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Research Article

Investigation of Left Atrial Spontaneous Echo Contrast as a Marker Indicating Ineffective Anticoagulation in Patients with Mitral Valve Replacement Receiving Warfarin

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Abstract

Objectives: This study aimed to evaluate predictive role of left atrial (LA) spontaneous echo contrast (SEC) for ineffective anticoagulation by assessing time in therapeutic range (TTR) via international normalized ratio (INR) monitoring in patients with mitral valve replacement (MVR) and to determine its relationship with increased thromboembolic events.

Methods: The study included patients with mechanical MVR. TTR was estimated using serial INR measurements. On transthoracic echocardiography, left ventricular end-systolic/end-diastolic diameters, LA diameter, ejection fraction were measured, and the presence of SEC was determined.

Results: The study included 65 patients with MVR (30 with LA SEC) and 35 without LA SEC. There was a trend for higher rates of cerebrovascular event in the patients with SEC than in those without (30% vs. 14.3%, p=0.046). The LA diameter was higher and the TTR was lower in the patients with SEC than in those without. There was a significant negative correlation between TTR and thromboembolic events. Multivariable logistic regression analysis revealed the TTR and LA diameter as independent factors affecting SEC.

Conclusion: In patients with MVR, low TTR and enlarged left atrium were independent predictors for future thromboembolic events. Monitoring INR is important to achieve higher TTR in the presence of LA SEC.

Keywords: International normalized ratio, mitral valve replacement, spontaneous echo contrast, time in therapeutic range, warfarin

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Anticoagulant treatment is of importance for prevention of thromboembolic complications in patients undergoing mechanical valve replacement. In case of using a vitamin K antagonist (such as warfarin) for this purpose, it is rather important to monitor bleeding and thromboembolic complications; thus, international normalized ratio (INR) should be maintained within therapeutic ranges recommended in the guidelines. On the other hand, the relationship between warfarin dose and INR value is unpredictable and INR value may considerably vary among patients as well as in an individual patient over time.[1] Moreover, the relationship between warfarin dose used and anticoagulant effect achieved is also variable and often unpredictable; many drugs, foods, and comorbid diseases

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can alter metabolism and thereby activity of warfarin.[1] This is due to the fact that warfarin is mainly metabolized by the cytochrome P450 system that is involved in the metabolism of many drugs and is a major source of drug-drug interactions.[1]

Warfarin activity is determined by the time in therapeutic range (TTR) which is calculated by serial INR measurements in recent studies investigating novel oral anticoagulants.[2] Previous studies have stated that TTR should be between 58% and 65% of the threshold value.[3] It has been demonstrated that a TTR of >70% reduces stroke risk in patients with atrial fibrillation (AF) and that a TTR of >60-65% is associated with a reduction in thromboembolic events.[4–7]

Spontaneous echo contrast (SEC) detected in the left atrium by transthoracic and transesophageal echocardiography is a dynamic image that appears as slowly swirling, smoke-like echoes. Previous studies have shown that several hematological and hemorheologic factors, such as blood flow velocity within the lumen and shear stress below a critical threshold, interactions between plasma proteins and red blood cells, and roll formation of red blood cells and anti-cardiolipin antibodies, may be responsible for SEC formation within the heart and great vessels. Presence of SEC on echocardiography has also been reported to be significantly associated with thrombus formation and thromboembolic events.[8–13]

In the present study, it was aimed to investigate whether left atrial (LA) SEC on echocardiography could be a marker of ineffective anticoagulation by assessing TTR via INR monitoring in patients with mitral valve replacement (MVR) and to determine the relationship of LA SEC with increased thromboembolic events.

