
Detection of left-to-right shunt in atrial septal defect by negative contrast echocardiography: A comparison of transthoracic and transesophageal approach

The occurrence of a right atrial negative contrast effect as an indicator of left-to-right shunt was studied in 101 patients with atrial septal defect by peripheral venous contrast injection during transthoracic and transesophageal echocardiography. Confirmation of the diagnosis was provided by cardiac catheterization or by autopsy in 72 (72%) patients. The defect could be visualized directly in 57 (57%) patients during the transthoracic and in 93 (93%) during the transesophageal examination (p < 0.001). A negative right atrial echocardiographic effect was observed in 53 of 92 (58%) patients from the transthoracic and in 86 of 92 (93%) patients from the transesophageal approach (p < 0.001). Among these were seven (7%) patients with an aneurysmal interatrial septum but no directly visible defect during conventional transesophageal imaging. Appearance of contrast in the left atrium indicating right-to-left shunting was seen in 70 of 92 (76%) patients from the transthoracic and in 91 of 92 (99%) patients from the transesophageal approach (p < 0.001). Contrast injection during transesophageal imaging also helped identify additional malformations in 12 (12%) patients. Thus transesophageal echocardiography with echo contrast injection is a very reliable diagnostic method in patients with suspected atrial septal defect. (AM HEART J 1993;126:909-917.)

S. Konstantinides, MD, W. Kasper, MD, A. Geibel, MD, T. Hofmann, MD, W. Köster, MD, and H. Just, MD Freiburg, Germany

From Innere Medizin III, Universitätsklinik Freiburg.
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Reprint requests: A. Geibel, MD, Innere Medizin III, Universitätsklinik Freiburg, Hagetanner Str. 66, 7800 Freiburg, Germany.
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The echocardiographic diagnosis of an atrial septal defect is based on the direct visualization of the defect and the observation of a right ventricular volume overload pattern.1 During conventional transthoracic imaging, echo dropouts in the midportion of the interatrial septum can be mistaken for a true defect and may thus result in a false diagnosis.1,2 Furthermore,
a right ventricular volume overload pattern is also observed in a variety of other congenital and acquired heart diseases. Transesophageal echocardiography has been repeatedly reported to provide excellent two-dimensional imaging of the interatrial septum and precise localization of atrial septal defects. Nevertheless, the definite diagnosis of an atrial septal defect relies, in addition, on direct proof of intracardiac shunt flow at atrial level. Echo contrast techniques and color Doppler flow imaging are both applicable in the detection of shunt flow. Since echo contrast and transesophageal imaging have been available for more than a decade, we performed this prospective study to evaluate the sensitivity of contrast echocardiography in the detection of shunt flow during transthoracic as compared with transesophageal imaging in an adult population with atrial septal defect.

**METHODS**

One hundred one consecutive patients with an atrial septal defect were studied in the echocardiographic imaging was analyzed in the supine and left lateral decubitus position. Informed consent was obtained from all patients for the transesophageal examination, which was performed after local anesthesia of the pharynx with lidocaine spray; periprocedural sedation with either diazepam (5 mg) or midazolam (2 mg) was necessary in 8 (8%) patients. One patient was unable to tolerate the procedure after successful probe insertion so that the transesophageal examination had to be interrupted; insertion of the probe and performance of the transesophageal study was uneventful and well tolerated by all other patients.

In those patients in which either the transthoracic or the transesophageal approach indicated that a defect was present, the size of the defect was estimated by measuring the maximum distance between the margin of the interatrial septum with frame-by-frame analysis of the cardiac cycle. During transthoracic imaging we tried to perform the measurements from the subcostal view whenever possible. Echo contrast injections were performed from an antecubital vein during the transthoracic and transesophageal examination. Contrast effects were generated by injecting either 10 ml of previously agitated oxidized glucose-labile solution, a commercially available plasma substitute solution 5% (Gelifundol), or with 4 to 6 ml of a galactose suspension able to enclose microbubbles of air in its crystalline structure suspension (Echovist). Each contrast injection was immediately followed by a 10 ml flush injection of a standard 0.9% saline solution. Contrast studies were considered adequate for evaluation only if complete homogenous opacification of the right atrium was achieved for at least three cardiac cycles. A negative contrast effect indicating left-to-right interatrial shunting was diagnosed when a sharply delineated washout phenomenon appeared on the right atrial side of the interatrial septum in continuity with the echo-free left atrium. Care was taken to exclude contrast washout due to unopacified blood flowing from the inferior vena cava or the coronary sinus. A right-to-left shunt at the atrial level was diagnosed when microbubbles appeared in the left atrium within 3 to 5 beats of right atrial opacification (positive contrast effect).

