Negative Contrast Echocardiography: A New Method for Detecting Left-to-Right Shunts

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SUMMARY Cross-sectional echocardiographic visualization of the interatrial septum in both normal persons and patients with atrial septal defects has been reported. Although septal defects can generally be visualized, false positives are frequently encountered. This study evaluated whether visualizing the patterns of contrast flow in the region of an apparent atrial septal defect by cross-sectional echocardiography could aid in the differentiation of true defects from false positives. We studied 25 patients — 13 with intact interatrial septa and 12 with atrial septal defects. Contrast was visualized in the right atrium in 24 of 25 patients (all 13 normal patients and 11 of 12 patients with atrial septal defects). In all patients with intact interatrial septum, the peripherally injected contrast material homogenously filled the right atrium, delineating the position and integrity of the interatrial septum. In two of 11 patients with atrial septal defects, evidence of right-to-left shunting through the defect confirmed its presence. In the remaining nine patients, the flow of blood from left atrium to right atrium, following the path of the left-to-right shunt, produced an echo-free area along the right margin of the interatrial septum, or an area of negative contrast. This phenomenon was produced by the non-contrast-containing blood flowing through the septum and displacing the contrast-containing blood from along the right-hand portion of the septum. This study suggests that peripheral injection of echocardiographic contrast material may be of value in detecting atrial septal defects in patients with predominant left-to-right shunting when contrast flows are evaluated using cross-sectional echocardiography.

M-MODE ECHOCARDIOGRAPHIC DIAGNOSIS of atrial septal defect relies on the observed effects of the increased right ventricular volume, on right ventricular size, and interventricular septal motion.1–4 Enlargement of the right ventricle and paradoxical septal motion may occur in any condition producing a right ventricular volume overload and, as a result, are not specific for a defect in the interatrial septum.5–7 When an atrial septal defect is associated with right-to-left shunting of blood, peripheral injection of cardiogreen dye characteristically results in passage of contrast from the right atrium to the left atrium.8–12 The echocardiographic appearance of contrast in the left atrium following peripheral injection is specific for a right-to-left shunt at the atrial level and thus permits establishing the diagnosis of atrial septal defect directly. In patients with left-to-right shunts, however, peripheral injection of contrast material has not proven useful, and the echocardiographic findings remain non-specific.

The recent development of cross-sectional echocardiography has enhanced our ability to record the dynamic spatial geometry of the heart and permitted direct visualization of the interatrial septum.13 Further experience with this technique has demonstrated that the interatrial septum can be recorded in most normal subjects and in most patients with atrial septal defects. Patients with intact atrial septa usually have an uninterrupted band of linear echoes extending from the inferomedial border of the aorta to the common posterior atrial wall, while patients with atrial septal defects will have a demonstrable area of echo dropout in a portion of the interatrial septum corresponding to the area of the defect. Although defects in the interatrial septum can be recorded almost universally in patients with anatomic lesions in this region, echo loss or dropout in the midportion of the septum may also be seen in normal subjects or patients with other forms of heart disease who have intact interatrial septa. These false positives occur with sufficient frequency to limit the value of cross-sectional echocardiography in the diagnosis of atrial septal defect.

During prior experimental and clinical studies we noted that peripheral injection of contrast material during cross-sectional scanning of the right atrium opacified the entire atrial chamber, outlining its margins, including the interatrial septum.13 Since flow patterns in the region of the interatrial septum should be abnormal in patients with atrial septal defects, regardless of the direction of the shunt, we hypothesized that contrast injection during cross-sectional study might demonstrate some characteristic abnormality in the pattern of contrast flow which would permit differentiation of false positives from true atrial septal defects. This study, therefore, was undertaken to determine whether peripheral injection of cardiogreen dye could enhance our ability to differentiate true defects in the interatrial septum from false positives and hence improve the diagnostic capability of cross-sectional echocardiography in patients with atrial septal defects, specifically those with left-to-right shunts.
Materials and Methods

Peripheral injections of cardiogreen dye were performed during the course of cross-sectional echocardiographic studies of the interatrial septum in 13 normal subjects and in 12 patients with hemodynamically documented atrial septal defects with predominant left-to-right shunting. In the septal defect group there were nine females and three males whose average age was 31 years (range 3–54 years). There were 10 patients with ostium secundum defects and two with ostium primum defects. The diagnosis in each case was established by routine cardiac catheterization and cineangiographic techniques. The ratio of pulmonary to systemic flow (Qp/Qs) in these patients averaged 3:1 (range 1.4–5.2:1).