Methods

Patients who had mechanical MVR and were followed in the Cardiology Department of Kayseri Training and Research Hospital were included in the present study. In patients, history of cerebrovascular events was recorded. The patients were classified as those with LA SEC and those without LA SEC based on their transthoracic echocardiography (TTE) examination. Exclusion criteria included having a recent history of surgical intervention, presence of a severe left ventricular (LV) systolic dysfunction (an ejection fraction (EF) of <35%), having isolated atrial valve replacement, having a history of acute coronary syndrome or cerebrovascular disease within the last 12 months, having valvular dysfunction, presence of disorders associated with acute phase reaction (such as infectious diseases and connective tissue diseases), presence of malignancy, presence of severe hepatic or renal failure, pregnancy, and use of aspirin or any anti-platelet agent. However, the primer aim of this study was evaluation of serebrovascular event risk according to SEC presence, the presence of left atrial thrombus was not determined by transesophageal echocardiography. The study was approved by the Local Ethics Committee and all patients provided written informed consent.

Patients' data regarding age, comorbid conditions such as diabetes mellitus, AF, previous thromboembolic event or coronary artery disease, smoking history, and medications were recorded. A comprehensive physical examination and electrocardiographic evaluations were performed in all patients. A 5 mL of blood into a standard tube and a 3 mL of blood into an EDTA-containing tube were collected from each patient for biochemical evaluations and complete blood count, respectively. In patients on warfarin treatment, percent TTR was estimated using serial INR measurements. Standard transthoracic and echocardiographic measurements were performed in all patients.

Echocardiographic Evaluation

Echocardiographic evaluation was performed in all patients at the lateral decubitus position after 5 min of resting using Philips HD 11 echocardiography device (Philips Medical System, Andover, USA) with a 3 MHz transducer. LV end-systolic diameter (LVESD), LV end-diastolic diameter (LVEDD), aortic root diameter, and LA diameter were measured on the parasternal long-axis view. EF was automatically calculated by the device using the Teicholz method. Mean and peak gradients of mitral valve were determined using continuous wave Doppler.

Two independent cardiologists assessed the presence of LA SEC on the parasternal and apical four-chamber views using gain settings of the echocardiography device. The presence of SEC was defined as a slowly swirling, smoke-like dynamic echo. The intensity of SEC was graded as follows: 1) Grade 0 (none), no change in echogenicity suggesting SEC at the left atrium (none), 2) Grade 1 (mild), SEC that can be occasionally seen during the cardiac cycle by gain settings at the LA main cavity, 3) Grade 2 (moderate), more intense SEC that can be seen both at the LA appendix and at the LA cavity throughout the cardiac cycle, and 4) Grade 3 (severe), SEC that can be readily seen as very slow but more intense swirling pattern across the left atrium at the lowest gain setting.[14–16]

Prosthetic valve thrombus was defined as homogeneous, smooth echo-density originating from the occluder or the valvular ring. Prosthetic valve thrombus can be discriminated from the suture line attaching to the annular ring and can limit the movements of mechanical valve occluder. Pannus was defined as fixed echo-densities accumulated

at the annulus and can extend to orifice as a continuum. Pannus can be brighter than thrombus and may involve calcification.[17, 18]

Measurement of International Normalized Ratio

The INR is used for monitoring effectiveness of anticoagulant agents, such as warfarin. In all patients, blood samples were drawn into sodium citrate (9:1 v/v) tubes and plasma INR level was studied within 4 hours after sampling by the Stago STA Compact analyzer (USA) using a coagulation method. In each patient, the warfarin dose was titrated to maintain a target INR level compatible with the treatment. The TTR was calculated based on 5 INR measurements performed at 3-week intervals assuming the lowest value accepted for effective anticoagulation as 2.0 and the maximum value accepted for increased bleeding risk as 4.0. The TTR was calculated using the following formula: TTR = number of measurements within range / total number of measurements.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS., Inc., Chicago, IL, USA) for Windows version 10.0. Descriptive statistics were expressed as mean and standard deviation and number (percentage, [%]). Quantitative data were compared using Student's t test or Mann-Whitney U test, where appropriate, whereas qualitative data were compared using Chi-square test or Fisher's exact test, where appropriate. Multivariable analysis using backward stepwise logistic regression was performed to identify independent predictors. A p value of <0.05 was considered statistically significant.

