Prognostic significance of spontaneous echocardiographic contrast detected by transthoracic and transesophageal echocardiography in the era of harmonic imaging

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Abstract

Introduction: Echocardiographic diagnosis of spontaneous intracardiac contrast is the reflection of interactions between erythrocytes and plasma proteins. Underlying conditions are associated with low blood flow velocities in the heart. We sought to determine whether spontaneous echo contrast (SEC) detected in the era of widespread use of harmonic imaging still reflects poor prognosis and risk of thromboembolism.
Material and methods: We retrospectively analyzed the database of a tertiary cardiology centre echocardiographic laboratory and identified 60 patients with SEC, but without solid intracardiac structures, and subsequently selected 60 sex- and age-matched controls without SEC. Data regarding baseline characteristics, treatment and clinical course during follow-up (median: 33.5 months; 95% CI: 24.79–40) were gained based on hospital and out-patient clinic documentation and telephone interviews. The clinical end-points included: all-cause death, cardiovascular death, stroke or transient ischemic attack (TIA), pulmonary embolism, peripheral embolism and composite thromboembolic end-point.
Results: We observed that in the whole study group (p = 0.0016) and in the subgroup evaluated by TTE (p = 0.005) SEC predicted higher mortality. In the group assessed by TEE, SEC correlated with higher probability of stroke or TIA (p = 0.04). By multivariate analysis, in all patients SEC was a predictor of cardiovascular death (OR = 7.63; p = 0.008) and its localization in the left atrium independently predisposed to thromboembolism (OR = 10.15; p = 0.012). Furthermore, left ventricular SEC detected by TTE also emerged as an independent determinant of higher mortality (OR = 5.26; p = 0.015).
Conclusions: Despite a lower threshold of detection using harmonic imaging SEC is still a risk factor of poor prognosis, especially when observed on transthoracic examination.

Key words: spontaneous echo contrast, survival, stroke, thromboembolism.

Introduction

Spontaneous echocardiographic contrast (SEC), also named "smoke" (Figure 1), is defined as an echodense whirling pattern which may be visible on either transthoracic or transesophageal echocardiogram [1, 2]. Its presence is considered to be closely related to thromboembolic events [2], even though platelets do not participate in smoke generation, because they are not echogenic. Spontaneous echocardiographic contrast is the sign of an interaction between erythrocytes and plasma proteins [3], espe-

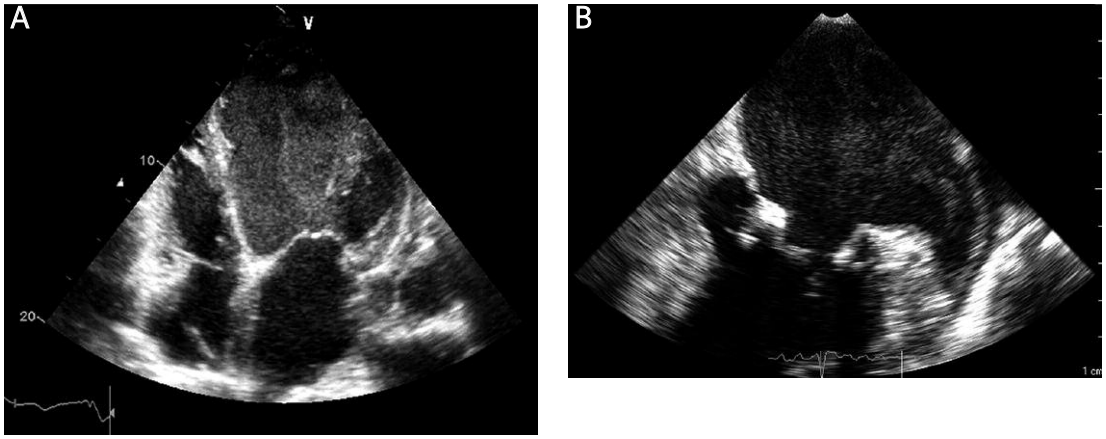

Figure 1. A – Transthoracic two-dimensional echocardiography, apical-four chamber view in a patient with dilated cardiomyopathy – SEC in dilated left ventricle. **B** – Transesophageal two-dimensional echocardiography in a patient with mitral stenosis – SEC in dilated left atrium

