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Value and limitations of contrast echocardiography in cardiac diagnosis

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Contrast echocardiography refers to the ability to opacify the central circulation with dense clouds of ultrasonic reflectances by means of the intravascular injection of a variety of fluids. The earliest recognition of ultrasonic contrast consisted of opacification of left and right heart chambers during the performance of echocardiography[1,2]. Subsequently, the peripheral intravenous injection of these and other fluids was found to produce similar opacification of the right-sided cardiac chambers. Contrast ultrasonic techniques have currently achieved an important clinical role in the diagnosis of right-to-left intracardiac shunts and tricuspid regurgitation[3,4]. Recently, the development of new ultrasonic contrast agents and quantitative videodensitometric methodology promises to enable the evaluation of cardiac output and left-to-right shunts by means of contrast echocardiography[5,6]. This paper will review the basics of contrast echocardiography as practiced in a clinical setting today as well as indicate potential roles for this technique in the future.

Mechanism of contrast effect

Substantial investigation has been directed toward identifying how ultrasonic contrast is produced. A number of potential mechanisms by which the intravascular injection of fluid could result in the production of ultrasonic reflectances have been proposed. The relative contribution of each of these mechanisms, if any, to the creation of contrast in a clinical setting is not known with certainty. It has been suggested that ultrasonic reflectances could be produced by differences in the temperature of acoustic properties of the injectate. Because it is now known that a contrast effect can be obtained by an injection of the patient's own

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blood, it is unlikely that either of these two factors contributes importantly to the opacification observed on the echocardiogram. The rapid intravascular instillation of fluid can result in the production of turbulence within the column of flow as well as cavitation at the site of injection. Experimentally, microcavitations can occur as a result of a Bernoulli effect, or a decrease in exhaust pressure secondary to an injection of great force through a narrow area, which produces watervapor bubbles. These microcavitations have been shown to be related to the Thoma rather than the Reynolds number[7]. Although either turbulence or cavitation could potentially result in ultrasonic reflectances, evidence to date has failed to substantiate an important role for either of these factors in the clinical production of the ultrasonic contrast effect. The force of hand injections performed clinically has been found to be inadequate to produce microbubbles by cavitations[7].

Several studies have demonstrated that the predominant factor responsible for the production of the ultrasonic contrast effect is the introduction of gas microbubbles into the circulation[7,8]. Only fluids containing microbubbles have been found to be capable of producing perceptible contrast in the clinical setting. The importance of microbubbles has been corroborated in patients by the fact that the most intense contrast echocardiograms have been produced after vigorously shaking the syringe of fluid to be injected. Although the introduction of even microscopic particles of air into the circulation offers the potential for side effects, including air embolus, the fact that numerous contrast echocardiograms have been performed in a wide variety of patients for many years without reported adverse effects suggests that the technique is safe as currently carried out.

Considerable attention has been directed toward the type of fluid used in contrast echocardiography. The early clinical studies describing contrast echocardiography emphasized the role of indocyanine green[2], and it was initially believed that this agent had unique properties that enabled the production of the contrast reflectances. Subsequently, it was demonstrated in fact that indocyanine green had surfactant properties which resulted in microbubbles of low surface tension and thus the ability to avoid dissolution[9]. More recently, contrast effect has been demonstrated to be readily producible by means of the injection of dextrose and water, normal saline, or even the patient's own blood. At present, these solutions constitute the standard agents used in clinical contrast echocardiography. However, as will be discussed, recent investigations have resulted in the development of several new contrast agents with unique properties, which promise to extend to the role of contrast echocardiography.

Techniques of clinical contrast echocardiography

The actual performance of contrast echocardiography in the clinical setting is quite simple and straightforward. In the majority of cases, the procedure is performed in the echocardiography laboratory in conjunction with standard ultrasonic imaging. At the University of Kentucky, we use a small plastic angiocatheter cannula (19 gauge) which is connected by a three-way stopcock to a standard intravenous infusion of either 5 percent dextrose and water or normal saline. The third port of the stopcock is attached to a 12 cc syringe through which 10 cc boluses of fluid are withdrawn from the IV bottle and rapidly injected into the vein. The procedure requires two individuals—one to perform the echocardiography and the second to inject the bolus of fluid simultaneously. Using this methodology, we have observed significant variability in the intensity of the contrast effect from patient to patient and within the same patient from injection to injection. Although the source of this variability is not certain, it significantly impedes quantitative observations. From the standpoint of technique, we have sometimes found it necessary to shake the syringe vigorously, to inject extremely forcefully, or to use a solution of indocyanine green dye to obtain technically