Results

The study included 65 patients with MVR, of whom 30 had LA SEC (mean age, 51.8±8.3 years; male/female: 11/19) and 35 had no LA SEC (mean age, 50.7±10.3 years; male/female: 10/25) based on the TTE examination. In the group with SEC, 28 patients had grade 1 SEC and 2 patients had grade 2 SEC. The demographic and general characteristics of the patients with and without SEC are presented in Table 1. No significant differences were determined between the groups in terms of demographic and general characteristics. 15 patients (%50) with atrial fibrillation in SEC positive group, 13 patients (%37) with atrial fibrillation in SEC negative group. There was no statistical difference between in these groups (p=0.156). The history of cerebrovascular event was present in 9 (30%) patients in the group with SEC and in 5 (14.3%) patients in the group without SEC; the difference was statistically significant (p=0.046). All cerebrovascular events were caused by thromboembolism.

The hematological and biochemical data of the patients with and without SEC are presented in Table 2. As roll formation of erythrocytes is thought as an important mechanism for SEC formation, hemoglobin levels were compared between the patients with and without SEC; however, no significant difference was determined between the groups (p=0.379). Similarly, the patients with and without SEC did not differ in terms of platelet count and mean platelet vol-

Table 1. Demographic and general characteristics of the patients with and without spontaneous echo contrast

Characteristics	Patients with SEC n=30	Patients without SEC n=35	p
Age, years, Mean±SD	51.8±8.3	50.7±10.3	0.631
Male/Female, n/n	11/19	10/25	0.377
Hypertension, n (%)	14 (46.7)	14 (40.0)	0.306
Diabetes mellitus, n (%)	5 (16.7)	7 (20.0)	0.540
Atrial fibrillation, n (%)	15 (50.0)	13 (37.1)	0.156
Coronary artery disease, n (%)	6 (20.0)	5 (14.3)	0.345
Cerebrovascular event, n (%)	9 (30.0)	5 (14.3)	0.046
Smoking, n (%)	13 (43.3)	11 (31.5)	0.177

SEC: spontaneous echo contrast; SD: standard deviation.

Table 2. Hematological and biochemical data of the patients with and without spontaneous echo contrast

	Patients with SEC n=30 Mean±SD	Patients without SEC n=35 Mean±SD	p
WBC, 10^3/uL	7.0±2.3	6.9±1.9	0.955
Hemoglobin, g/dL	13.3±2.2	13.7±1.7	0.379
Platelet, 10^3/uL	260.0±74.0	255.0±63.0	0.783
MPV, fL	9.9±0.8	9.9±0.9	0.979
PDW, ratio	15.8±0.3	16.0±0.3	0.057
Sedimentation rate, mm/h	15.7±14.3	14.3±15.9	0.727
CRP, mg/L	6.5±6.1	9.3±20.4	0.484
Glucose, mg/dL	102.0±20.0	106.0±28.0	0.526
Creatinine, mg/dL	1.16±0.2	0.8±0.2	0.329
ALP, U/L	90.0±34.0	91.0±54.0	0.934
Total bilirubin, mg/dL	0.7±0.4	0.8±0.4	0.699
Direct bilirubin, mg/dL	0.17 ± 0.08	0.16±0.08	0.891
Uric acid, mg/dL	5.6±1.8	5.4±1.7	0.720
LDH, U/L	453.0±207.0	476.0 ± 204.0	0.648
GGT, U/L	56.0±58.0	53.0 ±58.0	0.838
D-dimer, µg/L	254.0±429.0	198.0±211.0	0.498
Fibrinogen, mg/dL	349.0±90.0	351.0±107.0	0.926

SEC: spontaneous echo contrast; SD: standard deviation; WBC: white blood cell; MPV: mean platelet volume; PDW: platelet distribution width; CRP: C-reactive protein; ALP: alkaline phosphotase; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transferase.

ume (MPV) (p>0.05 for both); however, there was a trend for significance for platelet distribution width (PDW) values between the groups (p=0.057).

