Non-smoke spontaneous contrast in left atrium intensified by respiratory manoeuvres: a new transoesophageal echocardiographic observation

Guy Van Camp, Bernard Cosyns, Jean-Luc Vandenbossche

Abstract

Objective—To elucidate why different types of contrast appear in the left atrium during transoesophageal echocardiographic contrast studies. This should lead to a more uniform definition of true patent foramen ovale.

Background—The Valsalva manoeuvre and cough are routinely used to enhance right to left shunt for the detection of patent foramen ovale. No information is, however, available on the effect of these manoeuvres on the intrinsic echogenicity of blood in the left atrium.

Methods—30 consecutive patients referred for transoesophageal echocardiography were studied. Gain settings were relatively high so that no details were lost. The appearance of contrast during normal respiration, cough, and the Valsalva manoeuvre was looked for in the left atrium with and without venous injection of 10 ml of 5% dextrose. Frequency of contrast appearance in the left atrium was expressed as a percentage. Intensity of contrast, when present, was graded 1 (mild), 2 (moderate), or 3 (equal to right atrial contrast during injection). Timing was assessed in cardiac cycles after the end of respiratory manoeuvres.

Results—Left atrial contrast appeared as a "snowstorm" flowing from the right pulmonary veins towards the middle of the left atrium. It was present respectively with and without contrast injection in eight and five patients during normal respiration, in 15 and seven during a cough, and in 20 and 14 during the Valsalva manoeuvre. When present, the mean intensity of contrast was 1.0 during normal respiration, 1.4 during a cough, and 1.4 during the Valsalva manoeuvre. The mean delay of contrast appearance was 3-4 cycles after release of the Valsalva manoeuvre and after onset of cough.

Conclusions—Respiratory manoeuvres frequently induce the transient appearance of mild to moderate contrast in the left atrium, most often independently of venous injections. Mild contrast was seen only with high gain settings. This contrast is likely to be related to transient stasis in the pulmonary circulation. In some cases peripheral venous injections of dextrose solution produced, without any respiratory manoeuvre, a similar contrast after the first four cardiac cycles

of the right atrium filling, which is likely to represent recirculation of the injected bolus through the pulmonary capillary bed. Therefore respiratory manoeuvres should always be performed before contrast injections to allow better distinction between this background and true patent foramen ovale or pulmonary arteriovenous fistula.

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Since the observations of Lechat *et al*¹ and Webster *et al*,² contradictory views on the possible role of patent foramen ovale in cryptogenic stroke have been published.³⁻⁵ Stöllerberger *et al* showed the existence of significant disagreement between laboratories about contrast echocardiographic studies in the same group of 200 consecutive patients.⁶ A different interpretation of the same contrast studies has to be avoided. Therefore, agreement on the definitions and techniques of contrast echocardiography is an absolute condition.

In the detection of patent foramen ovale, the transoesophageal approach is more sensitive than surface echocardiography.¹ Respiratory manoeuvres can also enhance the sensitivity of the method.^{1,7} Most studies suggest that the appearance of contrast in the left atrium has to occur within three to four beats after the onset of right atrial contrast to represent true patency of the foramen ovale.^{1,7-9} Later contrast in the left atrium has occasionally been described and attributed to pulmonary arteriovenous fistula.¹⁸

To clarify these observations, we investigated the echogenicity of blood in the left atrium proximal to the atrial septum during cough and the Valsalva manoeuvre.

Patients and methods

PATIENTS

We examined 30 consecutive adult patients referred for routine transoesophageal echocardiography. The main indications were evaluation of native valve (eight patients), evaluation of prosthetic valve (six), search for a potential cardiac source of embolism (seven), aortic abnormalities (one), and inadequate surface echogenicity (eight).

METHODS

The procedure was performed under mild sedation, with at least 10 minutes' delay

Department of
Cardiology, St-Pierre
University Hospital,
Brussels
G Van Camp
B Cosyns
J-L Vandenbossche

Correspondence to:
Dr J-L Vandenbossche,
Service de Cardiologie,
Hôpital Universitaire Saint
Pierre, 322 rue Haute, 1000
Brussels, Belgium.

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between intravenous injection of the sedative and the recording of measurements. A catheter (Venflon No 2-18G) was inserted in an antecubital vein and 2-3 ml (2-3 mg) of midazolam solution was injected at least 10 minutes before measurements were taken. A continuous intravenous line was not used. The studies were performed with a standard, commercially available transducer (5 MHz). All procedures were performed with the same Toshiba 160 model. We adjusted the gain settings, the time gain compensation at the atrial depth, and the dynamic range to detect (a) right to left shunt through the foramen ovale of even a few microbubbles or (b) possible transmission of microbubbles through the lungs, which is supposed to produce weaker echoes in the left atrium. Therefore, the gain was adjusted one or two levels higher than for conventional transoesophageal echocardiography, but it never reached exceptional high gains. (Our Toshiba 160 model has a gain scale of 62-100 and a dynamic range scale of 30-90 dB. A standard gain setting equals 80 dB and standard dynamic range setting 50 dB. For our patent foramen ovale and snowstorm contrast studies we used gains of ± 86 dB and dynamic ranges of ± 45 dB.

