Left atrial Spontaneous Echo Contrast: Relationship with Clinical and Echocardiographic Parameters

Takahide Ito, MD, PhD¹ and Michihiro Suwa, MD, PhD²

¹Department of Cardiology, Osaka Medical College
²Department of Cardiovascular Medicine, Hokusetsu General Hospital

Corresponding author: Takahide Ito, MD, PhD
Department of Cardiology, Osaka Medical College, 2-7, Daigaku-machi, Takatsuki, Osaka 569-8686, Japan
Telephone number: +81-72-683-1221 (Japan)
Fax number: +81-72-684-6597 (Japan)
e-mail address: in3016@osaka-med.ac.jp

Short title : associates of spontaneous echo contrast

Key words : left atrial spontaneous echo contrast; transesophageal echocardiography; atrial fibrillation; biological markers; heart failure

Word counts of the full article, excluding references and figure legends: 2368
ABSTRACT

Spontaneous echo contrast (SEC) is known as a precursor of thrombus formation reflecting blood stasis in cardiac chambers and major vessels. Transesophageal echocardiography plays a pivotal role in detecting and grading SEC in the left atrial (LA) cavity. Assessing LA SEC can identify patients at increased risk for thromboembolic events. LA SEC also develops in patients who have sinus rhythm, especially in those with heart failure. Detection of LA SEC is not uncommon in subjects who have multiple cardiovascular comorbidities, although mechanisms behind this association are not fully understood. In patients with atrial fibrillation, a role of mitral regurgitation exerting against occurrence of LA SEC and subsequent thromboembolism is controversial. Moreover, alterations of blood coagulability and elevated certain biological markers in the blood contribute to occurrence of LA SEC. This review describes the pathogenesis of and assessment of SEC, in addition to the relationship between LA SEC and clinical, biological and echocardiographic parameters.
Introduction

It has been more than three decades that blood reflections within the cardiac chambers observed with echocardiography are known as spontaneous echo contrast (SEC), indicating presence of blood stagnation and thus a precursor thrombus formation [1,2]. The pathogenesis of SEC is complex, with multiple interrelated factors contributing. With the advent of transesophageal echocardiography (TEE), SEC came to more clearly be observed [3,4]. Since then a number of reports have been published on TEE-assessed SEC providing diagnostic, therapeutic, as well as prognostic information in various cardiac conditions. Appearance and severity of SEC, however, depends on technical factors such as gain settings, and no clearly standardized method for assessing SEC has existed. This review starts to describe the pathogenesis of and assessment of SEC, and then extends to the relationship of LA SEC with various clinical, biological and echocardiographic parameters.

Pathogenesis of SEC

In 1983, Sigel et al found in the experimental study that SEC reflected red cell aggregation by demonstrating that SEC severity, as determined by the videodensitometric method, correlated positively with hematocrit and fibrinogen concentration, and inversely with shear stress [5-7]. Black et al initially confirmed relationship between SEC and blood components in patients with atrial fibrillation (AF) and found that LA SEC appeared in relation to hematocrit, fibrinogen concentration, and LA dimension, but not to platelet count [8].

Fatkin et al emphasized importance of low shear stress conditions for the occurrence of SEC by demonstrating that echogenicity from human blood was increasing from high- to low-velocity settings with any given levels of hematocrit or fibrinogen concentration [9]. Clinically, a condition of low shear stress is often observed within the left atrium in patients with AF and in those with mitral valve disease [2, 10], and it can be surrogated by a decrease in LA appendage velocity [11,12].

Virchow’s triad of factors related to thrombus formation includes abnormal changes in flow, blood constituents, and vessel walls. SEC may fulfil the first two components for thrombogenesis [12]. For the remaining one component, abnormal changes in vessel walls (atrial wall), no direct evidence on SEC have existed. Figure 1 shows very severe SEC in the cardiac chambers from a patient with prior mitral valve replacement surgery. In a sense, post artificial valve
replacement surgery seems to be a condition of “abnormal changes in vessel walls”. Some investigators propose the mechanism behind SEC occurring after valve replacement lies in oxygen released from hemolysing red blood cells or in fibers emanating from a cloth-covered prosthesis [13].