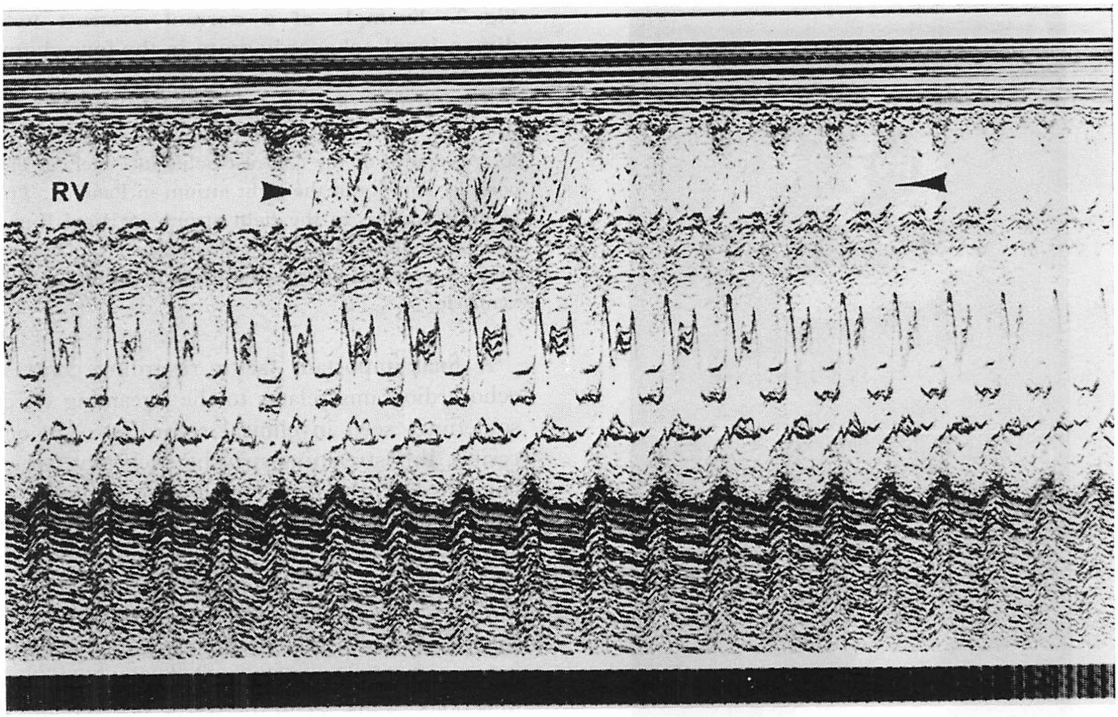

Fig. 1. Example of a normal M-mode contrast echocardiogram.
Contrast appears abruptly and clears quickly (arrows) from the area of the right ventricle (RV).

adequate contrast echocardiograms.

In special instances, contrast echocardiography may be combined with standard intracardiac catheterization[3,10]. In such instances the ultrasonic contrast agent is injected directly into a cardiac chamber or great vessel. Thus, we have occasionally used contrast echocardiography to diagnose the presence of valvular regurgitation in patients in whom radiographic angiography was contraindicated because of allergy to the iodinated contrast agent, inability to tolerate a volume load, or some other factor. We have also used contrast echocardiography to visualize intracardiac shunts during the course of cardiac catheterization. In these cases, echocardiography is performed in the catheterization laboratory and the ultrasonic contrast agent is delivered directly through the indwelling catheter. We have found indocyanine green to be a particularly useful contrast agent for studies performed during catheterization.

The normal contrast echocardiogram

In normal subjects, the injection of a fluid into a peripheral vein results in dense ultrasonic reflectances which sequentially fill and clear from the right atrium, right ventricle, and pulmonary artery following a short interval of several seconds. Examples of normal M-mode and two-dimensional contrast echocardiograms are shown in **Figs. 1 and 2**. Dependent upon the quantity of ultrasonic reflectances and the angulation of the ultrasonic beam, the contrast echos may appear as linear streaks or dense blobs on the M-mode tracing. The diameter of the pulmonary capillary bed is so small that contrast microbubbles capable of traversing this bed will dissolve owing to surface tension effects[9]. Therefore, no contrast effect is noted in the left heart chambers in normal subjects following the venous injection of fluid.