We looked for contrast in the left atrium in each patient during normal respiration, a cough, and the Valsalva manoeuvre. Patients unable to perform adequate respiratory manoeuvres were excluded. These observations were performed sequentially: firstly, without any intravenous injection and, secondly, during intravenous injections of air microbubbles. Microbubbles were obtained by agitating vigorously 10 ml of a dextrose solution, which was then rapidly injected through a three way tap. Injections were per-

formed during a cough and 1-3 seconds before release of the Valsalva manoeuvre. Patients in whom adequate filling of the right atrium with microbubbles by peripheral injections could not be obtained were excluded.

DEFINITIONS

Patency of the foramen ovale was considered if microbubbles appeared in the left atrium during the first four cardiac cycles after appearance of the contrast in the right atrium and when these microbubbles in both the left and the right atrium had the same echodensity (figure 1).

We often observed another contrast in the left atrium. It almost always had a weaker echodensity than microbubbles in the right atrium after contrast injection. We graded this contrast as 1 if it was mild but clearly distinct from background noise (high gain levels are necessary to visualise this contrast), as 3 if it was equal to right atrial contrast during injection (normal gain settings are used), and as 2 if it was of an intermediate intensity (snowstorm contrast is visible with normal gain settings; with high gain settings its echodensity resembles echodensity of right atrium microbubbles) (figure 2).

Using simultaneous M mode tracing and introducing a signal into the image, we also defined timing of contrast as the delay of appearance of contrast after onset and end of manoeuvres and after appearance of contrast in the right atrium. The third and important characteristic of this contrast was its direction: microbubbles of contrast injections crossed the foramen ovale in patent foramen ovale while the respiratory contrast clearly came from the pulmonary veins, its downward motion through the left atrium giving it a snowstorm appearance.

Figure 1
Transoesophageal view of the right (RA) and left (LA) atrium and the atrial septum in true patent foramen ovale (arrow). Microbubbles appear quickly in the left atrium with the same echodensity as microbubbles in the right atrium. M mode showing early appearance of contrast in the left atrium.

Figure 2
Transoesophageal view of the left atrium (LA), right atrium (RA), and atrial septum. Intense contrast in the left atrium is clearly present (arrows) after the Valsalva manoeuvre without any injection of contrast microbubbles (right atrium is free of contrast). Arrow on the M mode image indicates the onset of the release phase of the Valsalva manoeuvre.

STATISTICAL ANALYSIS

Comparison between the frequency of left atrial contrast with and without injection and comparison between the groups of patients with and without left atrial contrast were analysed by the χ^2 test with corresponding degrees of freedom; Yates's correction was used for small numbers. When contrast was present, differences between the intensity of the contrast between normal respiration, a cough, and the Valsalva manoeuvre and between observations with and without injection were compared by unpaired Student's *t* test.

Results

ECHOGRAPHIC DESCRIPTION OF CONTRAST

During close examination of left atrial echogenicity and with relatively high gain settings, we often found contrast in the left atrium that was different from the microbubbles in the right atrium after injection of contrast. It almost always had a weaker echodensity and it always came from the top of the left atrium (pulmonary veins), which gave a so called snowstorm appearance (figure 2). It was totally different from the cloud aspect of smoke contrast. In two of our patients the snowstorm contrast during the Valsalva manoeuvre was so important that its echodensity resembled that of right atrium microbubbles even when normal gain settings were used.

PREVALENCE, TIMING, AND INTENSITY OF LEFT ATRIAL CONTRAST INDUCED BY RESPIRATORY MANOEUVRES

Without injection of microbubbles, the snowstorm contrast induced by the Valsalva manoeuvre was present in 14 out of 30 patients (47%) and that induced by a cough

in seven out of 30 (23%). In five cases (17%) mild left atrial contrast was seen even during apparently normal quiet respiration. Intravenous injections increased slightly the incidence of left atrial contrast (table 1). In two patients the snowstorm contrast was seen only during a cough and not during the Valsalva manoeuvre. All the other snowstorm contrasts were detected by the Valsalva manoeuvre. Contrast appeared in some patients as early as one cardiac cycle after the onset of a cough and after release of the manoeuvre. In general, there was a mean delay of 3–4 beats after release of the Valsalva manoeuvre and after the onset of a cough. When visible, the contrast appeared 5–10 cycles after contrast injection and right atrial filling during normal respiration. The maximal duration of contrast was less or equal to 20 beats. The intensity of contrast (mean (SD)), when present, was mild in normal respiration (1.0 (0)) and mild to moderate during a cough and the Valsalva manoeuvre (1.4 (0.5)), only reaching the intensity of microbubbles in the right atrium in two of our patients during the Valsalva manoeuvre.

CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS

We evaluated possible associations between the presence of contrast and clinical and echocardiographic variables which could potentially increase left atrial echogenicity

Table 1 Incidence of contrast induced by respiratory manoeuvres in 30 patients. Values are numbers (percentages)

	Normal respiration	Cough	Valsalva
Without injection	5 (17)	7 (23)	14 (47)
With injection	8 (27)	15 (50)	20 (67)

Table 2 Relation between presence of respiratory contrast and clinical data. Values are numbers (percentages) of patients unless stated otherwise

	Respiratory contrast:		P value
	Present (n = 22)	Absent (n = 8)	
Mean age (range) (years)	55 (21–78)	65 (59–73)	>0.05
AF	5 (23)	2 (25)	>0.05
CVA	6 (27)	0	>0.05
PHT	1 (5)	0	>0.05
MD	5 (23)	6 (75)	>0.05

AF = Atrial fibrillation; VCA = Cerebrovascular accident; PHT = Pulmonary hypertension; MD = Mitral valve disease.

(tables 2 and 3). There was no significant difference in incidence of these clinical subsets in patients with and without contrast except for patients with mitral valve disease: this contrast was more common in the group of patients without mitral valve disease ($P = 0.03$). The presence of this contrast seems also to be independent of decreased left ventricular function, left atrial enlargement, stasis defined as smoke pattern, or presence of a true patent foramen ovale.

Discussion

PATENT FORAMEN OVALE

The potential role of patent foramen ovale in cryptogenic stroke in young patients, and recently also in all age groups, has been suggested by several physicians.¹²⁴⁵⁸ A lot of questions, however, remain unanswered.³ To prevent overdiagnosis of patent foramen ovale and overestimating its role in cryptogenic stroke, unanimity about definitions and techniques used during echocardiographic studies is a necessity. There is agreement about the superiority of transoesophageal contrast echocardiography over the precordial technique in detecting patent foramen ovale.^{10–12} Colour flow mapping during transoesophageal echocardiography can be a complementary technique, but it is probably less sensitive than contrast echocardiography.¹³

RESPIRATORY MANOEUVRES DURING CONTRAST ECHOCARDIOGRAPHY

The usefulness of provocative respiratory manoeuvres (coughing and the Valsalva manoeuvre) to enhance the sensitivity of the technique is also widely accepted.²³¹⁴ Haemodynamic effects of the Valsalva manoeuvre are now well understood: the increase in intrathoracic pressure generated

during the strain phase of the Valsalva manoeuvre impedes the return of venous blood to the heart. At release this is stopped abruptly with an overshoot of venous return. The important effect of the manoeuvre on the filling of the right and left heart is well illustrated by the recent work of McIntyre *et al*, who used the peripheral-artery pulse to estimate the pulmonary wedge pressure during the Valsalva manoeuvre.¹⁵

SNOWSTORM CONTRAST IN THE LEFT ATRIUM

On the other hand, recent reports have mentioned the occurrence, on rare occasions, of another contrast in the left atrium during contrast echocardiographic studies.⁸⁹ This contrast was seen passing into the left atrium from the direction of the pulmonary veins and was detected only three or more cardiac cycles after the appearance of contrast in the right atrium. In all these cases the microbubbles were consistently smaller than those seen passing immediately across the atrial septum. The patients were considered to have pulmonary arteriovenous fistula. Indeed, in patients with pulmonary arteriovenous fistula contrast appeared in the left atrium after a longer delay than it did in patients with interatrial shunting due to patent foramen ovale or interatrial septum defect.¹⁶ Vandenbergarde *et al* mentioned a spontaneous contrast, different from smoke, which was sometimes present at normal respiration and sometimes only during the Valsalva manoeuvre. They described this contrast as multiple scattered echoes which typically came and went and emerged from the pulmonary veins.¹⁷ They did not, however, mention the presence of an intravenous line or an intravenous injection of any solution before the transoesophageal procedure.

Our results show that respiratory manoeuvres induce contrast in the left atrium without any injection in a fairly high percentage of patients. This fairly common finding, mentioned only once by Vandenbergarde *et al*, can be explained by two extreme conditions present in this study: gain settings were high and we were particularly interested in this phenomenon. Special care was taken to avoid any injection of solution during the 10 minutes before the measurements to rule out contamination by either air microbubbles or the solution itself. Moreover, in four additional cases transoesophageal echocardiography was performed without any venous catheter to ascertain that this respiratory contrast was strictly independent of any venous manipulations and bubble entrapment within the pulmonary capillary bed. In these four cases the same respiratory contrast was observed. Pulmonary arteriovenous fistula can therefore not be incriminated in these cases.

