Contrast-enhanced tissue Doppler imaging of the left atrial appendage is a new quantitative measure of spontaneous echocardiographic contrast in atrial fibrillation

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Aims Although left atrial appendage spontaneous echo contrast (LAASEC) is a marker of increased thromboembolic risk in atrial fibrillation, it has previously only been evaluated qualitatively. We sought to determine if an intravenous contrast echocardiographic agent combined with tissue Doppler imaging (TDI) of the LAA could accurately quantify LAASEC in patients with atrial fibrillation.

Methods and results We prospectively identified 55 patients with persistent atrial arrhythmias (mean age 63 ± 13 years) undergoing a transesophageal echocardiography (TEE), with LAASEC prior to direct current cardioversion. In addition to off-line calculation of backscatter index and shear rate, quantification of the velocity in a color TDI region of interest was performed in the LAA cavity following a 0.5-mL intravenous bolus of Optison. LAASEC was qualitatively graded by a blinded reader as mild (n = 29) or severe (n = 26), and was compared off-line to TEE-derived quantitative variables.

Compared to patients with mild LAASEC, those with severe LAASEC had significantly decreased LAA emptying velocity, LAA-TDI mean velocities and shear rate. Over the whole group, the mean maximal velocity of the LAA using TDI correlated with LAA emptying velocity (r = 0.59; P < 0.0001), shear rate (r = 0.55; P < 0.0001) and LAA area (r = 0.34; P = 0.014). Severe LAASEC was found with 72% sensitivity and 82% specificity if TDI mean velocity was > 6.13 cm/s. On logistic regression analysis, LAA-TDI was the only predictor of qualitative LAASEC grade.

Conclusion Contrast-enhanced TDI is an original new tool that provides a quantification of the mean velocity of LAASEC that might improve our decision making in patients with atrial fibrillation.

KEYWORDS Left atrium; Atrial fibrillation; Tissue Doppler imaging; Spontaneous echocardiographic contrast; Stroke

Introduction

Atrial fibrillation is the most common arrhythmia and its prevalence increases as the population ages.¹ The rate of ischaemic stroke among patients with non-rheumatic atrial fibrillation averages 5% per year, which is 2 to 7 times the rate for people without atrial fibrillation.² Currently, there is a controversy between proponents of conservative management approaches (AFFIRM, RACE, HOT CAFE) and aggressive strategies including cardioversion and radiofrequency ablation even in patients with recognized chronic heart failure or permanent atrial fibrillation.³ ⁶ Transoesophageal echocardiography (TEE) has emerged as a useful technique in the risk stratification of thromboembolism by the finding of thrombus, spontaneous echo contrast (SEC) and complex atheroma.¹ SEC has been defined as dynamic smoke-like echoes detected by TEE that are associated with thrombus formation and an increased risk of systemic thromboembolism. It may be visualized in almost 60% of patients with atrial fibrillation.⁷ These smoke-like echoes are characterized by increased gray-scale intensity and a distinctive "swirling pattern," which are thought to result from aggregates of red blood cells in the presence of low shear rates.⁸

Clinically, SEC severity is graded qualitatively as mild to severe based on the detection of dynamic intracavity echoes at high or low gain settings.⁹ However, this qualitative assessment is highly influenced by the level of...
experience of the operator. Previously, we have described a quantitative approach to grade SEC severity using the backscatter index.\textsuperscript{10} We demonstrated the ability of this quantitative technique to describe SEC, and fast Fourier transformation of the backscatter indicated that the motion of the SEC was characterized by low frequencies and high amplitudes.\textsuperscript{11} This type of approach is not widely available and is limited by elaborate post-processing. We, therefore, sought to quantify the degree of SEC using tissue Doppler imaging (TDI). With the use of commercially available contrast agents that are able to fill left heart cavities and enhance the Doppler signal, we hypothesized that left atrial appendage (LAA) SEC could be accurately quantified using TDI. The objective of this study was to determine the ability of TDI, with the administration of a contrast agent, to quantify the severity of SEC in the LAA.