cially fibrinogen. This interaction between fibrinogen and erythrocytes has stoichiometric character. If the hematocrit level is relatively low, a higher concentration of fibrinogen is required for the formation of SEC and vice-versa [2]. The following entities have been identified as predisposing to the appearance of SEC: atrial fibrillation (AF), mitral stenosis, mitral valve prosthesis, left atrial enlargement, impaired myocardial contractility and decreased left ventricular ejection fraction. All of them are directly associated with reduced blood flow velocity [1, 4], which is one of the components of Virchow's triad [5, 6]. Conversely, the presence of mitral regurgitation is known as a protective condition against this phenomenon [4, 7, 8].

The prognostic significance of SEC remains unclear, especially in the era of harmonic ultrasonographic imaging and higher frequencies used for routine imaging. The majority of evidence concerning the prognostic significance of SEC was obtained before introduction and widespread use of harmonic imaging [9, 10]. It was established that harmonic mode greatly enhances the detection of SEC as compared with conventional fundamental imaging [11, 12]. However, it may be hypothesized that increased sensitivity may result in lower specificity and thus result in reduction or total abolition of the association between SEC and higher incidence of thromboembolic events as reported in the era of fundamental imaging. Therefore, we aimed to investigate the prognostic value of SEC in a heterogeneous cohort of cardiac patients undergoing transthoracic or transesophageal harmonic echocardiographic examination.

Material and methods

Patients

We retrospectively analyzed the database of reports of a tertiary cardiology centre echocardiographic laboratory containing data of 34 125 transthoracic and transesophageal examinations (both in-patients and out-patients) performed between 2001 and 2009 with the use of harmonic imaging. We identified 221 subjects with reported SEC. After exclusion of patients with additional, solid structures in cardiac cavities (vegetations, thrombi and intracardiac tumors) 161 patients were selected. Furthermore, we excluded patients with incomplete contact details in the laboratory's records and the final study group comprised 60 patients.

The control group of 60 patients (without SEC) was randomly selected from the group of subjects who were in the echo lab's database and matched the study group according to echocardiographic study type (transthoracic, transesophageal), demographic characteristics (age and gender), left ventricular ejection fraction, significant valve pathologies and approximate duration of follow-up. Patients with additional, intracardiac structures were excluded.

Information regarding baseline clinical characteristics, clinical course and treatment (including antiplatelet or anticoagulation regimen) were collected based on hospital documentation and telephone interviews using a standardized questionnaire. Presence of CAD was determined using the clinical standard – presence of symptoms, results of stress tests or coronary angiography and history of myocardial infarction or revascularization. The following endpoints were defined: all-cause death, cardiovascular death, stroke or transient ischemic attack (TIA), pulmonary embolism, peripheral embolism and composite thromboembolic end-point.

Statistical analysis

To investigate normality of data distribution we used D'Agostino-Pearson test. Differences between baseline characteristics of patients with and without SEC were assessed using Student *t* test or Mann-Whitney *U* test for independent samples

depending on normality of distribution. For dichotomous data Fisher's exact test or χ^2 test was applied. The assessment of time-to-event data was conducted by Kaplan-Meier method and survival between the study and the control group was compared using the logrank test. The effect of covariates on outcomes was determined using the Cox proportional hazard regression in a stepwise manner. The variables that significantly affected probability of an event were identified by univariate analysis and thereafter included in the multivariate model. A 2-tailed probability value lower than 0.05 was considered statistically significant.