The normal group consisted of three females and 10 males. The mean age of this group was 44 years (range 20–80 years). The normal subjects were volunteers without history or physical evidence of cardiac disease or patients with other forms of heart disease demonstrated at cardiac catheterization to have intact interatrial septa.

Cross-sectional echocardiographic examinations were performed using a commercially available mechanical sector scanner (Smith Kline Instruments, Ekosector I). This device consisted of a modified Ekoline 20A echograph with a pulse repetition rate of approximately 4 kHz. Two types of scanner probes were used in this study. Most examinations were performed using a single 2.25 MHz transducer which was mechanically driven through a 30° sector arc. A rotary transducer system consisting of four 2.25 MHz transducers mechanically rotated through a full 360° was also used. The latter transducer system yielded a sector arc of 82.5° with a line density of 64 lines/field. Additional studies were performed using a Varian Associates phased array Sector Scanner with an 80° scanning arc. The images thus produced were recorded directly on standard one-half inch video cassettes using a Sanyo VTC-7100 cassette recorder. The cross-sectional images produced by these systems could be viewed in real-time during the examination or subsequently from the videotape in a real-time, slow-motion, or single-frame format. Individual frames were converted to hard copy using a standard Polaroid photographic system.

Cross-sectional studies were performed in each case with patients in either the supine or 30° left lateral position. When examining the interatrial septum, the sweep of the cross-sectional probe was aligned parallel to the short axis of the aortic root. The area included in the 30° cross-sectional scan therefore included the medial portion of the left atrium, the interatrial septum, and the left side or medial portion of the right atrium. Figure 1 shows the relationship of the 30° scan to the atria in this region. Using the larger 82.5° scan format it was possible to encompass both atrial cavities. In individual cases, additional views of the interatrial septum were obtained from the cardiac apex and subxiphoid region; however, for purposes of data analysis only the short-axis views were used.

During the course of these cross-sectional scans, we injected indocyanine green dye to define the normal patterns of contrast flow in the region of the atrial septum and to determine whether any characteristic abnormality in this flow pattern could be detected in patients with atrial septal defects. We used a two-syringe technique for all injections. Each injection consisted of 1 ml of indocyanine green dye followed rapidly by a 5 ml saline flush. In order to define the patterns of contrast flow in the region of the septum, dye was injected at multiple levels including the left atrium, right atrium, superior vena cava, inferior vena cava, femoral and brachial veins. Multiple injections were used in the region of the interatrial septum in both normal subjects and patients with atrial septal defect. In the final analysis of data, we used only flow patterns observed after peripheral brachial vein injection.

Results

Flow Patterns in the Region of the Normal Interatrial Septum

In each of the 13 normal patients, after either direct injection into the right atrium or peripheral injection, the contrast material homogeneously filled the right atrium, outlining its boundaries, particularly the right side of the interatrial septum. Figure 2 shows an experimental study in which contrast was injected directly into the right atrium. In this figure the continuous echoes from the interatrial septum before injection, as well as the homogenous opacification of the right atrium after the contrast injection, can be visualized. After the contrast injection, the septum itself is no longer visible; however, the outline of the septal position can clearly be defined by the margin of the area of opacification. Figure 3, a similar recording from a patient with a repaired atrial septal defect, shows that the septal patch produced a more dense vertical band of linear echoes between the right and...
left atria. After a peripheral injection of contrast material into a superficial vein of the right forearm there is homogenous opacification of the right atrium which outlines the right septal border. Also, the normal downstream path of contrast flow into the right ventricle and right ventricular outflow tract is also visualized.

In most normal subjects it was possible, either by improper transducer angulation or normal loss of echo production as the plane of the scanning transducer was aligned parallel to the interatrial septum, to create an area of echo loss or dropout in the midportion of the septum simulating an atrial septal defect. Figure 4 shows an apparent or false positive atrial septal defect recorded in a patient with an intact interatrial septum. Despite this seeming loss of septal integrity, after injection of contrast material, the right atrium is homogenously filled with echoes which outline the right septal margin. This delineation of the right side of the septum by contrast confirms its presence and integrity despite the fact that the structure itself is poorly recorded.

