Effect of left ventricular diastolic dysfunction on left atrial appendage function and thrombotic potential in nonvalvular atrial fibrillation

Muhammed Bora Demirçelik, Mustafa Çetin[1], Hülya Çiçekcioğlu[1], Özgül Uçar[1], Mustafa Duran[2]

Deparment of Cardiology, Faculty of Medicine, Fatih University; Ankara-*Turkey*
[1]Clinic of Cardiology, Ankara Numune Education and Researching Hospital; Ankara-*Turkey*
[2]Clinic of Cardiology, Kayseri Education and Researching Hospital; Kayseri-*Turkey*

Abstract

Objective: We aimed to investigate effects of left ventricular diastolic dysfunction on left atrial appendage functions, spontaneous echo contrast and thrombus formation in patients with nonvalvular atrial fibrillation.

Methods: In 58 patients with chronic nonvalvular atrial fibrilation and preserved left ventricular systolic function, left atrial appendage functions, left atrial spontaneous echo contrast grading and left ventricular diastolic functions were evaluated using transthoracic and transoesophageal echocardiogram. Patients divided in two groups: Group D (n=30): Patients with diastolic dysfunction, Group N (n=28): Patients without diastolic dysfunction. Categorical variables in two groups were evaluated with Pearson's chi-square or Fisher's exact test. The significance of the lineer correlation between the degree of spontaneous echo contrast (SEC) and clinical measurements was evaluated with Spearman's correlation analysis.

Results: Peak pulmonary vein D velocity of the Group D was significantly higher than the Group N (p=0.006). However, left atrial appendage emptying velocity, left atrial appendage lateral wall velocity, peak pulmonary vein S, pulmonary vein S/D ratio were found to be significantly lower in Group D (p=0.028, p<0.001, p<0.001; p<0.001). Statistically significant negative correlation was found between SEC in left atrium and left atrial appendage emptying, filling, pulmonary vein S/D levels and lateral wall velocities respectively (r=-0.438, r=-0.328, r=-0.233, r=-0.447). Left atrial appendage emptying, filling, pulmonary vein S/D levels and lateral wall velocities were significantly lower in SEC 2-3-4 than SEC 1 (p=0.003, p=0.029, p<0.001, p=0.002).

Conclusion: In patients with nonvalvular atrial fibrillation and preserved left ventricular ejection fraction, left atrial appendage functions are decreased in patients with left ventricular diastolic dysfunction. Left ventricular diastolic dysfunction may constitute a potential risk for formation of thrombus and stroke. *(Anadolu Kardiyol Derg 2014; 14: 256-60)*

Key words: diastolic dysfunction, atrial appendage function, thrombus formation, atrial fibrillation

Introduction

Atrial fibrillation (AF) is a chronic arrhythmia encountered most frequently in clinical practice and confers a 5-fold risk of stroke (1). In patients with AF, impairment in left ventricular (LV) systolic functions leads to increased LV and left atrium (LA) filling pressures along with function loss in left atrial appendage (LAA), blood stasis and hence to spontaneous echo contrast (SEC) and formation of thrombus (2, 3). Likewise, in patients with disturbed diastolic function, increasing LV end-diastolic pressure and LA pressure give rise to decrease in filling and emptying velocities of LAA (2, 3).Thus, as blood stasis and formation of SEC will be enhanced in LAA, the formation of thrombus will be facilitated. So evaluation of the left atrial appendage functions in patients with diastolic dysfunction are important by transesophageal echocardiography (TEE). SEC and thrombus formation also gaining importance in the relationship between the functions of LAA in these patients. Studies evaluating LAA function by TEE are less frequent in the literature especially in patients with nonvalvular atrial fibrillation. The aim of the present study was to investigate the effect of LV diastolic dysfunction on LAA functions, SEC and thrombus formation.

Methods

Study design and patient selection

This study was designed as an observational study. After approval was obtained from ethics committee, we enrolled con-

Address for Correspondence: Dr. Muhammed Bora Demirçelik, Vatan Cad.
No: 81 Demetevler, Ankara-*Türkiye*
Phone: +90 312 346 22 22-3003 E-mail: drdemircelik@yahoo.com
Accepted Date: 24.06.2013 **Available Online Date:** 10.01.2014

DOI:10.5152/akd.2014.4833

secutive 58 patients with nonrheumatic, paroxysmals or persistent AF from January 2007 to March 2009 who underwent transthoracic echocardiography and transesophageal echocardiography within a 30-day period. We confirmed presence of AF in each patient by ≥1 AF episode documented with electrocardiography (Nihon Kohden Corporation ECG 1250K Tokyo, Japan). We excluded patients with valvular stenosis or previous valve surgery. We also excluded patients with pacemaker or with New York Heart Association class IV heart failure, because E/e′ might not properly estimate LV filling pressure in these patients (3). If a patient underwent multiple transthoracic or transesophageal echocardiographic examinations, we chose the earliest examination as an index study. Patients with other arrhythmia were excluded (e.g. SVT, VT). Those with previous use of anticoagulant drug, who have moderate or severe valve deficiency, whose LV ejection fraction (EF) was below 50% were not included in the study and instantly diastolic heart failure hospitalization were excluded.

