taken into clinical trials and is expected to receive FDA approval in the near future. After hypobaric activation, perfluorocarbon liquid droplets undergo a phase conversion to become microbubbles. Potential indications include enhancement of ventricular chambers, improvement of endocardial border delineation in adults with suboptimal echoes undergoing ventricular function studies, improved assessment of ejection fraction measurements, and wall-motion studies. EchoGen® emulsion may also be used in assessing myocardial perfusion in adult patients by providing myocardial tissue enhancement within the left ventricular wall. The agent is being studied for use in patients undergoing ultrasound examination to provide B-mode gray-scale contrast enhancement and Doppler-signalenhancement. (Data on file, SONUS Pharmaceuticals, Bothell, Wash. 1996.)

Potential clinical benefits include real-time visualization of the left ventricular wall and calculation of ejection fraction; diagnosis of the presence, location, and extent of coronary artery disease (CAD); diagnosis of valvular blood-flow abnormalities, including regurgitations by color Doppler and/or spectral Doppler signals; visualization and localization of myocardial perfusion deficits by a negative contrast effect; visualization of subtle changes in tissue densities via gray-scale imaging; visualization of blood flow in real time; and detection of adequate revascularization following surgical procedures.

Other Investigational Agents

Other agents under development include:

- Aerosomes (ImaRx, Tucson, Ariz.), uses nitrogen-filled liposomes.[38]
- Quantison (Andaris, Nottingham, UK), a cardiac ultrasound imaging agent consisting of air-filled albumin microcapsules, has undergone clinical testing. Gray-scale myocardial perfusion imaging is a possibility.
- NUS (Nycomed/Mallinckrodt, Oslo, Norway) and SHU 563A (Schering AG, Berlin, Germany) consist of polymer-encapsulated microbubbles.[39]

Future Developments

In the future, CE will likely play a number of important roles in diagnostic and clinical pathways, such as serving as a "diagnostic gatekeeper" to other tests and procedures, improving patient care, reducing costs, and allowing earlier diagnosis and fewer invasive procedures.[40] Potential applications of CE include post-thrombolytic and post-percutaneous transluminal coronary angioplasty assessment; definitive testing for CAD; postdirect angioplasty detection of reocclusion; post-elective angioplasty detection of re-stenosis; assessment of valvular disease and coronary flow reserve; salvage of suboptimal echocardiograms; enhanced color and spectral Doppler signals; left ventricular wall-motion visualization in real time; simplified detection of atrial and septal shunts; calculation of ejection fraction/CAD presence, location, and extent; and visualization and localization of myocardial perfusion deficits. The use of transient imaging, harmonic imaging, harmonic power Doppler imaging, and stimulated acoustic emission will further increase the future applications of CE.[41–43]

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