Flow Patterns in the Region of the Interatrial Septum in Patients with Atrial Septal Defects

To determine the flow patterns in the region of the interatrial septum and hence the expected path of contrast passage through the right atrium in patients with atrial septal defects and left-to-right shunts, multiple injections of contrast material were initially performed in the left and right atria as well as the proximal inferior and superior vena cava during cardiac catheterization. Figures 5 and 6 show the flow patterns observed during these injections. In figure 5 a catheter has been passed from the right atrium through an interatrial septal defect into the left atrium. In figure 5, panel A, the catheter can be seen to traverse an apparent defect in the interatrial septum. If the septum were intact, injected contrast material would homogenously fill the left atrium in a manner similar to the right atrial contrast pattern observed after right-sided injection (figs. 1–3). In addition, if the catheter were oriented parallel to the flow of blood, injected contrast material would wash away from the catheter tip and continue further downstream. In this case (as seen in figs. 5B and 5C), however, slow injection of contrast material results in the contrast being washed back along the barrel of the catheter from the left atrium into the right atrium. This pattern of contrast flow parallels the path of blood flow from the left atrium back through the defect into the right atrium. Figure 6 shows a similar pattern of blood flow using a slightly different injection technique. In panel A, a recording from a second patient with an atrial septal defect, the area of echo loss in the midportion of the septum again reflects the location of the defect. In panel B dye has been injected directly into the left atrium, and the flow of the contrast material back through the defect from the left atrium to the right atrium opacifies both left and right atria. In panel C contrast material has been injected into the superior vena cava, where it follows the normal path of blood flow into the right atrium. Due to the presence of the atrial septal defect, however, non-contrast-containing blood flows simultaneously from the left atrium through the defect into the right atrium. This non-contrast-containing blood washes the contrast-containing blood away from the right side of the defect causing an area of negative contrast on the right atrial side of the atrial septal defect. Panel C, therefore, is a negative or reverse image of panel B. Panel B shows

![Figure 2](http://circ.ahajournals.org/))
Figure 3. Short-axis, cross-sectional study of the interatrial septum in a patient with a repaired atrial septal defect. The intensity of echo production from the septal patch is increased. Panel A is a control recording. Panel B is recorded after peripheral injection of contrast material. After contrast injection the right atrium (RA), as well as the basal portion of the right ventricle (RV) and right ventricular outflow tract (RVOT) are homogenously filled with contrast echoes. The aorta (Ao) and left atrium (LA) remain echo free.

Contrast Flow After Peripheral Injection in Patients with Atrial Septal Defects

Peripheral injection of cardiogreen dye in the 12 patients with atrial septal defects produced two different patterns of contrast flow. In two cases, after
Peripheral injection, contrast was observed to pass from the right atrium to the left atrium due to mixing of blood at the level of the atrial septum. The appearance of contrast in the left atrium was considered specific for a defect in the atrial septum, and no further study was necessary. In nine cases peripheral injection of contrast material did not produce any observable passage of dye from right to left atrium. In each of these cases, however, a negative contrast effect was produced in the right atrium due to the passage of non-dye-containing blood from the left atrium through the defect into the right atrium which displaced the contrast-containing blood from the right side of the septum. Figure 7 shows this negative contrast pattern in a patient with an ostium secundum atrial septal defect. Panel A shows a cross-sectional recording of the defect before injection of contrast material. In panel B contrast material has been injected peripherally, and the clear, non-contrast-containing area in the right atrium bracketing the septal defect corresponds to the passage of non-contrast-containing blood from the left atrium into the right atrium. This negative contrast effect produced by the non-contrast-containing blood passing through the septum serves to confirm the presence of the left-to-right shunt at this level. Figure 8 shows this phenomenon viewed from the subxiphoid region. Panel A shows the control appearance of the large ostium secundum defect (vertical arrow) before contrast injection. In panel B, contrast has been injected into the left atrium and can be seen to flow through the area of the defect into the right atrium. After peripheral injection the contrast is again forced away from the right side of the interatrial septum by the large left-to-right shunt, filling the right ventricle but failing to opacify the right septal margin (fig. 8C).

In the final patient, despite multiple injections, we were unable to generate sufficient contrast in the right atrium to delineate flow patterns in the region of the septum.