**Assessment of LA SEC**

Assessment of LA SEC is useful because it can help stratify patients at high risk for embolic events and requiring anticoagulation treatment [8]. The severity of LA SEC has been assessed in a qualitative as well as quantitative fashion. LA SEC is qualified simply as none, mild, and severe [2,14], although most of the investigators take a semi-quantitative method proposed by Fatkin et al, who demonstrated an excellent correlation of visual grading of SEC (grade 0 to 4+) against video-densitometry analysis [9,15]. The scoring system for LA SEC, proposed by Fatkin et al [11], and examples of TEE images for correspondent SEC grades are shown in Table 1 and Figure 2, respectively.

Klein et al developed a sophisticated method of quantifying LA SEC using integrated backscatter [16]. They found a good correlation between integrated backscatter-derived intensity of LA SEC and the qualitative measures. Another observation on integrated backscatter used to assess LA SEC was that the intensity of SEC in the LA appendage was greater than that of SEC in the main LA cavity, supporting the fact that a thrombus favors the LA appendage rather than the main LA cavity [17]. With either qualitative or quantitative method for assessing SEC to form, however, care should be taken for optimal analysis to minimize influence of ultrasound system controls such as gain settings [12].

Here is how to grade LA SEC while optimizing the ultrasound machine settings in our institution (Table 1 and Figure 2). First of all, in most cases, we perform TEE with the time-gain-control at the basic positon, whereas the total gain control is used only for discriminating SEC grade 1+ from 2+. With SEC grade 2+, SEC is visible at any allowable levels of the gain setting (Table 1). Secondly, one should pay attention not only to blood density but also to the swirling pattern of SEC; to our experiences, the swirling pattern can be seen with more than SEC grades 3+. The swirling speed of SEC looks much lower with SEC grade 4+ compared with 3+ (Table 1 and Figure 2). Also, LA appendage sludge (mentioned later) is prone to occur with SEC grade 4+.

LA SEC is not infrequently observed with transthoracic echocardiography (TTE), especially in mitral valve disease (Figure 3). Beppu et al found that LA SEC was
commonly seen in patients with mitral stenosis and that its presence was 
associated with lower cardiac output, larger LA size, and smaller mitral valve area 
[18]. Although LA SEC is difficult to see with TTE due to a relatively low-frequency 
transducer used and to attenuated ultrasound signals, the development of transthoracic harmonic imaging, which involves transmitting ultrasound at one 
frequency and receiving at twice the transmitted frequency, has allowed relatively 
easier detection of LA SEC. Ha et al reported that among 38 patients with mitral 
stenosis, the sensitivity for detection of LA SEC was 100% with harmonic imaging 
and 13.2% with non-harmonic (fundamental) imaging [19]. Harmonic imaging is 
basically incorporated in currently available high-end ultrasound machines.

LA appendage sludge
With increasing use of TEE in the era of pulmonary vein isolation to assess for LA 
thrombus, sludge within the LA appendage have attracted interest to clinicians. 
LA appendage sludge indicates a dynamic, viscid, layered echo dense finding 
without a discrete mass (Figure 4). It appears denser than SEC and less dense 
than thrombus, and thus considered to be a stage of the spectrum between SEC 
and thrombus formation [20,21]. This is explained by previous observation that 
sludge was abolished with appropriate anticoagulation in contrast to SEC [22,23].

Similar to LA SEC, LA appendage sludge can be a risk of thromboembolism, but 
data on this association are scarce. Lowe et al found 47 out of 340 patients with 
AF who underwent TEE prior to direct cardioversion or pulmonary vein isolation 
[20]. They found that LA appendage sludge was associated with enlarged left 
atrium, reduced LA appendage velocity, and reduced LV ejection fraction, and 
that sludge was an independent predictor of embolic events and all-cause 
mortality [20]. Hajjiri et al observed that 8 of 1,076 patients had LA appendage 
sludge, and that none of the sludge-positive patients experienced embolic events 
during or after pulmonary vein isolation procedure [21]. A large-scale prospective 
study is needed to determine how to interpret and deal with LA appendage sludge.

LA SEC and mitral regurgitation
In 1990’s, several investigators suggested that mitral regurgitation (MR) 
prevented SEC and thrombus formation in the LA cavity [24-26]. This way of 
thinking is reasonable since turbulent flow into the LA cavity makes shear stress 
increase thereby preventing red blood cells from aggregating. In fact, it was 
observed that among patients with nonvalvular AF, those with significant MR had
lower integrated backscatter values in the LA cavity compared with those without [14].