The echocardiographic studies were analyzed independently by two observers. In four (4%) cases of disagreement, the interpretation of a third observer was required to establish final judgment. Two patients had transient complications from echo contrast injection. One patient experienced dizziness and a tingling sensation of the right upper extremity.
A short respiratory arrest with clinical evidence of arterial hypoxemia occurred in another patient upon contrast injection during the transesophageal examination. In this patient, cardiac catheterization revealed severe pulmonary arterial hypertension resulting in shunt reversal.

Statistical analysis. Clinical and echocardiographic results are described as mean value ± SD. Chi-square test was used to determine statistical significance between transthoracic and transesophageal results, which were considered to be significantly different when confidence limits exceeded 95% (p < 0.05). The correlation of different parameters was tested by a linear regression analysis.

RESULTS

Visualization of the defect. An atrial septal defect was considered to be present in 57 (57%) patients during conventional transthoracic imaging. The defect was more likely to be detected in patients with a primum defect (86%) than in patients with a secundum or a sinus venosus defect (58% and 22%, respectively; Table I).

A complete diagnostic evaluation of the atrial septal defect during the transesophageal examination could be performed in 100 of 101 patients. One patient with a secundum defect diagnosed at cardiac catheterization and both negative and positive contrast effect on transthoracic echocardiography was unable to tolerate the endoscope even after intravenous sedation so that transesophageal echocardiography had to be terminated before clear visualization of the defect. The atrial septal defect could be directly visualized on two-dimensional transesophageal echocardiography in 93 (93%) patients (p < 0.001 vs the transthoracic approach), that is in all patients with a primum or sinus venosus defect (7 and 9 patients, respectively) and in 77 of 84 (92%) patients with a secundum defect (Table I). If only the patients with an atrial septal defect confirmed at cardiac catheterization were considered for comparison, direct visualization was possible in 65 (94%) of 69 patients as opposed to 43 (62%) of 69 patients from the transthoracic approach (p < 0.001, Table II). There was no statistically significant difference in the sensitivity of either approach between those pa-
Size of atrial septal defect
Transthoracic vs transesophageal imaging

Fig. 1. Comparison between transthoracic and transesophageal echocardiography in measurement of size of atrial septal defect.

In 7 (7%) patients with subsequently diagnosed secundum atrial septal defect during the echo contrast study (negative contrast effect), the cross-sectional image was that of an aneurysmal interatrial septum with a very thin membrane at the site of the apparently intact fossa ovalis. The presence of a secundum atrial septal defect with significant left-to-right shunting was confirmed by right heart catheterization in five of these patients.

In those patients in which a defect was considered to be present from the transthoracic approach, the estimated size of the defect amounted to $25 \pm 9$ mm (range 11 to 45 mm). The size of the defect measured during the transesophageal echocardiogram was $22 \pm 9$ mm and ranged from 10 to 46 mm. A comparison of the defect size obtained from either approach revealed a poor correlation with $r = 0.65$ (standard error of the estimate = 7.2 mm, $p < 0.0001$; Fig. 1).

Echo contrast examination. Adequate echo contrast studies from both the transthoracic and transesophageal approach were obtained in 92 (92%) patients who formed the basis for subsequent comparison. A negative contrast effect was observed in 53 (58%) of the 92 patients from the transthoracic and in 86 (93%) patients from the transesophageal approach ($p < 0.001$, Table I). The occurrence of the negative contrast effect during transthoracic echocardiography was 67% in patients with a primum defect, 62% in those with a secundum defect, and only 13% in patients with a sinus venosus defect. The 53 patients with a demonstrable negative contrast effect from the transthoracic view had significantly larger defects as measured during the transesophageal examination than the 39 patients with a false-negative study ($24 \pm 9$ vs $19 \pm 9$ mm; $p < 0.05$).

During the transesophageal examination a negative contrast effect could be observed in 8 (100%) patients with sinus venosus defect, in 6 (100%) patients with a primum defect, and in 72 (92%) of 78 patients with a secundum defect. In 7 (7%) patients whose defects had not been visualized with certainty by cross-sectional transesophageal echocardiography, echo contrast injection established the diagnosis of left-to-right shunt.