**Methods**

**Study population**

We prospectively studied 55 patients (65 ± 13 years old) with persistent atrial fibrillation and LAA-SEC, undergoing a clinically indicated TEE prior to cardioversion. All patients enrolled in the study were >18 years of age with atrial fibrillation of >2 days’ duration or atrial flutter with a documented history of atrial fibrillation. Patients allergic to blood products or having a contraindication for receiving blood products were excluded from the study. The study received approval from the Institutional Review Board of The Cleveland Clinic, Cleveland, OH, USA.

**Image acquisition**

All patients underwent a complete TEE examination with standard views using a HDI 5000 (ATL-Philips, Bothell, WA) with a multiplane TEE probe (5 MHz phased array transducer).\textsuperscript{12} Following the clinical study, specific LAA images using TDI were obtained according to the study research protocol. All patients underwent a complete thoracic echocardiogram before the TEE study using a 2.5 MHz transducer using standard views and a commercially available HDI 5000 (Phillips) machine. Left ventricular function (ejection fraction) was quantified from raw data using dedicated HDI Lab software (Philips Medical System, Andover, MA). A 5 x 5 mm region of interest was placed into the mouth of the LAA, and in the middle of the left ventricle (for normalization of the backscatter signals).

**Data analysis**

All echocardiographic measurements were made off-line. The SEC was quantified from raw data using dedicated HDI Lab software (Philips Medical System, Andover, MA). A 5 x 5 mm region of interest was used for all patients. The region of interest was manually positioned on the image for quantification of both gray scale and tissue Doppler signals. Particular attention was made not to include endocardial interface in the region of interest over the five analyzed cardiac beats. The region of interest was placed into the mouth of the LAA, and in the middle of the left ventricle (for normalization of the backscatter signals). The data over five cardiac beats were averaged. The HDI Lab provided the instantaneous values of velocity (TDI, cm/s) and mean gray-scale level (decibels) for the chosen region of interest. The velocity parameter was very different from the pulsed Doppler emptying flow recordings. Using TDI and contrast, the ‘swirling pattern’ of the SEC was analyzed. The velocity parameter was thus an average of the positive velocity in a region of interest averaged over five consecutive beats. These values were inserted into spreadsheet (Excel Office 97, Microsoft) for subsequent analyses. The TDI index was based on the average of maximal velocities over the whole region of interest. The backscatter index was calculated from the average of maximal gray-scale levels normalized by the mean gray-scale level of the left ventricular cavity.

The presence of SEC, sludge or thrombus in the LAA was qualitatively evaluated by two independent experienced observers (no SEC, mild SEC, severe SEC, sludge and thrombus).\textsuperscript{9,16} Severe SEC consisted of dynamic intracavitary echoes observed at a low-gain setting while mild SEC consisted of dynamic intracavity echoes observed at a high-gain setting. Sludge was defined as dense intracavity echoes with a slow ‘swirling pattern’ forming a layering effect; while thrombus was a delineated structure distinct from the LAA endocardium.\textsuperscript{9}

The definition of mild versus severe LAA-SEC was done using the same machine settings and dynamic images.

Tissue Doppler images were acquired with a velocity range set at ±12.5 cm/s and a pulse repetition frequency between 20 and 60 kHz. All echocardiographic examinations were stored digitally (DICOM format) and reviewed off-line (Prosolv Cardiovascular Analyzer, Problem Solving Concepts, IN). Additionally, cineloops of five cardiac cycles in gray scale and TDI modes were recorded simultaneously as specific files on an optical disk for further analysis using dedicated software (HDI Lab, Philips Medical System, Andover, MA). A 0.5-mL bolus of Optison (Human Albumin Microspheres; Amersham Health, Princeton, NJ) was administered through a peripheral vein. The mechanical index was set at 0.4.

Figure 1 shows an example of a color TDI image of the LAA without contrast (A). No information was thus recordable in the LAA cavity. Using contrast, it was possible to improve LAA cavity delineation (B), and the conjunction of color TDI and contrast allowed recording a velocity signal in the LAA cavity (C). Cineloops with and without ultrasound contrast agent were recorded.