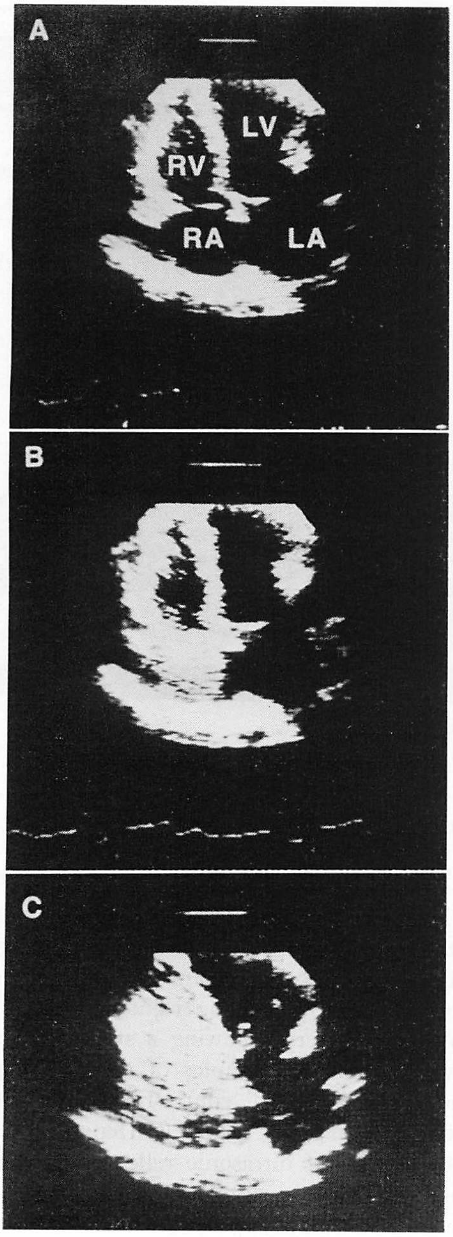

Fig. 2. Example of a normal contrast two-dimensional echocardiogram in the four-chamber apical view.

Right atrium (RA), right ventricle (RV), left ventricle (LV), and left atrium (LA) are visualized prior to appearance of the contrast bolus in Panel A. The contrast appears in the right atrium in Panel A. The contrast appears in the right atrium in Panel B and fills the right ventricle as well in Panel C. Observe that no contrast appears in the left atrium or left ventricle.

The net appearance of a normal contrast echocardiogram thereby consists of the abrupt filling of the right heart chambers with ultrasonic reflectances, which clear promptly with blood flow into the pulmonary vascular bed without echoes appearing in the left-sided chambers.

A final important factor regarding contrast echocardiograms relates to the streaming effect sometimes seen in clinical recordings. On occasion, this streaming may be such that, when combined with the tomographic nature of ultrasound recordings, an area of the right atrium (or even the entire right atrium) is unopacified by the contrast injection. Preliminary observations in our laboratory have suggested that differential streaming patterns may occur from upper and lower extremity injections. This factor needs to be recognized as a normal variant and has implications regarding the detection of intracardiac shunts, as will be discussed.

Applications of contrast echocardiography

At present, the clinical applications of contrast echocardiography fall into two general categories: the verification of cardiac anatomy and the evaluation of cardiac blood flow. The use of contrast echocardiography to assess cardiac anatomy includes the performance of central ultrasonic contrast injections into identified areas of the cardiovascular system as well as peripheral ultrasonic contrast injections, with the purpose of verifying or quantitating intracardiac structures observed on echocardiogram. The role of contrast echocardiography in the assessment of blood flow patterns has primarily involved the detection of intracardiac shunts and valvular regurgitation. More recently, contrast echocardiography has been used to produce hard copy records of contrast appearance and disappearance reflecting cardiac output and function, as well as myocardial opacification indicative of coronary blood flow.

Verification of cardiac anatomy

The verification of cardiac anatomy was one of the first uses of contrast echocardiography[2,10~13]. Thus, the ultrasonic opacification of a cardiac chamber or vessel following the injection of a fluid directly into this structure confirmed its identification on echocardiogram. In this way, verification of the echocardiographic representation of the cardiac chambers and great vessel was obtained.