Evaluation of biochemistry results revealed no significant differences between the patients with and without SEC in terms of erythrocyte sedimentation rate (ESR) and the levels of C-reactive protein (CRP), uric acid, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and bilirubin, which can be considered markers of inflammatory process (p>0.05 for all). Moreover, no significant differences were determined between the patents with and without SEC in terms of the results of hepatic and renal function tests (creatinine, bilirubin, GGT, alkaline phosphatase) and biochemical markers of thromboembolic events including D-dimer and fibrinogen levels (p>0.05 for all).

Transthoracic echocardiography findings of the patients with and without SEC are presented in Table 3. According to the TTE findings, the mean LVEF, LVESD, and LVEDD were comparable between the patients with and without SEC (p>0.05 for each). The mean LA diameter was found to be significantly higher in the patients with SEC than in those without SEC (p=0.002). Although the difference between the patients with and without SEC was not significant in terms of prosthetic valve area and mitral valve peak and mean gradients, there was a trend to a higher mean gradient and a lower valve area in the patients with SEC as compared with those without SEC (p=0.089 and p=0.093, respectively).

The mean TTR was found to be significantly lower in the patients with SEC than in those without SEC (66.2±22.7% and 86.1±12.4%, respectively; p<0.001). The correlation analysis revealed a significant negative correlation between TTR and any thromboembolic event (r=-0.263, p=0.034).

The results of multivariable logistic regression analysis are presented in Table 4. Accordingly, the TTR and LA diameter were found as independent factors affecting SEC development (p=0.001 and p=0.005, respectively). Although there was a correlation between SEC development and mean gradient of the replaced valve, it did not reach statistical significance as an independent risk factor (p=0.097).

Table 3. Transthoracic echocardiography findings of the patients with and without spontaneous echo contrast

	Patients with SEC n=30 Mean±SD	Patients without SEC n=35 Mean±SD	p
LVESD, cm	3.2±0.7	3.07±0.7	0.321
LVEDD, cm	4.6±0.6	4.4±0.6	0.442
LVEF, %	56.5±11.3	61.02±12.2	0.136
LA diameter, cm	5.2±1.1	4.4±0.7	**0.002**
Aortic root diameter, cm	3.1±0.4	3.1±0.3	0.503
MV peak gradient, mmHg	21.4±3.8	16.3±2.9	0.304
MV mean gradient, mmHg	4.2±1.5	3.7±1.09	0.089
MVA, cm^2	2.3±0.8	2.5±0.7	0.093

SEC: spontaneous echo contrast; SD: standard deviation; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LA: left atrial; MV: mitral valve; MVA: Mitral valve area.

Discussion

In the present study conducted on the patients with MVR, a significant difference was found between those with and without SEC in terms of thromboembolic events. The rate of previous thromboembolic events was significantly higher in the patients with SEC than in those without. In addition, the TTR and LA diameter were found as independent predictors for the presence of SEC in the patients with mechanical mitral valve prosthesis.

Thromboembolism represents one of the most important causes of morbidity and mortality in patients with prosthetic valve.[19] The annual incidence of thromboembolic complications ranges from 0.7 to 3.1% in patients with MVR.[19] Fluctuations in INR level are one of the factors affecting the incidence of thromboembolism during treatment. In addition, it has been found that presence of SEC, a common finding in patients with prosthetic valve, has a significant association with thrombus formation; that is, it may be an alarming sign for thrombus and thromboembolic events.[13]

In a study on patients with non-valvular AF, Tsai et al.[12] found the history of peripheral and cerebral embolism to be more common in patients with LA SEC. Moreover, they reported the rate of anticoagulant drug use as 20% in patients with LA SEC and attributed higher rates of thromboembolic events in this group to inadequate anticoagulation.[12] LA thrombus is frequently observed in studies investigating SEC.[21]

Table 4. Predictive factors for the presence of spontaneous echo contrast in the patients with mitral valve replacement by multivariable logistic regression analysis

Variables	OR	95% CI	p	OR	95% CI	p
TTR	0.940	0.907-0.973	0.001	0.931	0.895-0.969	0.001
LA diameter	2.329	1.298-4.177	0.005	2.779	1.415-5.461	0.003
Mean gradient	1.407	0.940-2.105	0.097			

OR: odds ratio; CI: confidence interval; TTR: time in therapeutic range; LA: left atrial.