**Figure 1** Examples of LAA with color TDI (coloration of walls) at baseline (A); with contrast agent injection (enhancement of border detection) (B); and with TDI and contrast agent injection for quantification of the SEC (C).
All values are presented as mean ± standard deviation. Student’s t-tests were used to compare values for TDI and backscatter index for the two qualitative grades of SEC. The correlations between left appendage emptying flows, left appendage maximal area, gray-scale levels and tissue Doppler data were evaluated by the Spearman rank-order correlation coefficient and by linear regression analysis. A Wald forward logistic regression model was used to identify independent correlates of the qualitative assessment of the SEC. The sensitivity and specificity were determined by constructing receiver operating curves. The sensitivity/specificity cut-off points are reported as percentages with corresponding 95% confidence intervals. A P-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 10.0 (SPSS Inc., Chicago, IL) and NCSS 2002 (McGraw-Hill, New York, NY) for constructing receiver operating curves.

Results

Clinical and conventional echocardiographic characteristics

Table 1 displays the characteristics of the study population according to the SEC qualitative grade. The patients were mainly male with a history of hypertension. The mean arterial pressure was $130/75 ± 20/10$ mmHg and the mean left ventricular ejection fraction was $39 ± 13\%$ (range 18%–60%).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the population displayed in two groups as a function of whether spontaneous echo-contrast was considered mild or severe on qualitative analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 mild SEC ($n = 29$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>23 (79 –)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>22 (75)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>NYHA Class I, n (%)</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Previous embolic event, n (%)</td>
<td>3</td>
</tr>
<tr>
<td>Arterial pressure (mmHg)</td>
<td>125/73 ± 18/12</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>39.7 ± 12.7</td>
</tr>
<tr>
<td>Mitral regurgitation grade (/4)</td>
<td>1.35 ± 0.9</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>28.2 ± 8.5</td>
</tr>
<tr>
<td>LAA area (cm²)</td>
<td>4.7 ± 1.5</td>
</tr>
<tr>
<td>LAA flows (cm/s)</td>
<td>0.37 ± 0.10</td>
</tr>
<tr>
<td>Shear rate (/s)</td>
<td>0.86 ± 0.38</td>
</tr>
<tr>
<td>TDI index (cm/s)</td>
<td>7.5 ± 2.2</td>
</tr>
<tr>
<td>Backscatter index (decibels)</td>
<td>1.54 ± 0.92</td>
</tr>
</tbody>
</table>

NYHA Class I, New York Heart Association Functional Class I; LAA, left atrial appendage; TDI, tissue Doppler imaging; n.s., not significant.
LAA characteristics

Table 1 also lists the LAA conventionally assessed parameters dividing the population into two groups: mild SEC, $n = 29$ and severe SEC, $n = 26$. There were no patients with LAA sludge, thrombus or the absence of SEC.

Significant differences in LAA size and function (emptying flows and shear rate) were observed between the two groups.

Backscatter index using gray-scale intensity

At baseline (without contrast injection), the difference between the left ventricle ($1.15 \pm 0.35$) used for normalization and the LAA ($2.17 \pm 1.43$) was significant ($P < 0.001$). The difference between the severe ($2.81 \pm 1.57$) and mild ($1.54 \pm 0.92$) SEC groups was also significant ($P = 0.001$). In 10 (18%) of the 55 patients, the backscatter index was not able to be calculated due to reverberation of a mitral prosthetic valve or ring ($n = 7$) or poor image quality ($n = 3$).

TDI index

Without contrast injection, the LAA backscatter information was below the threshold for detection and it was not possible to extract quantitative TDI velocity information (Figure 1). With the use of intravenous Optison, the difference in TDI velocities between severe SEC ($3.6 \pm 1.7$ cm/s) and mild SEC ($7.5 \pm 2.2$ cm/s) was significant ($P < 0.0001$) (Figure 2).