Results

Baseline characteristics

The study population consisted of 60 patients with SEC and 60 matched controls. Within each group there were 35 subjects evaluated by transthoracic echocardiography (TTE) and 25 by transesophageal echocardiography (TEE). There were no significant differences in baseline clinical and demographic characteristics (Table I) or in baseline echocardiographic characteristics (Table II) between subjects with SEC and controls, except for right ventricular end-diastolic diameter (p = 0.03). However, compared with the control group, patients with SEC assessed by TTE were characterized by lower values of BMI than control subjects (p = 0.02), whereas the group with SEC detected using TEE had higher prevalence of atrial fibrillation (p = 0.02) and greater left ventricular end-diastolic diameter (p = 0.04) than control subjects.

In the majority of patients undergoing TTE, SEC was localized in the left ventricle (33 patients, 94%). In the TEE group SEC was detected predominantly in the left atrium (18 patients, 72%) – in most (12 patients, 48%) cases in the left atrial appendage (Table III).

Follow-up

The medians of follow-up duration were 35 months (95% CI: 20.94–46.37 months) and 33.5 months (95% CI: 22.94–40.06 months) in the group with and without SEC (p = 0.97), respectively.

During the follow-up period in the subpopulation assessed by TTE there were 12 (34%) deaths in patients with SEC and 2 (6%) deaths in controls. In patients examined by TEE there were 3 (12%) deaths in subjects with SEC. All cases of death were due to cardiovascular reasons. Furthermore, we observed 2 (6%) ischemic strokes in the TTE subgroup with SEC, 2 (6%) in the TTE subgroup without SEC, as well as 3 (12%) ischemic strokes, 1 (4%) TIA and 2 (8%) pulmonary emboli in group with SEC undergoing TEE. Moreover, in controls there was 1 (3%) pulmonary embolism (TTE) and 1 (4%) peripheral embolism (TEE).

As shown in Figure 2, SEC was associated with poorer survival (A) – hazard ratio, HR = 7.41; 95% CI: 2.86–19.17; p = 0.0016. However Kaplan-Meier curves for survival free of stroke or TIA (B) and free of any thromboembolic event (C) did not differ significantly between the group with and without smoke.

To gain insight into the factors affecting prognosis, the Cox proportional hazard regression in

Table I. Baseline demographic and clinical characteristics of the study group. Data are presented as the number (%) of patients or mean value ± standard deviation when appropriate

Parameter	Overall			TTE			TEE		
	SEC (n = 60)	No SEC (n = 60)	Value of p	SEC (n = 35)	No SEC (n = 35)	Value of p	SEC (n = 25)	No SEC (n = 25)	Value of p
Age [years]	60 ±10	61 ±10	0.75	61 ±10	62 ±9	0.62	59 ±9	58 ±10	0.93
Male, n (%)	44 (73)	44 (73)	1.00	33 (94)	33 (94)	1.00	11 (44)	11 (44)	1.00
Height [m]	1.7 ±0.08	1.7 ±0.09	0.75	1.72 ±0.07	1.72 ±0.08	0.78	1.68 ±0.09	1.67 ±0.10	0.51
Weight [kg]	77 ±15	81 ±19	0.19	73 ±14	83 ±18	0.05	79 ±15	79 ±19	0.75
BMI [kg/m^2]	26 ±4	28 ±7	0.11	25 ±4	28 ±5	0.02*	28 ±3	29 ±9	0.86
AF, n (%)	34 (57)	30 (50)	0.58	11 (31)	15 (43)	0.46	23 (92)	15 (60)	0.02*
AFL, n (%)	1 (2)	3 (5)	0.62	0	0		1 (4)	3 (12)	0.61
CAD, n (%)	42 (70)	43 (72)	1.00	27 (77)	30 (86)	0.54	15 (60)	13 (52)	0.78
Hypertension, n (%)	38 (63)	48 (80)	0.07	20 (57)	26 (74)	0.21	18 (72)	22 (88)	0.29
Diabetes, n (%)	8 (13)	12 (20)	0.46	3 (9)	4 (11)	1.00	5 (20)	8 (32)	0.52
Smoking, n (%)	18 (30)	9 (15)	0.08	12 (34)	7 (20)	0.28	6 (24)	2 (8)	0.25
Prior stroke or TIA, n (%)	8 (13)	5 (8)	0.56	3 (9)	3 (9)	1.00	5 (20)	2 (8)	0.42