At present, perhaps the most commonly used application of contrast echocardiography to verify cardiac anatomy involves the precise identification of the endocardial surface of the ventricular chambers. Because the endocardium of the ventricles represents a low intensity target for echocardiography, frequently there is confusion over the precise location of this interface. The dilemma is compounded by the frequent appearance of chordae tendineae or particularly bright intramyocardial echoes within the left ventricular walls. The endocardium can be accurately defined on the contrast echocardiogram as the outer border of reflectances within the right or left ventricle. Such definition of the endocardium has been of particular value in the assessment of hypertrophic cardiomyopathy, in which asymmetric septal hypertrophy is a cardinal feature. More recently, echocardiography has been used to confirm the nature of abnormal structures observed on echogram. For example, in the setting of a persistent left superior vena cava emptying into the coronary sinus, a prominent venous channel can be observed coursing behind the left atrium in the area of the atrioventricular groove. An injection of contrast into the left basilic vein will opacify this venous channel prior to entering into the right atrium. This finding is useful not only to confirm the nature of the structure posterior to the left atrium but also to establish the existence of a persistent left superior vena cava[14].

Identification of intracardiac shunts

The major application of contrast echocardiography today involves the demonstration of intracardiac shunting. Specifically, contrast echocardiography provides a highly accurate method by which to establish the presence of right-to-left shunting. The demonstrating of left-to-right shunting is obtained with less certainty, and the establishment of extracardiac shunting may be reached only by inference.

As previously stated, ultrasonic reflectances constituting the contrast effect are filtered as the blood courses through the pulmonary capillary bed. Accordingly, no contrast effect is observable in the left-sided cardiac chambers in normal subjects. The appearance of contrast in the left atrium, left ventricle, or aorta thereby establishes the presence of an abnormal communication between the right and left heart circuits. Contrast echocardiography has been shown to be highly specific and quite sensitive in the recognition of right-to-left shunting[3,15,16].

The precise site of a shunt cannot be visualized on the M-mode echocardiogram. Therefore, the localization of a cardiac defect must be deduced from the left-sided chambers, which are opacified, as well as by the temporal sequence of the appearance of the reflectances on M-mode tracings. Thus, an atrial septal defect with right-to-left shunting results in contrast observed sequentially in the left atrium, left ventricle, and aorta, whereas contrast traversing a ventricular septal defect does not opacify the left atrium, and a patent ductus arteriosus produces reflectances only in the aorta. However, because of streaming it is often difficult to observe contrast echoes in the left atrium in the presence of an atrial septal defect with right-to-left shunt. Thereby, the existence of a lesion at the atrial rather than the ventricular level must often be inferred by the fact that reflectances are initially observed within the mitral valve orifice and subsequently within the cavity of the left ventricle.

Two-dimensional echocardiography enables the visualization of the actual right-to-left intracardiac shunt (**Figs. 3, 4**). Most authorities

Fig. 3. Illustration of four stop-frames of the two-dimensional echocardiogram in the four-chamber view in a patient with an atrial septal defect and a shunt from right atrium to left atrium.

Frame A is taken prior to the appearance of dye. In frames B and C, the right atrium (RA) and right ventricle (RV) opacify, and minor contrast can be observed flowing through the mitral orifice (arrows). Frame D shows a substantial amount of contrast in the left ventricle (LV) as well as the right ventricle. LA=left atrium.

have found the four-chamber apical view to be optimal in this regard, because it profiles both the interventricular and interatrial septa and allows the simultaneous visualization of all four cardiac chambers. By enabling a wide area of the atria and ventricles to be imaged, two-dimensional echocardiography has enabled the detection of even small numbers of microbubbles crossing a right-to-left shunt[17]. At present, no quantitative measurements regarding the magnitude of shunting have been available from two-dimensional echocardiography.

In the setting of congenital heart disease, left-to-right shunting is the rule rather than the exception because of the lesser compliance and higher pressures in the left-sided cardiac chambers. Although echocardiography cannot directly visualize a left-to-right shunt, as it can right-to-left flow, a method has been developed by which to infer the presence of such defects[18]. This technique is based upon the fact that, in the presence of left-to-right shunting through an intracardiac defect, blood that is unopacified with ultrasonic reflectances will course as a jet into a chamber that is totally filled with echo