Study protocol and definitions

We confirmed presence of AF in each patient by ≥1 AF episode documented with electrocardiography. (Nihon Kohden Corporation ECG 1250K Tokyo, Japan) After informed consent was obtained from the patients, all patients underwent transthoracic (TTE) and transoesophageal echocardiogram (TOE) (6 MHz transducer GE Medical Systems VIVID 7). In TTE if the ratio of mitral early diastolic (E) velocity obtained from mitral valve tips with pulsed wave Doppler using apical four-cavity imaging to Ea velocity measured from lateral mitral annulus with tissue Doppler was over 11 and if in TOE pulmonary systolic/diastolic (S/D) ratio was less than 1, measurements averaged over 5 to 10 cardiac cycles, the subject was considered to have diastolic dysfunction (4). LAA area, and LAA emptying and filling velocities were measured with TOE. LAA velocity values were obtained by placing pulsed wave Doppler to the orifice of LAA. Gradings of the LA and LAA SEC were made according to the scale below:

0: No echogenity is detected in LAA

+1 Mild SEC: It can not be determined without increasing gain. Minimal echogenity determined temporarily during cardiac cycle (Gain value larger or equal to 10 dB is considered high gain).

+2 Mild-Moderate SEC: A turbulance like form more intensive than +1, but location is the same as +1. It can be determined without increasing gain.

+3 Moderate SEC: In LAA, intensive turbulance like movement occurs throughout all cardiac cycle. It is less intense in LA.

+4 Severe SEC: In LAA and LA cavity, intensive echo density and very slow turbulant flow is present.

Statistical analysis

All statistical analysis assessments were done using Statistical Package for Social Science (SPSS) for Windows 11.5. Whether the continuous variables were distributed normally was investigated by Shapiro Wilk test. Descriptive statistics were expressed as mean±standard deviation for continuous variables and as the number of cases and (%) for categorical variables. The difference between groups in terms of normally distributed continuous variables was analysed with Student's t test and the significance of the difference between continuous variables not normally distributed with Mann-Whitney U test. Categorical variables were evaluated with Pearson's chi-square or Fisher's exact test. The significance of the lineer correlation between the degree of SEC and clinical measurements was evaluated with Spearman's Correlation analysis. P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

In this study diastolic dysfunction was detected in 30 patients (Group D) while it was not detected in 28 patients (Group N). Mean left ventricle ejection fraction value (LVEF) was 66.83%±7.20 in Group D and 61.82%±6.93 in the Group N (p=0.012). Mean age of the Group D was significantly higher than Group N (69.1±9.1, 63.4±12.2, p=0.049). Groups were matched in terms of sex, body mass index (BMI), hypertension, diabetes, coronary artery disease, hyperlipidemia, cerebrovascular event history and $CHADS_2$ score (p>0.05) (Table 1). There was no significant difference between Group D and Group N, with respect to LA size, LV diastolic and systolic diameters, right atrium maximum size, LAA area (p>0.05).

Correlation between TEE parametres and SEC, thrombus

However, in Group D, pulmonary vein D level was found to be significanly higher than group N (p=0.006) while, LAA emptying and filling velocity, LAA lateral wall velocity and pulmonary vein S/D levels were significantly lower than Group N (p=0.028, p<0.001, p<0.001, p<0.001) (Table 2). Thrombus in group D was higher than group N (p=0.03) (Table 3). No significant correlation was found between SEC in left atrium and age, BMI, left and right atrium size, LAA area (p > 0.05) Nevertheless, negative correlation was found between SEC in LA and respectively, LAA emptying, filling, pulmonary vein S/D levels and lateral wall velocities (r=-0.438, r=-0.328, r=-0.233, r=-0.447) (Table 4).

In LA, no statistically significant difference was found between grade 1 SEC group and Grade 2-3-4 SEC groups with respect to mean age, sex, MI, hypertension, heart failure, LA size, maximum size of right atrium (p>0.05).