*BMI – body mass index, AF – atrial fibrillation, AFL – atrial flutter, CAD – coronary artery disease, TIA – transient ischemic attack, *p < 0.05*

Table II. Baseline echocardiographic characteristics of the study group. Data are presented as the mean value ± standard deviation or number (%) of patients

Parameter	Overall			TTE			TEE		
	SEC (n = 60)	No SEC (n = 60)	Value of p	SEC (n = 60)	No SEC (n = 60)	Value of p	SEC (n = 60)	No SEC (n = 60)	Value of p
LVEF [%]	39 ±16	40 ±15	0.82	30 ±11	31 ±11	0.71	52 ±12	52 ±12	0.95
LVEDD [mm]	56 ±11	55 ±14	0.59	58 ±12	58 ±16	0.40	52 ±7	49 ±9	0.04*
LA [mm]	46 ±7	46 ±11	0.84	44 ±7	46 ±12	0.07	48 ±7	46 ±9	0.12
Ao [mm]	34 ±6	36 ±7	0.21	35 ±4	36 ±7	0.10	34 ±10	35 ±6	0.84
RA [cm^2]	14 ±2	14 ±3	0.35	14 ±2	14 ±3	0.72	14 ±2	15 ±2	0.24
RV [mm]	11 ±1	12 ±2	0.03*	11 ±1	12 ±3	0.10	11 ±1	12 ±2	0.09
Valve stenosis aortic, n (%)	1 (2)	1 (2)	1.00	1 (3)	0	1.00	0	1 (4)	1.00
Valve insufficiency, n (%):									
Mitral	8 (13)	6 (10)	0.78	7 (20)	6 (17)	1.00	1 (4)	0	1.00
Aortic	2 (3)	1 (2)	1.00	1 (3)	0	1.00	1 (4)	1 (4)	1.00
Tricuspid	4 (7)	1 (2)	0.36	2 (6)	1 (3)	0.61	2 (8)	0	0.45
Valve prosthesis, n (%):									
Mitral	6 (10)	2 (3)	0.27	0	0		6 (24)	2 (8)	0.25
Aortic	3 (5)	1 (2)	0.62	0	0		3 (12)	1 (4)	0.61

*LVEF – left ventricular ejection fraction, LVEDD – left ventricular end-diastolic diameter, LA – left atrium diameter, Ao – aorta, RA – right atrium area, RV – right ventricle diameter; *p < 0.05*

a stepwise manner was conducted. Univariate analysis revealed that SEC (odds ratio, OR = 7.62; 95% CI: 1.74–33.26; p = 0.007), its localization in the left ventricle (OR = 4.34; 95% CI: 1.65–11.40; p = 0.003) and the presence of SEC in more than one cardiac chamber (OR = 6.55; 95% CI: 1.84–23.28; p = 0.004) were significant risk factors of death. However, among these variables, only SEC reached the significance level in the multivariate analysis (OR = 7.63; 95% CI: 1.71–34.05; p = 0.008). The presence of SEC in the left atrium was a significant prognostic factor of composite thromboembolic end-point in the univariate (OR = 3.57; 95% CI: 1.01–12.60; p = 0.049) and multivariate model (OR = 10.15; 95% CI: 1.67–61.60; p = 0.012).

In comparison with controls, patients with SEC were more often prescribed anticoagulant therapy (p = 0.04) and more often suffered from bleeding complications (p = 0.01). More detailed data are shown in Table IV.

Follow-up in patients with SEC detected by TTE

The risk of death was significantly higher (HR = 6.35; 95% CI: 2.23–18.11; p = 0.005) in subjects with SEC evaluated using TTE compared with the control group (Figure 2 A).