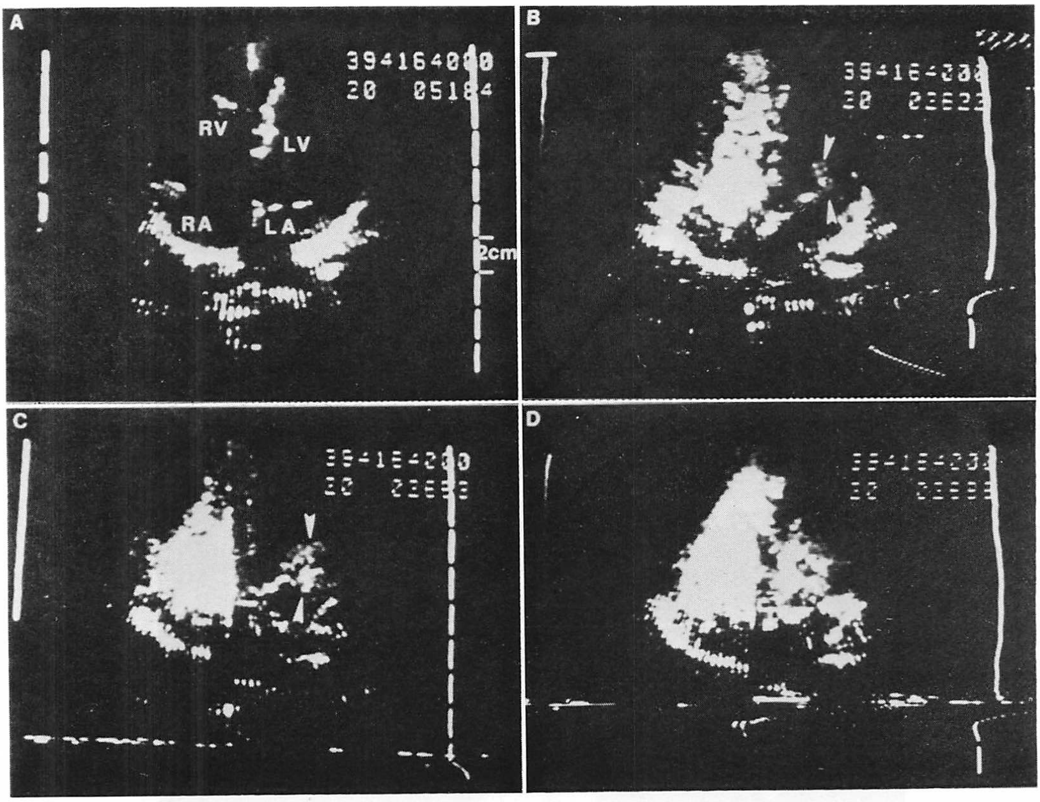

Fig. 4. Two-dimensional contrast echocardiogram in a patient with a ventricular septal defect.

Frame A shows the echocardiogram prior to the appearance of contrast, with an absence of the interventricular septum (IS) at the junction of the interatrial septum. Frame B shows the appearance of contrast in the right atrium (RV) and right ventricle (RV) with minor flow into the area of the septal defect. Frames C and D illustrate the flow of contrast material through the ventricular septal defect into the left ventricle (LV). LA=left atrium.

signals during contrast echocardiography. Accordingly, the left-to-right shunt will be visualized as a negative contrast effect in an otherwise totally opacified chamber. Such negative jets will, of course, be confined to the right atrium or right ventricle in the presence of atrial or ventricular septal defects, respectively. Although this technique has proven to be of value in the detection of left-to-right shunts, it is limited by the streaming effect sometimes observed in the right atrium. Thus, only a well-delineated jet into an otherwise well-opacified chamber should be interpreted as being consistent with a septal defect.

Numerous studies have demonstrated that bidirectional shunting occurs in greater than 90 percent of intracardiac intercommunications. Thus, although it may be of miniscule magnitude, most patients with septal defects will have at least some element of right-to-left shunt. This situation has been used to diagnose these lesions by two-dimensional echocardiography by virtue of the detection of even a few microbubbles within the left-sided cardiac chambers[17]. In our experience, performing the Valsalva maneuver during contrast echocardio-