Movsowitz et al and later Hwang et al reported that among AF patients of various etiologies, those with more-than-mild MR was much less associated with LA SEC compared those with mild or less MR [24, 25]. Similar findings were observed when AF patients were restricted to “nonvalvular” [26]. Other investigators, however, did not find MR severity in nonvalvular AF patients to have as much an effect on a history of stroke irrespective of the severity of LA SEC [27]. There has recently been increasing evidence that LA thrombus or SEC appears after MitraClip procedure, which may prompt cardiologists to set an appropriate anticoagulation regimen during and after this procedure [28-30].

Although shear stress is considered to correlate directly with blood velocity and inversely with chamber diameter [2], increased LA size as a result of severe, and longstanding MR may exert as a counterpart of SEC appearance, rather, as an exacerbating factor of it. Moreover, severe MR can often be associated with heart failure, which is identified as a prothrombotic state [31].

Impact of heart failure on LA SEC
From the therapeutic viewpoint, the presence or absence of LA SEC may be of great importance in the management of heart failure patients. Among patients with nonvalvular AF, plasma B-type natriuretic peptide (BNP) and the tissue Doppler-derived E/e’, both surrogates for LV filling pressure, were shown to be predictive of LA thrombus and SEC [32,33]. Taking into consideration that “heart failure” is built in CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc score, in addition, association between SEC and heart failure is plausible.

Tabata et al found that elevated pulmonary artery wedge pressure was associated with reduced LA appendage velocities even in patients in sinus rhythm, and that some of the patients had LA SEC and/or appendage thrombus [34]. Their findings are supported by the clinical as well as experimental observation that LA appendage velocities decreased with increased loading conditions [35,36]. Taken together, no doubt that in heart failure patients, treatment toward decreasing LV filling pressure would be one of the tasks of immediate importance to reduce a risk of embolic events (Figure 5).

LA SEC and CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc scores
Quite a few reports have appeared for the past decade on the relationship of
TEE-derived parameters with CHADS2/CHA2DS2-VASc score. In many cases, the prevalence of LA SEC was shown to increase as CHADS2/CHA2DS2-VASc score became higher [37,38]. A possible explanation for this association is that elevated CHADS2/CHA2DS2-VASc score is often accompanied by conditions predisposed to thrombosis such as increased LA volume and impaired LV systolic function [39,40].

In addition, components listed on CHADS2/CHA2DS2-VASc score (hypertension, diabetes, heart failure, etc.) involve a certain nature of inflammatory state, and thus there may be various inflammatory cytokines (IL-6, TGF-α, CRP, etc.) as abnormal blood constituents flowing not only into the systemic circulation but also into the left atrium [41,42]. Interestingly, patients with multiple cardiovascular risk factors were shown to have intra-aortic SEC observed with TEE [43]. Figure 6 shows TEE images of the cases in which intra-aortic SEC is found concomitantly with LA SEC in patients with nonvalvular AF.

**Biomarkers and LA SEC**

As mentioned, SEC indicates not only hypercoagulable but also inflammatory state, although information is limited on the relationship between LA SEC and biomarkers in the blood. Various inflammatory cytokines were shown to elevate in AF patients [41]. Among patients with nonvalvular AF, for example, C-reactive protein (CRP) levels were found to be associated with CHADS2 score in an incremental fashion. This raises the hypothesis that LA SEC correlates with CRP levels, and studies found that the incidence of LA SEC increased with elevated CHADS2 score and CRP levels [44,45].

There are numerous reports on the association between LA SEC and coagulation markers. Heppell et al showed that altered hemostatic factors such as D-dimer, β-thromboglobulin, and von Willebrand factor were all predictive of LA SEC and thrombus formation [46]. A recent meta-analysis demonstrated that D-dimer measurements were useful for the identification of LA thrombus and SEC with sensitivity and specificity of 75% and 81%, respectively [47]. Among AF patients who underwent pulmonary vein isolation, the incidence of elevated D-dimer levels was higher in the left atrium than in the systemic circulation, with the trend being more pronounced in those who had large LA size [48].

Not referring about SEC though, it was found that in AF patients, some platelet factors in the blood (platelet factor 4 and plasmin-α 2-plasmin inhibitor complex) similarly elevated in patients with chronic AF vs those with paroxysmal AF [49].
This finding may substantiate the notion that patients with paroxysmal AF have as much a risk for embolic events as those with non-paroxysmal AF, and thus definitely require anticoagulant treatment.