A positive contrast effect, that is, the appearance of echo contrast in the left atrium resulting from transient right-to-left shunting, could be seen in 70 (76%) patients during transthoracic and in all but 1 (99%) patient during transesophageal imaging ($p < 0.001$, Table I). The results of the contrast
Fig. 2. A, Transesophageal echocardiography performed in 1985 (when old way of left-right orientation was used, i.e., left atrium on left side of screen) in a patient with secundum atrial septal defect revealed persistent left superior vena cava (LSVC) not detected from the transthoracic approach. B, Lumen of this vessel is opacified after echo contrast injection from left antecubital vein. LA, Left atrium; LV, left ventricle.

Studies remained unchanged when only the subgroup of 62 patients with an adequate echo contrast examination and confirmation of the defect by cardiac catheterization was considered. A negative contrast effect was observed in 56 (90%) patients from the transesophageal, as opposed to 34 (55%) from the transthoracic approach ($p < 0.001$, Table II). The frequency of positive contrast effect also remained significantly higher from the transesophageal than from the transthoracic approach (100% vs 76%, $p < 0.001$) in the subpopulation of angiographically studied patients (Table II).

Additional malformations. A left superior vena cava was diagnosed in 3 (3%) patients during the transesophageal echocardiogram (Fig. 2, A) but was observed in only one patient from the transthoracic
Fig. 3. A, Transesophageal examination demonstrated a sinus venosus defect (D) and, in addition, anomalous drainage of one pulmonary vein (PV) in superior vena cava (SVC). B, After echo contrast injection, washout phenomenon was observed on right atrial side of the defect and superior vena cava.

approach. Five of 9 (56%) patients with a sinus venosus defect and 4 (5%) of 84 patients with a secundum defect had partial anomalous pulmonary venous drainage demonstrated on transesophageal echocardiography (Fig. 3, A). In none of these patients could the malformation be detected during transthoracic imaging. Echo contrast injection helped delineate these malformations. In the patients with a persistent left superior vena cava, a positive echo contrast appeared in this vessel after contrast injection in the left arm (Fig. 2, B). Anomalous pulmonary venous drainage became apparent as a washout phe-
nomenon because of inflow of unopacified blood from the pulmonary vein into the opacified superior vena cava (Fig. 3, B).

DISCUSSION

The concept of contrast echocardiography has existed since the late 1960s, but the technique remained without important clinical applications for several years. The first extensive reports came from Seward et al. and Valdes Cruz et al., who described their experience with M-mode contrast echocardiography in normal individuals and patients with various congenital cardiac defects, including atrial septal defects. These investigators emphasized the easiness, safety, reproducibility, and sensitivity of the method in evaluating intracardiac blood flow patterns and especially in detecting right-to-left shunts. Their results were soon reproduced by others who reported that a positive left atrial contrast effect has a 73% to 100% sensitivity in demonstrating small right-to-left shunting in patients with an atrial septal defect, even in the absence of pulmonary arterial hypertension. More recently, Van Hare and Silverman confirmed the high sensitivity of the procedure in a large number of patients studied from the transthoracic approach. In our series a positive contrast effect was seen in 99% of the patients during the transesophageal echocardiogram. However, this observation is not specific enough to establish the diagnosis of an atrial septal defect because several authors have reported that a small amount of right-to-left atrial shunting demonstrated by a positive contrast effect also occurs in the setting of a patent foramen ovale without a true defect.

The definite diagnosis of an atrial septal defect should therefore rely on the demonstration of left-to-right shunt at atrial level. Weyman et al. were the first to report an 82% sensitivity from the transthoracic approach in detecting left-to-right interatrial flow and no false-positive results in patients with an atrial septal defect. Other authors agreed with the high diagnostic specificity of the negative contrast effect but, except for one study, observed a considerably lower sensitivity ranging from 43% to 69%. 