This contrast was observed during quiet respiration in five out of 30 patients. Although contrast was present in these patients without respiratory manoeuvres and we asked them to breathe normally, we cannot exclude that some of these patients had deep respiratory cycles producing some variations in pulmonary venous return. Since analyses were

Table 3 Relation between presence of respiratory contrast and echocardiographic data. Values are numbers (percentages) of patients

	Respiratory contrast:		P value
	Present (n = 22)	Absent (n = 8)	
DLVF	3 (14)	1 (13)	>0.05
LAE	7 (32)	6 (75)	>0.05
St LA	2 (9)	1 (13)	>0.05
PFO*	5 (23)	2 (25)	>0.05

DLVF = decreased left ventricular function; LAE = left atrial enlargement; St LA = stasis (smoke) in left atrium; PFO = patent foramen ovale.
*Microbubbles with the same echodensity as right atrial microbubbles appearing in left atrium within the first four cardiac cycles after filling of the right atrium with the injected microbubbles.

retrospective from close examination of video recordings, we cannot ascertain that these five patients with contrast during normal respiration had not such ample respiratory cycles. The contrast occurs within 20 beats after the onset of manoeuvres and as early as one beat after release of the Valsalva manoeuvre in some patients. This contrast is most often independent of venous injections. Nevertheless, we also observed that during contrast injections a similar contrast could be observed, even during normal quiet respiration in three patients who did not have any contrast before injections. Similarly, microbubble injections during manoeuvres produced consistently a higher percentage of positive results in contrast studies than did manoeuvres alone (15/30 *v* 7/30 for a cough and 20/30 *v* 14/30 for the Valsalva manoeuvre).

ORIGIN OF SNOWSTORM CONTRAST

Clearly, two distinct phenomena are present.

The first is observed without venous injections and is likely to be related to the transient stasis in the pulmonary circulation induced by respiratory manoeuvres. The fact that this contrast consistently moves parallel to the atrial septum, from the junction of the right pulmonary vein, suggests this mechanism. Experimental studies suggest that slow flow becomes echogenic because of rouleaux formation.¹⁸⁻²⁰ Recent intravascular ultrasound studies have shown that the Valsalva manoeuvre immediately induces contrast in the internal jugular vein.²¹ We propose therefore that respiratory manoeuvres induce stasis in the pulmonary veins, which causes the formation of rouleaux; these are released in the left atrium. This is probably the reason why this snowstorm contrast was less apparent in patients with mitral insufficiency: stasis is cleared by the washing effect of mitral insufficiency.

The second phenomenon is clearly related to contrast injection. For air microbubbles to be able to cross capillaries they should be smaller than 8 μm , the average diameter of these capillaries. At that size air microbubbles dissolve in 190 ms to 550 ms, depending on the degree of saturation of the surrounding fluids.²² Because blood transit time from the pulmonary capillaries to the left atrium is 2 seconds or more, these small microbubbles cannot appear in the left atrium. Therefore, appearance of contrast in the left atrium could therefore be either microbubbles that are able to pass the pulmonary filter because the capillaries are dilated or reflections of ultrasound echoes caused by inhomogeneity within blood as a result of differences in acoustic impedance produced by the rapid injection of a bolus of 10 ml dextrose solution. Although both hypotheses are speculative, they cannot be totally rejected.

OTHER CIRCUMSTANCES IN WHICH LEFT ATRIAL CONTRAST WAS OBSERVED

Recently, patients with end stage hepatic failure have been shown to have left cavity filling

with microbubbles during venous microbubble injections. Such patients, however, have dilated pulmonary capillaries producing arteriovenous shunting.^{23,24} None of our patients had significant liver disease, which rules out this hypothesis. Early transthoracic echocardiographic studies showed that forceful injection of dextrose solution through a wedged catheter can cause contrast to pass through the pulmonary bed.²⁵ Because modern transoesophageal echocardiography using high frequency transducers is sensitive, it may be able to detect either a small amount of microbubbles that have passed through the pulmonary bed or simply some inhomogeneity in acoustic impedance of blood produced by the rapid injection of 10 ml dextrose solution.

CONCLUSIONS

We have three main conclusions:

(1) Left atrial snowstorm contrast induced by respiratory manoeuvres or injections of contrast, or both, is a frequent transoesophageal observation.

(2) Since respiratory manoeuvres are routinely used during contrast studies to detect patent foramen ovale, it is crucial in preventing overdiagnosis to distinguish true passage through a patent foramen ovale from snowstorm contrast.

(3) We therefore suggest that respiratory manoeuvres should always be performed before contrast injections, to allow comparison and better distinction between this snowstorm background and true patent foramen ovale or pulmonary arteriovenous fistula.

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