In addition to association of SEC with thrombus formation, its association with other clinical and echocardiographic findings has also been frequently evaluated. In their study on patients with dilated cardiomyopathy, Siostrzonek et al.[8] investigated the effects of rheological factors on the development of LA thrombus and found no significant differences in cardiac index, LA diameter, and AF between the study groups. In the present study, while increased LA diameter was found as an independent predictor for SEC development, LVEF, LVESD, and LVEDD were not found as independent predictors. This result is consistent with previous data and it may be suggested that enlarged left atrium can contribute to formation of SEC and thrombus by decelerating blood flow and decreasing contractile function. In 1856, Virchow[22] defined injured vessel wall, alterations in blood flow (stasis), and hypercoagulability as primary causes of thrombus. Increased LA volume may predispose to stasis and lead to thrombus formation especially in patients with AF.

In the present study, LA SEC was observed to be more common in the patients with AF; however, the difference did not reach statistical significance. In their study on 272 patients with non-valvular AF, Leung et al.[23] detected SEC in 161 (59%) patients and reported the annual incidence of stroke or embolism as 12% in the patients with SEC and as 3% in the patients without SEC during a 17-month follow-up period. In the presence of AF, stasis occurs in blood flow due to decrease in contractile function of the left atrium and the risk for thromboembolic complications increases. Although the presence of SEC in the patients with AF was more frequent in the present study, the lack of a statistical significance was attributed to the relatively small sample size. The decrease in LVEF may also lead to SEC formation by causing stasis. In their study on patients with (n=42) and without (n=40) SEC, Chimowitz et al.[24] found that LV dysfunction was significantly higher in the patients with SEC. Accordingly, in the present study, which aimed to identify the association between the presence of SEC and anticoagulant therapy, the patients with LV dysfunction were excluded by considering LV dysfunction as an independent factor for SEC development.

In the present study, TTR was found to be negatively correlated with the presence of SEC. A significant difference was determined between the patients with and without SEC in terms of TTR levels. The presence of LA SEC was less commonly observed in the patients with higher TTR levels under warfarin use. In the logistic regression analysis, TTR was identified as an independent factor having decreasing effect on the SEC development. In other words, the presence of SEC in the patients with MVR could be considered as a retrospective sign of insufficient anticoagulant levels.

The risk for thromboembolism was found to be higher in the patients with lower TTR. In the patients with SEC, a significant negative correlation was determined between TTR and history of thromboembolic events. It was thought that the presence of SEC could be a marker for low TTR as well as a predictor for increased risk for stroke. In the study by Leung et al.,[23] the annual incidence of embolism was reported as 5% and 2.2% in the patients with and without SEC, respectively, who had no history of thromboembolism. In multivariable analysis, Leung et al.[23] showed that SEC was the only positive predictor, whereas anticoagulant therapy was the only negative predictor for the prevention of thromboembolic events.

Conclusion

In conclusion, low TTR and enlarged LA were found as independent predictors for future thromboembolic events in the patients with a history of MVR. In mitral valve disorders, while deciding surgery as well as the optimal surgical time and the features of the valve to be used, taking the enlargement of the left atrium into account could contribute to decrease thromboembolic complications at the postoperative period. In patients with MVR, it is also important to monitor INR value of the patients in order to achieve higher TTR in case left atrial SEC is detected.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee (Kayseri Training and Research Hospital EPK-2014/018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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