Univariate and multivariate analysis

Figure 3 shows the linear regression analysis between the TDI index and LAA emptying flows (A); TDI index and LAA shear rate (B); backscatter index and LAA emptying flows (C); and backscatter index and shear rate (D). The $r$ value, related equations, and standard error of the estimate (SEE) are displayed on each graph.

Figure 4 Receiver operating curves for the TDI index, backscatter index, shear rate, and LAA emptying flows in the prediction of severe SEC.
None of the two quantitative indices of SEC was correlated with the degree of mitral regurgitation or age. The Spearman correlation coefficient between the qualitative analysis of the SEC and the TDI index was $r = -0.70$ ($P < 0.001$). For the backscatter index, it was $0.45$ ($P = 0.003$). Using multivariate analysis, the only predictor of the qualitative score of SEC was the TDI index with a Chi-square of 32.022 ($P < 0.0001$).

**Receiver operator curves**

*Figure 4* displays the receiver operating curves of the TDI index, backscatter index, and LAA emptying flows and shear rate in predicting severe SEC. The sensitivity of the TDI index in predicting a severe SEC was 72% while the specificity was 82% with a cut-off value of 6.13 cm/s. The area under the curve was 0.81 with a standard error of 0.06. For LAA shear rate, with a cut-off value of 0.54/s, the sensitivity was 82%, the specificity was 80% and the area under the curve 0.82. For LAA emptying velocity, using a cut-off value of 0.29 cm/s, the sensitivity was 76%, the specificity 79% and the area under the curve 0.88.

**Discussion**

For the first time, this study describes the ability of TDI (in association with an intravenous bolus of contrast agent), to provide quantitative information on the pro-thrombotic milieu represented by the LAA cavity in atrial fibrillation patients. We demonstrated that the TDI mean velocity of a region of interest placed in the LAA recorded using a contrast agent injection was the best quantitative parameter to predict severe SEC. The correlation of the LAA emptying velocity and shear rate was better using this new TDI parameter than using the backscatter index. However, the TDI index was not another approach to quantify LAA emptying or function, but rather an original quantitative parameter of the SEC.

Tissue Doppler signals are characterized by higher amplitude and lower frequencies than typical Doppler flow signals. Therefore, assessment of moving tissue velocities requires specific adjustment (high-pass filter) of the Doppler settings. Several studies have demonstrated the clinical interest of this application of Doppler properties to provide an objective regional evaluation of the myocardium. We sought to quantify SEC with Doppler parameters set to detect tissue rather than flow. SEC derives from an aggregate of blood cells characterized by a low velocity, high amplitude swirling motion. It should be noted that TDI can only quantify SEC in the LAA if velocities are low and if the ultrasound beams meet enough reflectors. In our study, we show that a contrast agent was required to obtain a tissue Doppler analysis of the stagnant blood within the LAA cavity. Without a contrast agent, a tissue Doppler setting was not able to provide relevant velocity information. After the selection of a region of interest in the LAA, dedicated software provided a calculation of the mean velocity of the region of interest, thus creating the TDI index. When we compared this new contrast enhanced TDI index with previously proposed ones, such as, backscatter, we were able to demonstrate the relevance of this new methodology. TDI has been described as a useful tool for qualitative analysis of cardiac masses, particularly the vegetations of endocarditis. Bartel et al. also described the ability of tissue Doppler M-mode to differentiate a LAA thrombus from a pectinate muscle using the phase of the motion of each structure. We have previously reported the use of tissue Doppler M-mode to differentiate normal from an abnormal myocardium in a case of a heart metastasis of an epidermoid tumor. Nevertheless, the TDI index was proposed and dedicated to quantify the 'swirling pattern' of the SEC and was proved to be distinct from the measure of LAA emptying flow or the potential measure of LAA wall motion.