Conclusions
LA SEC occurs under alterations of various pathological conditions such as those related to anatomical, hemodynamic, and biological changes. This raises the hypothesis that therapeutic strategies to modify such parameters can reduce SEC thereby reducing a risk of embolic events. Disorganized LA contraction involved with AF is another important consideration as pathogenesis of LA SEC, which may facilitate AF patients to recovering with sinus rhythm to prevent atrial thrombosis (Figure 5). Large prospective studies are needed to verify such hypothesis.

Funding
This paper did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Declaration of interest
The authors declare no conflict of interest that could that could be perceived as prejudicing the impartiality of the review.
References


23. Ito T, Suwa M, Nakamura T, Miyazaki S, Hirota Y & Kawamura K 1999 Influence of warfarin therapy on left atrial spontaneous echo contrast in
nonvalvular atrial fibrillation. Am J Cardiol 84 857-859.


Figure legends

Figure 1
Very dense SEC in both atria imaged on transesophageal echocardiography from a patient with prior mitral valve replacement surgery. LA, left atrium; PV, prosthetic valve; RA, right atrium

Figure 2
Representative transesophageal echocardiographic images in 4 cases showing SEC grades 1+ to 4+, respectively. Note that with SEC grade 1+, minimal echogenicity can be seen within the left atrial appendage (LAA), and that with SEC grade 4+, the swirling pattern is remarkable compared with SEC grade 3+. LA, left atrium; LV, left ventricle

Figure 3
Transthoracic echocardiographic images before and after percutaneous transluminal mitral commissurotomy (PTMC) from a patient with severe mitral stenosis. Note that before PTMC, SEC (arrowheads) was seen in the left atrium (LA) with both M-mode (mid) and 2-dimensional methods (bottom) despite sinus rhythm, and that after PTMC, SEC disappeared concomitantly with improved mitral valve opening (arrow) (top).

Figure 4
Left atrial appendage sludge (S). LAA, left atrial appendage

Figure 5
Transesophageal echocardiographic recordings during the time-course of anticoagulation therapy from a patient with nonvalvular atrial fibrillation complicated by heart failure. At the beginning (A), a thrombus occupying the left atrial appendage (LAA) was present. Starting with heart failure treatment with therapeutic anticoagulation (B), the B-type natriuretic peptide (BNP) level decreased and LAA thrombus resolved (top) although SEC and LAA dysfunction (bottom) still were observed. Two months later (C), when the patients had spontaneously been recovered to sinus rhythm, a further decrease in the BNP level and a marked increase in the LAA velocities (bottom) were observed.
Figure 6

A, Dense SEC in the descending aorta (Ao) coincidently found with LA SEC from a patient with nonvalvular atrial fibrillation. B, Slight SEC in the descending aorta (Ao) with a mural plaque (arrow) observed from another patient with nonvalvular atrial fibrillation. Note that SEC in the right atrium (RA), swiftly flowing from the superior vena cava (SVC), is denser than SEC in the LA, indicating that some pathological factors that generate RA SEC might be involved in this patient.
BNP = 1536 pg/mL

2 weeks later
BNP = 209 pg/mL

2 months later
BNP = 85 pg/mL
Figure 6

A

LA
LAA
LV

Ao

B

Ao

LA
SVC

RA
### Table 1 Scoring system for LA SEC [11]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None (absence of echogenicity)</td>
</tr>
<tr>
<td>1+</td>
<td>Mild (minimal echogenicity located in the LA appendage or sparely distributed in the main cavity of the left atrium; may be detectable only transiently during the cardiac cycle; imperceptible at operating gain settings for two dimensional echocardiographic analysis)</td>
</tr>
<tr>
<td>2+</td>
<td>Mild to moderate (more dense swirling pattern than grade 1+ but with similar distribution; detectable without increased gain settings)</td>
</tr>
<tr>
<td>3+</td>
<td>Moderate (dense swirling pattern in the LAA, generally associated with somewhat lesser intensity in the main cavity; may fluctuate in intensity but detectable constantly throughout the cardiac cycle)</td>
</tr>
<tr>
<td>4+</td>
<td>Severe (intense echo density and very slow swirling patterns in the LAA, usually with similar density in the main cavity)</td>
</tr>
</tbody>
</table>