In univariate Cox regression analysis SEC (OR = 6.51; 95% CI: 1.46–29.07; p = 0.015), the left ventricular localization of SEC (OR = 3.61; 95% CI: 1.14–11.46; p = 0.03) and the appearance of smoke in more than one cardiac chamber (OR = 5.02; 95% CI: 1.11–22.67; p = 0.037) were risk factors of higher mortality. After adjustment for other risk factors in the multivariate model only SEC in the left ventricle (OR = 5.26; 95% CI: 1.40–19.82; p = 0.015) remained a significant predictor. The presence of smoke in any other localization did not influence other end-points.

Table III. Localization of SEC. Data are presented as the number (%) of patients

Localization	All patients (n = 60)	TTE (n = 35)	TEE (n = 25)
LAA, n (%)	12 (20)	0	12 (48)
LA, n (%)	21 (35)	3 (9)	18 (72)
LV, n (%)	33 (55)	33 (94)	0
AoDesc, n (%)	2 (3)	0	2 (8)
RA, n (%)	6 (10)	3 (9)	3 (12)
RV, n (%)	2 (3)	2 (6)	0
VCI, n (%)	2 (3)	2 (6)	0
More than one chamber	5 (8)	3 (9)	2 (8)

LAA – left atrial appendage, LA – left atrium, LV – left ventricle, AoDesc – descending aorta, RA – right atrium, RV – right ventricle, VCI – vena cava inferior

Follow-up in patients with SEC detected by TEE

General survival (Figure 2 A) and survival free of composite thromboembolic end-point (Figure 2 C)