**Discussion**

Gramiak et al. originally reported that rapid intracardiac injection of various substances, including saline and indocyanine green dye, produced a cloud of echoes at the site of injection and downstream which followed the pattern of blood flow.\textsuperscript{14, 15} Historically, the ability to produce echoes at known locations within the heart provided the first in vivo method for direct echocardiographic identification of specific cardiac structures.\textsuperscript{14-16} As recognition of the source of individual echoes improved, the need to use contrast injection to identify cardiac structures diminished, and the use of injected contrast, once produced, to follow the path of blood flow, became an increasingly important clinical application.\textsuperscript{8-11}

In the course of early contrast studies, it was noted that while the sequence of contrast appearance consistently paralleled blood flow, the contrast effect was lost during passage through either the systemic or pulmonary capillary beds.\textsuperscript{16} Based on these observations, it was suggested that the unexpected
Panel A is a short-axis, cross-sectional recording from a second patient with an atrial septal defect. The defect appears as an echo-free space in the mid-portion of the interatrial septum. In Panel B contrast has been injected directly into the left atrium (LA) and contrast flow can be visualized back through the atrial septal defect from the left atrium to the right atrium (RA). Panel C is recorded following a peripheral injection of contrast. In this recording there is normal flow of contrast from the peripheral vein into the right atrium and right ventricular outflow tract (RVOT). In the right atrium bracketing the margin of the atrial septal defect, however, there is a clear, echo-free area which corresponds to the path of blood flowing from left to right through the atrial septal defect. This area represents the contrast-containing blood being washed away from the right septal margin. Panel C, therefore, is a reverse or negative image of panel B.

Appearance of contrast crossing intracardiac septae could be considered evidence of an intracardiac shunt. Subsequent reports have confirmed the sensitivity of echocardiographic contrast studies as a means of detecting both intra- and extracardiac shunts.8-12 Although primary emphasis has previously been on the pattern and rate of contrast appearance within the heart, the effect of non-contrast-containing blood on the contrast pattern has also been noted. In their original studies on the aortic root,14 Gramiak and Shah observed that rapid saline injection filled the entire aortic root with a dense cloud of echoes during diastole. During systole, however, a rectangular defect in this dense echo pattern appeared, caused by non-contrast-containing blood entering the aorta from the left ventricle and displacing the contrast-containing blood from the region of the valve orifice. Subsequently it has been emphasized that when contrast appears in the left ventricle after peripheral injection of dye, examination of the area beneath the mitral valve is necessary to confirm the presence of an shunt.

Panel A is a control recording of the interatrial septum from another patient with an ostium secundum atrial septal defect. Panel B, recorded after peripheral injection, again illustrates an area of negative contrast (NEG CONTR) in the right atrium (RA) bracketing the region of the atrial septal defect. LA = left atrium; PA = pulmonary artery; AO = aortic root.
leaflet is crucial in determining the location of the right-to-left shunt. When the area beneath these leaflets is echo-free, the blood flowing from the left atrium into the left ventricle does not contain contrast and, by inference, the shunt must be at the ventricular level. Conversely, if the area beneath the leaflets contains contrast, at least a portion of the shunt must be at the atrial level. Thus the ability of the non-contrast-containing blood to displace contrast-containing blood and produce a non-opacified or echo-free area within an otherwise homogeneously echo-filled or opacified chamber has been well documented.

In the present study we found both the normal flow of contrast in the blood and the effects of non-contrast-containing blood on the pattern of contrast flow to be helpful in detecting atrial septal defects. We expected that when an atrial septal defect was present, mixing of blood at the atrial level would result in some contrast material crossing the septum from right to left, confirming the presence of the defect. Although passage of dye from right to left was routinely observed following both right atrial and high inferior vena cava injections, clearly defined right-to-left shunting was detected in only two cases after peripheral injection into either the brachial or femoral veins.

The unexpected observation that a non-opacified or echo-free area appeared immediately to the right of the intra-atrial septum after peripheral contrast injection in most patients in the atrial septal defect group, during at least a portion of the cardiac cycle, offered an alternative method for detecting these defects. These non-contrast-containing areas characteristically occurred immediately to the right of the septum bracketing the margins of the septal defect. A similar area of negative contrast was never observed in patients with intact intra-atrial septae. Studies of the pattern of contrast flow in the region of the septum suggested that the area of negative contrast was produced by the non-contrast-containing blood flowing through the intra-atrial septum from left to right displacing the contrast-containing blood within the right atrium from the right atrial margin of the septal defect. The degree of negative contrast was observed to vary throughout the cardiac cycle with the maximum negative contrast effect surrounding the point of peak anterior motion of the aortic root which would correspond to end systole or initial diastole. The timing of this peak negative contrast effect, therefore, agrees with the findings of Levin et al. who demonstrated that the maximum gradient across the defect and peak shunt flow occurred during end systole and initial diastole. Although it did not appear reasonable to attempt to quantitate the area of negative contrast, there was at least a qualitative relationship between the size of the area of negative contrast and total shunt flow.