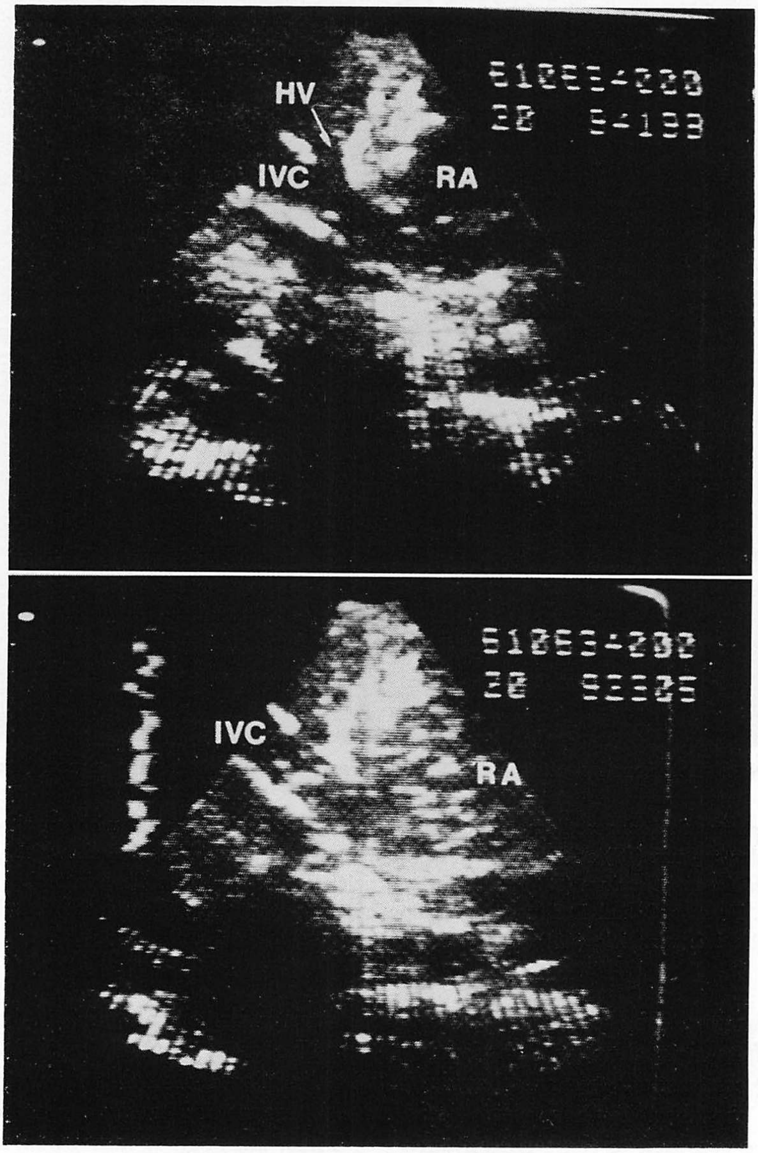

Fig. 5. Two-dimensional contrast echocardiogram obtained with the transducer in the subcostal position while imaging the inferior vena cava (IVC), **the hepatic vein** (HV), **and the right atrium** (RA).

The upper panel was obtained prior to the appearance of contiast which was injected into the right brachial vein. The lower panel shows the echocardiogram following the appearance of contrast in the right atrium which refluxes into both the inferior vena cava and the hepatic vein.

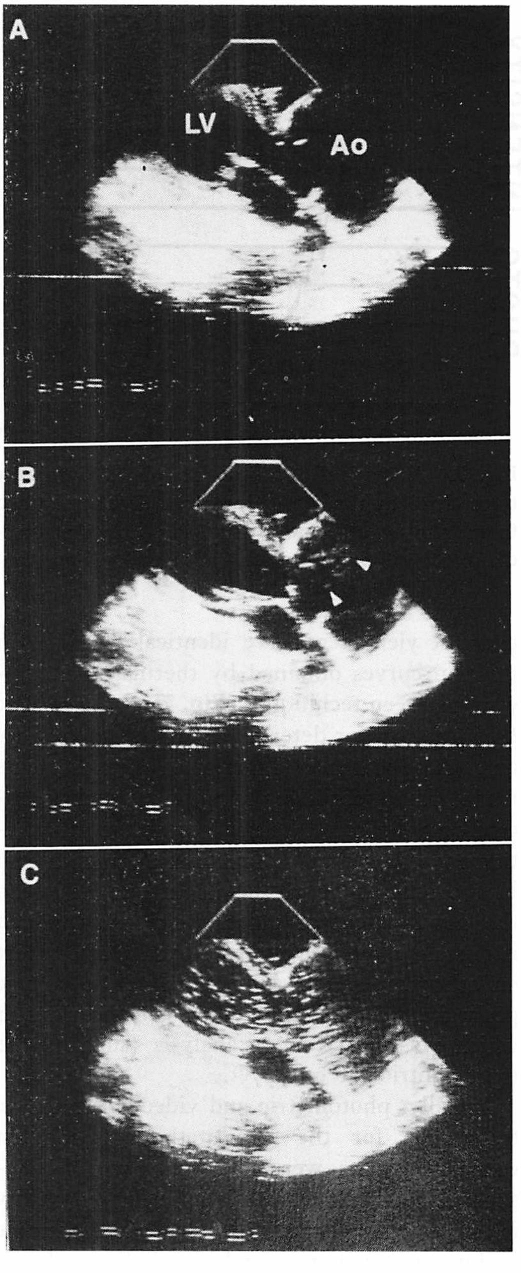

Fig. 6. Contrast echocardiogram in a patient with aortic regurgitation performed during cardiac catheterization with a catheter positioned in the aortic rot.