The difficulties in appreciating the interatrial septum by conventional transthoracic imaging in adults became obvious early enough in the development of echocardiography to discourage clinicians from making the diagnosis of a defect based on M-mode or two-dimensional characteristics of the septum alone. Echo dropout in the region of the fossa ovalis frequently occurs and may lead to false diagnoses of large "defects." Furthermore, visualization of sinus venosus defects is often impossible even from the subcostal approach, especially in adults. These poor results were confirmed in our study, where a clearly visible defect was detected during the transthoracic echocardiogram in 57% of the patients and only 22% of those with a sinus venosus defect. Furthermore, an attempted estimation of the defect size showed large variations as demonstrated by its poor correlation with the measurements performed during the transesophageal examination.

The development of transesophageal echocardiography improved the evaluation of the atrial septum and allowed the accurate diagnosis and size estimation of atrial septal defects. Most authors report a 95% to 100% sensitivity rate in direct visualization of the defect. In the present series, the atrial septal defect could be clearly seen and its size measured during transesophageal echocardiography in 93% of our patients. In seven patients with a secundum defect, the initial diagnosis was of an aneurysmal apparently intact septum but echo contrast injection revealed the presence of left-to-right interatrial shunt.

We compared the results of echo contrast injections performed during both the transthoracic and transesophageal examination in consecutive patients with atrial septal defect. Eight (8%) patients were excluded from comparison because of inadequate quality of the echo contrast study. Transesophageal echocardiography alone yielded a high sensitivity by correctly identifying the defect in 93 (93%) of the 100 patients examined. These results are in accordance with the already mentioned previous reports. A negative contrast effect, which establishes the diagnosis of left-to-right interatrial shunt, was observed in 58% of our patients during transthoracic and in 93% during transesophageal imaging. On the other hand, Hanrath et al. reported a sensitivity of 11% during transthoracic and 37% during transesophageal imaging, respectively. This discrepancy may lie on the need for qualitative adequacy of the contrast studies, namely the complete right atrial opacification after echo contrast injection.

If direct visualization of the defect were possible in every patient during transesophageal imaging, contrast echocardiography would add only little additional information. However, in 7% of our patients with an aneurysmal septum and no visible defect, contrast injection established the diagnosis of a secundum defect with left-to-right shunt by demon-
stratifying a clear right atrial negative contrast effect. In five of these patients the diagnosis of a secundum atrial septal defect was confirmed by invasive measurements. In addition, we could detect an accompanying vascular malformation as a persistent left superior vena cava or partial anomalous pulmonary venous drainage in 3% and 9% of the patients, respectively, by the combination of transesophageal and contrast echocardiography. Only one patient with a left superior vena cava was correctly identified from the transthoracic approach. Although previous studies have reported on the importance of transesophageal echocardiography \(^\text{7}\) or contrast transthoracic echocardiography \(^\text{36,37}\) for diagnosing these disorders, a systematic combination of the two methods has not yet been described in adults.

Contrast echocardiography is a safe procedure; large surveys have reported that serious complications are extremely rare \(^\text{38}\) or practically nonexistent. \(^\text{30}\) This fact could be confirmed in our series, where noncharacteristic, short-lasting dizziness was observed in one patient and transient arterial hypoxemia occurred in another patient with severe pulmonary hypertension. Care should, however, always be taken to avoid the injection of macroscopic bubbles, which might place the patients at risk of paradoxical systemic embolization. \(^\text{30}\)

We did not compare the accuracy of contrast echocardiography to that of Doppler color flow mapping in the evaluation of atrial septal defects during transthoracic or transesophageal imaging. Recent studies indicate that the transesophageal method has equally high diagnostic sensitivity from the transthoracic approach as observed in our series after echo contrast injection. \(^\text{8,9}\) On the other hand, color Doppler flow imaging from the transthoracic approach was reported to slightly increase the sensitivity of contrast echocardiography in one small series. \(^\text{16}\)

Conclusions. The results of our study show that transesophageal echocardiography with echo contrast injection is a very reliable diagnostic procedure when the transthoracic examination remains inconclusive in a patient with suspected atrial septal defect. Despite the high sensitivity of transesophageal imaging in directly visualizing the defect, uncertainty may persist in a minority of patients with aneurysmal interatrial septum. In these cases the injection of echo contrast will help establish the diagnosis. In addition, accompanying malformations such as persistent left superior vena cava or anomalous pulmonary venous drainage can be reliably detected by combination of transesophageal and contrast echocardiography. Nevertheless, it is also evident that transthoracic contrast echocardiography still has an important place in the initial diagnostic evaluation of patients with atrial septal defect.

**REFERENCES**