The backscatter index quantifies the gray-scale level of a region of interest in the atrial or LAA cavity and was based on videodensitometry of the gray-scale images performed on DICOM files. We previously used the raw data to objectively quantify the gray-scale level of the SEC. Ultrasonic tissue parameters have been reported for the quantification of the SEC and to characterize abnormal states of the myocardium. The backscatter index used in the present study was not the one used by Bashir et al. Instead of using the DICOM file, Bashir et al. used the radiofrequency backscatter signal to quantify SEC. However, despite the number of studies devoted to echocardiographic quantification of tissue texture, the backscatter index using the RF signal is still a research tool and cannot be considered as a gold standard method. It requires specialized dedicated software and necessitates image standardization with respect to a reference point (for example, in the inter-atrial septum or the pericardium). Technical limitations are also important in view of the requirement of excellent 2-D image quality. Artifacts may overestimate the backscatter index and we excluded 17% of the backscatter index in our study for technical reasons.

TEE is the main imaging technique that can provide a detailed analysis of the LAA and a description of potential SEC. Very preliminary experience with MRI has been reported but this imaging modality has yet to be fully validated. In vitro, SEC and its ultrasonic backscatter are influenced by erythrocyte density, fibrinogen level, flow velocity and transducer frequency. The higher the frequency of the transducer, the clearer the SEC, thus, enabling observation of rouleaux formation and red cell aggregation. This phenomenon is thought to be a pro-thrombotic and systemic embolic risk factor. In the SPAF-III trial, multivariate analysis identified a correlation between LAA emptying flows $< 20$ cm/s and dense severe SEC ($P < 0.001$), LAA thrombus ($P < 0.01$) and subsequent cardioembolic events ($P < 0.01$). Dense SEC was shown to be a stronger independent predictor of all strokes (cardioembolic or not). SEC is influenced not only by LAA emptying flow but also by age, LV function, and plasma fibrinogen level. This specificity of SEC to define a local thrombogenic potential emphasizes the importance of an easy and reproducible quantitative tool severity of SEC. Anticoagulation therapy does not appear to affect the degree of SEC but can dissolve potential thrombi. As SEC is the TEE risk factor most strongly associated with thrombus and recent embolic events, it is important in the risk stratification of atrial fibrillation patients and in the decision-making in regard to long-term anticoagulation with warfarin. As the large multicenter trials (including AFFIRM and RACE studies) are encouraging the use of warfarin in most atrial fibrillation patients, clinicians remain sometimes reluctant to use it considering
the patient’s co-morbidities, age and associated treatments. New atrial fibrillation guidelines are focusing on the total risk for thromboembolism. Thus, the use of TDI and a contrast agent to calculate the TDI index may be useful to accurately quantify the severity of the SEC and aid the clinician in prescribing anticoagulation. This new parameter was more pertinent than the qualitative or the backscatter index measurements of SEC in our study. Furthermore, it is our experience that the commercially available contrast agent can enhance the visualization of the degree of SEC. In this study, the DTI index was used to quantify this observation by measuring the mean positive velocities.

Study limitations

In this first study of TDI and contrast injection to detect SEC in the LAA of patients in atrial fibrillation, we demonstrated the ability of this velocity information to characterize a ‘functional’ structure, which may have clinical significance. However, there are several limitations to our study. We did not compare TDI with radiofrequency backscatter signal but with a gray-scale level extracted from raw data after logarithmic compression and signal processing by the echo-scanner. Additionally, our study population was limited to only patients with LAA-SEC and not thrombus. However, contrast-enhanced opacification of the LAA may often help distinguish the presence of sludge or thrombus by showing a filling defect in the LAA. In the TDI analysis, only the positive components of the velocities (movement toward the transducer) were used to determine the maximal values of the region of interest, as the negative values were coded as ‘zero’ by the software.

We used on bolus of Optison to opacify the LAA cavity. Alternatively, a continuous infusion of Optison might be proposed if the relevance of this approach to quantify the SEC is confirmed.

Conclusion

We demonstrate for the first time in a comparative prospective study the ability of contrast-enhanced TDI index to quantify SEC using the mean velocities of TDI signal. It appears to be as accurate as quantification from the gray-scale information and expert qualitative analysis and it might improve our decision making in patients with atrial fibrillation. The validity of this new approach will need to be confirmed in large-scale studies.

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References