In A, the marked dilation of the aorta (Ao) is demonstrated in this patient with Marfan's syndrome. In Panel B, contrast appears in the aortic root (arrows). In Panel C, the contrast refluxes backward into the left ventricle (LV), indicating the presence of aortic regurgitation.

gram may aid in the detection of minimal right-to-left shunting in the presence of a predominant systemic-to-pulmonary circuit shunt. In addition, minimal degrees of right-to-left shunting may be more easily detected by Doppler recordings than echo imaging.

Valvular regurgitation

Contrast echocardiography has proven to be of diagnostic value in the recognition of valvular regurgitation[3,7]. From a noninvasive standpoint the tricuspid valve is only structure that can be conveniently assessed by this technique. However, direct intracardiac injections during echographic imaging can be used to assess regurgitation of other valves.

Contrast echocardiography has been demonstrated to be of value in recognition of tricuspid regurgitation[4,19]. Thus, several studies have demonstrated that, in the presence of tricuspid regurgitation, a swirling or to-and-fro pattern of microbubble motion can be observed in the right atrium and ventricle on two-dimensional echocardiogram. More important, when the inferior vena cava is imaged from the subcostal view in patients with advanced degrees of tricuspid regurgitation, contrast may be observed to reflux into this vessel from the right atrium during systole following instillation of the injectate into an upper extremity vein (**Fig. 5**). Although transient minor reflux of several microbubbles into the inferior vena cava during atrial contraction may be observed in some normal subjects, the persistent reflux of large amounts of contrast into the inferior vena cava represents an accurate indication of tricuspid regurgitation. A reversal of the trajectory direction of contrast echoes on M-mode during systole has also been reported in patients with tricuspid regurgitation.

On occasion, contrast echocardiography may be used to great advantage in the setting of cardiac catheterization. This is particularly true in patients with valvular regurgitation, in whom the injection of the ultrasonic contrast agent into a chamber distal to the valve in question may be performed, with evaluation of the chamber proximal to the valve for potential reflux of the contrast agent (**Fig. 6**). Although quantitative standards for the severity of valvular regurgitation by contrast echocardiography similar to those for angiography have not been established, echocardiography in this fashion combined with hemodynamic measurements is often adequate to guide surgical therapy.

Quantitation of contrast effect

Although contrast echocardiography has provided important clinical information in a variety of disease settings, the information obtained from this technique has been almost entirely qualitative. Thus, although contrast was noted to be present or absent in a given cardiac structure on echogram, the magnitude of contrast and the time course of appearance and disappearance could not be assessed. Because these quantitative factors regarding contrast are clearly related to blood flow, it is of great importance to establish methods by which to measure these parameters.

Early work in our laboratory indicated that the contrast effect on the echogram could be measured by means of recording the intensity of luminescence (light) emanating from a two-dimensional contrast echocardiogram by a simple photometer (light meter)[20]. Specifically, a two-dimensional echocardiogram in the four-chamber apical view was performed, and the sample area of a light meter was positioned within the boundaries of the right ventricle on the monitor. Subsequently, the light emanating from the appearance of contrast was converted into an analog signal and recorded on hard copy by a strip chart printout. The resulting tracing enabled the measurement of the contrast effect in units of light intensity (foot lamberts). In addition, the time-history tracing of the change in light intensity on the monitor with the appearance and disappearance of ultrasonic contrast yielded a curve identical to indicator dilution curves obtained by thermal and indocyanine green techniques (**Fig. 7**). Since cardiac flow was a major determinant of the appearance and disappearance functions, measurements made from contrast two-dimensional echocardiography could be used to derive information regarding cardiac function. A further step in the refinement of this technique has been the development of videodensitometry, which is capable of presenting the intensity of contrast on echogram as the summation of the voltage peaks from a given area of the television raster which was selected for analysis (such as the right ventricular cavity)[21].

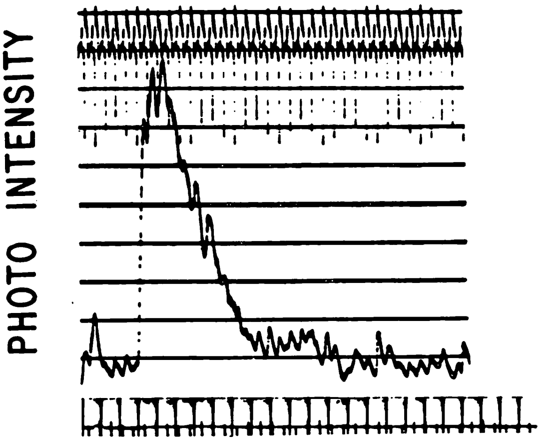

Fig. 7. A typical tracing of photo intensity over time in the right ventricle obtained from from photometric analysis of a contrast two-dimensional echogram.