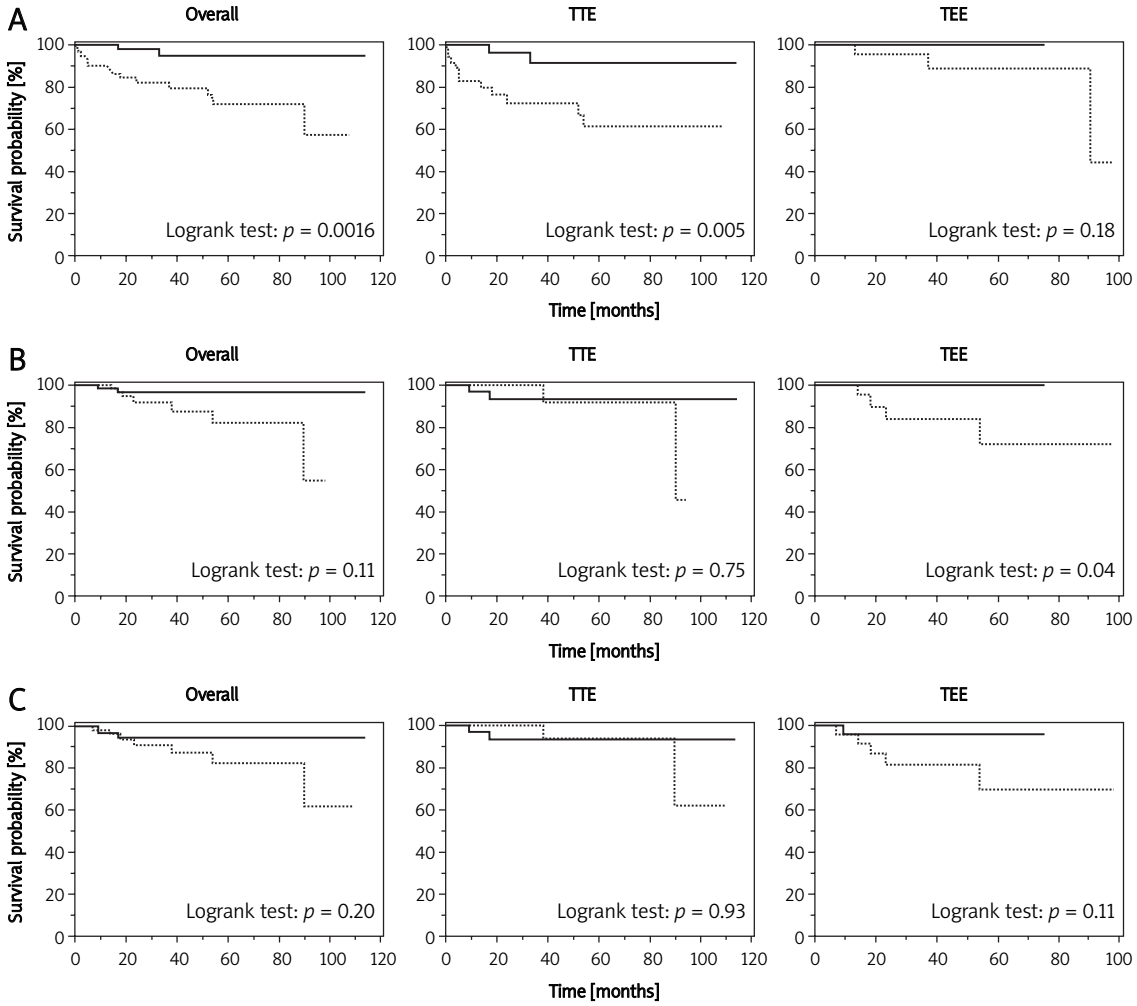

Figure 2. Kaplan-Meier curves for survival free of cardiovascular death (**A**), stroke or TIA (**B**) and thromboembolism (**C**) in group with (dashed line) and without SEC (continuous line)

did not differ significantly among patients undergoing TEE. Subjects with SEC had higher probability of stroke or TIA ($p = 0.04$) (Figure 2 B).

Univariate analysis showed that the presence of SEC in more than one cardiac chamber predicted death (OR = 23; 95% CI: 1.46–362.57; $p = 0.027$). However, in the multivariate model this covariate did not remain statistically significant.

In the TEE group, patients with coincident atrial fibrillation ($p = 0.26$) or mitral prosthesis ($p = 0.53$) did not have significantly higher probability of a thromboembolic event and moreover anticoagulant regimen also did not significantly change prognosis in this aspect ($p = 0.34$).

Discussion

Our case-control study indicates that in the era of harmonic imaging SEC remains an important prognostic factor. Survival analysis revealed that the presence of SEC was associated with higher mortality in the group of patients with SEC. This relationship was present in patients with SEC detected by TTE, whereas in the subgroup with SEC detected by TEE it did not reach statistical significance. However, in the TEE group SEC correlated with higher probability of stroke or TIA.

Spontaneous echo contrast may be visible by TTE, but it is described more often in TEE studies [6, 9, 13, 14]. In previous studies SEC was recognized as a relatively rare finding on TTE [6, 13]. We found no study about SEC detected by TTE in the context of further clinical prognosis, except for retrospective research on echocardiographic data of patients with diagnosed stroke [15]. Most previous studies concerning SEC have focused on risk factors predisposing to its occurrence [1–4, 16] or its associations with previous thromboembolism and with the coincidence of formed cardiac thrombi [9, 16–18].

The majority of previously published studies regarding SEC did not take into consideration its various localizations. We assessed the prognosis of patients with SEC detectable in any cardiac cavity. In a retrospective analysis Mahajan *et al*. proved

Table IV. Antiplatelet and anticoagulant therapy in the study group. Data are presented as the number (%) of patients