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**Figure 8.** Cross-sectional recording of the interatrial septum and associated defect from the subxiphoid approach. Panel A is a control recording with the area of the defect indicated by the vertical arrow. In the diagram below panel A, the plane of the septum is indicated by the horizontal broken line. In panel B contrast (CONTR) has been injected into the left atrium. The cloud of echoes initially flows back across the defect from left to right following the path of the interatrial shunt. In panel C contrast has been injected peripherally. The contrast-containing blood is now displaced from the right side of the interatrial septum by the non-contrast-containing blood flowing through the defect producing a large area of negative contrast in the right atrium (RA). LA = left atrium; RV = right ventricle; LV = left ventricle; TV = tricuspid valve.
During contrast injections, non-contrast-containing blood will continuously enter the right atrium from sources other than a defect in the intra-atrial septum. In normal patients, inflow from the inferior vena cava and coronary sinus will be non-contrast-containing, while various types of heart disease, such as tricuspid insufficiency, may also contribute non-contrast-containing blood to the right atrial pool.

The inferior vena cava represents the major source of non-contrast-containing blood in normal patients. During long-axis studies of the lateral portion of the right atrium the confluence of the contrast-containing blood from the superior vena cava and the non-contrast-containing blood from the inferior vena cava can be visualized. At the right septal margin, however, the contrast pattern appears uniformly homogenous suggesting that mixing has occurred during transit of blood across the atrial chamber. A second source of non-contrast-containing blood is the coronary sinus. It is common in both normal patients and patients with heart disease to observe a discrete, non-contrast-containing area along the posterior margin of the right atrial wall. Although as yet unproven, we have attributed this isolated area of negative contrast to inflow from the coronary sinus. This area of negative contrast is always bounded posteriorly by the posterior atrial wall and to date has caused no confusion with the negative contrast area opposite an atrial septal defect. Another possible source of non-contrast-containing blood is backflow through the tricuspid valve in patients with tricuspid insufficiency. The negative contrast effect does not become clearly evident in the right atrium until the chamber is filled with contrast. The atrium as a rule does not become completely opacified until several cycles after the initial appearance of the contrast. By this time the early arriving contrast has already traversed the tricuspid orifice so that any regurgitant blood coming back through the tricuspid valve will also be contrast-containing. Although we have not examined patients with combined atrial septal defect and tricuspid regurgitation, we have examined a number of patients with isolated tricuspid insufficiency and have not noted a negative contrast effect in the right atrium or behind the tricuspid valve in any of these cases.

Finally, left-to-right shunting at the atrial level may occur as a result of pathologic conditions other than ostium secundum or primum defects (e.g., anomalous pulmonary venous connection or sinus venosus atrial septal defect). The potential for shunting at multiple levels within the right atrium militates against random contrast injection in hopes of detecting a left-to-right shunt. We have found these studies to be helpful only when one asks the specific question, “Given a patient who on cross-sectional study has evidence of an apparent defect in the intra-atrial septum, does the area represent a true atrial septal defect or merely a false positive?” Contrast injection can help answer this question when the area of echo loss or echo drop-out can be recorded simultaneously with peripheral injection of contrast material. When the defect is a false positive, the injected contrast should homogenously outline the right-hand margin of the septum, confirming both its location and continuity. In the presence of a true atrial septal defect with right-to-left shunting, contrast will cross the septum, providing a definitive diagnosis. When left-to-right shunting predominates, the defect can be detected in most cases either by minute amounts of associated right-to-left shunting or by the effects of the non-contrast-containing blood passing from left to right across the defect, displacing the normal flow of contrast in the right atrium and creating an echo-free or contrast-free space along the right side of the septum. This area of negative contrast indicates that blood is flowing from left to right through the area in question and again confirms the presence of the defect in the intra-atrial septum.

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