Initially, photometric and videodensitometric techniques for the quantitation of contrast echocardiograms were used to assess the reproducibility of the technique itself. Variability in peak contrast intensity was demonstrable within most patients, and was believed to be related to the differing amount of microbubbles included in each injectate. These data led to standardization of the technique of contrast echocardiography itself, and stimulated the evaluation of a number of contrast agents such as carbon dioxide, pressurized blood, and CO_2

releasing sugars, which yielded reproducibility[22].

Indicator dilution curves obtained from photometric and densitometric analysis of contrast echocardiograms were also compared with measurements of cardiac output. At first, only the disappearance characteristics of the curves were analyzed, because peak contrast was often variable. It was observed that the disappearance time of the contrast echocardiographic curve was markedly prolonged in patients with significant diminution in the cardiac output[19]. Disappearance times were also prolonged in the setting of tricuspid regurgitation. Although evaluation in an in vivo experimental model demonstrated that planimetry of the contrast echo indicator curves correlated extremely well with directional changes in cardiac output within individual experiments, the failure to devise a calibration factor has thus far limited this technique in assessing cardiac output in patients[6]. Nevertheless, this technique for the assessment of cardiac output by means of videodensitometric recording of the time course of contrast appearance and disappearance in the right ventricle holds promise as a simple method by which to assess directional changes in cardiac function in patients in critical care units.

New contrast agents

The quantitation of contrast echocardiographic recordings stimulated an interest in the development of new contrast agents whose gas content and size could be controlled. Such agents would enable an injectate of known mass to be used in contrast echocardiograms. Moreover, the potential existed for specialized microbubbles to be capable of transit through the pulmonary vascular bed, and thereby left heart opacification.

A number of experimental microbubble preparations have been developed[23]. Gelatin encapsulated CO_2 microbubbles that are biodegradeable and measure precisely 40 micron in diameter have been manufactured. Such microbubbles enable striking reproducibility of contrast echocardiograms in terms of peak intensity and also appearance and disappearance characteristics. The gelatin encapsulated microbubbles also offer the ability to calculate the mass of contrast injected, so as to potentially solve the Hamilton equation for cardiac output. A saccharide microbubble-producing agent that yields microbubbles of a mean of 10 to 12 micron diameter has also been developed. These microbubbles have been demonstrated to be capable of transit through the pulmonary vascular bed with resultant left heart opacification[22]. Thus far, use of these new contrast agents has been limited to the experimental laboratory. However, if toxicity studies demonstrate the agents to be safe, it is anticipated that they will be used clinically in the near future.

Myocardial perfusion and intracardiac pressure measurements

Contrast echocardiography has also opened up the potential to extend the use of ultrasound to evaluation of regional myocardial perfusion and to the measurement of cardiac pressures. Thus, recent studies have demonstrated that the intracoronary injection of the saccharide microbubble-producing agent could result in opacification of the myocardium on the echogram in the experimental animal[23]. This technique has also been demonstrated to be capable of assessing differences in regional myocardial blood flow. As regards cardiac pressures, advantage has been taken of the fact that the resonating frequency of a microbubble of known size in a solution is directly related to the pressure of that fluid. Accordingly, microbubbles of known size will resonate at a frequency proportional to the pressure in the right ventricle or pulmonary artery when present in those chambers[24]. This resonating frequency can be detected by conventional ultrasonic techniques and may the be converted to actual pressure values. Although both the techniques of myocardia perfusion and cardiac pressure measurements by means of contrast echocardiography are in their infancy and require substantially more work to be developed, they have enormous importance owing to the potential to provide critically important data regarding heart disease that cannot be obtained by any other noninvasive technique. Therefore, it is anticipated that considerable effort will continue in this area.

Conclusions

Contrast echocardiography offers the unique potential to opacify the central circulation by the simple intravascular injection of a variety of fluids. Contrast echocardiography has thus far provided valuable diagnostic information in a relatively limited number of patients. However, technical developments offer the potential to extend the application of contrast echocardiography to the diagnosis of additional disease entities, as well as to the measurement of cardiac output and cardiac pressures. It is anticipated that contrast echocardiography will provide an increasingly important noninvasive diagnostic modality in the future.

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