Parameter	Overall			TTE			TEE		
	SEC (n = 60)	No SEC (n = 60)	Value of p	SEC (n = 60)	No SEC (n = 60)	Value of p	SEC (n = 60)	No SEC (n = 60)	Value of p
Antiplatelet therapy, n (%)	26 (43)	39 (65)	0.03*	22 (63)	25 (71)	0.61	4 (16)	14 (56)	< 0.01*
Acetylsalicylic acid, n (%)	26 (43)	38 (63)	0.04*	22 (63)	25 (71)	0.61	4 (16)	13 (52)	0.02*
Clopidogrel, n (%)	6 (10)	11 (18)	0.30	6 (17)	6 (17)	1.00	0	5 (20)	0.05
Ticlopidine, n (%)	1 (2)	0	1.00	1 (3)	0	1.00	0	0	
Anticoagulant therapy, n (%)	33 (53)	21 (35)	0.04*	10 (29)	9 (26)	1.00	23 (92)	12 (48)	0.001*
Acenocoumarol, n (%)	29 (47)	20 (33)	0.13	10 (29)	9 (26)	1.00	19 (76)	11 (44)	0.04*
Warfarin, n (%)	4 (7)	1 (2)	0.36	0	0		4 (16)	1 (4)	0.35
Bleeding complications, n (%)	13 (22)	3 (5)	0.01*	4 (11)	1 (3)	0.36	9 (36)	2 (8)	0.04*

*$p < 0.05$

that left ventricular SEC is a significantly more common finding in patients with severe systolic dysfunction in sinus rhythm who suffered from cardioembolic stroke in comparison with age and gender-matched controls without stroke ($p < 0.01$). However, the authors did not assess SEC in the aspect of its independent impact on prognosis [15]. Spontaneous echo contrast detected in the left ventricle is a visible marker of abnormal contractility, decreased ejection fraction and complex hemorheologic abnormalities. All these conditions lead to adverse prognosis. Abnormal ejection fraction is usually followed by other comorbidities additionally affecting survival [19]. Spontaneous echo contrast has been proved to be a phenomenon independently integrated with elevated whole blood viscosity and higher concentrations of fibrinogen, and it should be considered in the context of hemorheologic imbalance. This effect can be additionally heightened by concomitant metabolic disorders, such as hyperlipidemia [20], hyperinsulinemia and insulin resistance [21].

In our study, SEC present in the left atrial cavity was associated with subsequent thromboembolic events in all subjects. This is consistent with previous studies [6, 9] performed by means of TEE in the era of fundamental imaging. Left atrial SEC detected by TEE has been proved to be independently related to previous thromboembolism or the incidence of thrombi [6, 9, 14, 22]. Leung *et al*. showed that smoke situated in the left atrium found at TEE predicted higher probability of stroke or other embolism ($p = 0.003$) and higher probability of death ($p = 0.02$). The authors documented SEC as an independent marker of stroke or other embolic events [10]. In another study on patients with dilated cardiomyopathy, SEC in the left atrium ($p = 0.03$), but not in the aorta, was a predictor of thromboembolism [23]. Shen *et al*. reveled that left atrial SEC found during TEE in subjects with dilated cardiomyopathy was a predictor of worse survival ($p < 0.02$) [24].

Sadanandan *et al*. proved that SEC independently predicts cerebrovascular accidents, even more powerfully ($p = 0.03$) than the left atrial diameter or left atrial appendage emptying velocity [25]. On the other hand, in a literature review Patel *et al*. evaluated the safety of early cardioversion for atrial fibrillation in subjects with SEC visualized by TEE and they concluded that regardless of anticoagulation, risk of acute ischemic stroke as an early complication of such therapy is low [26].

Steinberg *et al*. reported that smoke in the descending aorta independently predisposed to myocardial infarction ($p < 0.005$) and cardiac death ($p < 0.0001$) [27]. However, in our study we could not confirm these findings due to the low number of patients with SEC in the descending aorta in our group.

Limitations of our study include retrospective structure and a relatively small group of patients. Furthermore, echocardiographic examinations were carried out by several operators and assessment of particular parameters might be influenced by the subjectivity of echocardiographers. In particular, individual thresholds for usual detection and propensity to report this phenomenon might vary. However, the control group was derived from the studies performed by the same operators of echo systems. The efficiency of the anticoagulant regimen could not be determined during the entire follow-up period because of our study design.

In conclusion, the most important aspect of this article is that the presence of SEC as reported in the state of our routine echocardiograms has significant adverse prognostic implications even despite a lowered threshold of detection and higher sensitivity in the era of harmonic imaging. Further prospective studies in a larger group of patients are necessary to clarify the raised issues.

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