There was significant difference between groups with regard to LAA emptying, filling and lateral wall velocity, which was significantly lower in SEC 2-3-4 group than SEC 1 groups respectively (p=0.003, p=0.029, p<0.001, p=0.002) (Fig. 1- 3 and Table 5).

Discussion

In the present study, decrease in LAA velocities in patients with diastolic dysfunction, was established to be a marker for LAA SEC formation. This increase in SEC was not associated with LAA thrombus formation which we believe may emanate from the low numbers of patients and low risk of thrombus in the selected patient group. We also emphasized the importance of TEE to show LAA functions.

It is thought that primary source of cardioembolic ischemic stroke occurring in AF patients is the formation of thrombus in LAA. It has been shown by serial TOE examinations in LA and in LAA during conversion of AF to sinus rhythm that there is slowing of conduction velocity of LAA as a consequence of the organised mechanic contraction loss during AF (5-7). The decrease of flow in LA and LAA during AF is associated with SEC, thrombus formation and embolic events (8, 9). Especially under low flow conditions TTE or TOE imaging may detect SEC or smoke in the form of turbulant pus at varying intensity (10). Spontaneous echo contrast may be a sign of stasis related to AF (11-12).

In AF, complex thromboembolic mechanisms are influential and interaction of risk factors associated with atrial stasis, endothelial dysfunction, and systemic, perhaps local hypercoagulability is involved. In AF patients, many factors such as prior stroke, age, hypertension, diabetes, female sex, peripheral artery disease and structural heart disease play part in the increase of stroke risk. It has been shown in AF patients that LV systolic dysfunction, is associated with both LA thrombus and non-cardioembolic stroke (13). LV function is an important determinant of LAA velocities. In individuals with non-valvular AF and LV systolic dysfunction velocity of LAA was find to be lower (14). The impact of LV diastolic dysfunction on LAA velocity is less defined and diastolic dysfunction as a potential risk factor for stroke has not been systematically documented.

In the determination of LAA functions, the measurement of LAA velocity and LAA EF is the main method however in patient with AF measurement of LAA EF is not possible because there is not contraction in LAA. In the present study LAA filling and emptying velocities were found to be significantly lower in those with LV diastolic dysfunction than those who do not have it. Lateral wall velocity of LAA measured with tissue Doppler were also found to be low in the patient group with diastolic dysfunction. The measurement of LAA lateral wall velocity with TOE will be useful in demonstrating the functions of LAA.

In the early period of heart failure, LAA emptying velocity increases in order that LA hemodynamic function can be maintained, but if HF progresses, LA mechanic function is impaired and LAA emptying velocity decreases as a consequence of the drop in LAA compliance. Decrease in LAA function increases the frequency of LA thrombus development and is an important predictor of cardiac mortality. Conditions that increase the filling pressure of LV impairs LAA flow (15). In individuals with LV systolic dysfunction, increased pulmonary capillary wedge pressure, (PCWP) decreases LAA flow velocity (16). As LV diastolic dysfunction coexists with the increase in PCWP, it may similarly lead to impairment in LA functions and to decrease in LAA flow velocity (16). Increased diastolic filling pressure is associated with a higher rate of LAA thrombus in AF, partly through blood stasis or impaired LAA function.

Table 1. Demographic data in Group N and Group D

Variables	Group N (n=28)	Group D (n=30)	*P
Age, year	63.4±12.2	69.1±9.1	0.049
Female sex, n, %	15 (53.6%)	19 (63.3%)	0.451
Body mass index, kg/m^2	28.5±4.0	28.2±3.7	0.763
Hypertension, n, %	14 (50%)	19 (63.3%)	0.306
Diabetes, n, %	2 (7.1%)	3 (10%)	1.000
CAD, n, %	5 (17.9%)	5 (16.7%)	1.000
Hyperlipidemia, n, %	1 (3.6%)	2 (6.7%)	1.000
CVE, n, %	1 (3.6%)	-	0.483
$CHADS_2$ score	1.5±1.2	1.5±1.3	0.96

*Mann-Whitney U test, Student t-test
CAD - coronary artery disease; CVE - cerebrovascular event; Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction

Table 2. Echocardiographic measurements in Group N and D

Variables	Group N (n=28)	Group D (n=30)	*P
LA size, cm^2	4.61±0.71	4.72±0.53	0.494
LVED diameter, cm	4.82±0.56	4.73±0.44	0.521
LVES diameter, cm	3.20±0.48	3.02±0.52	0.176
EF, %	61.82±6.93	66.83±7.20	0.012
RA maximum size, cm^2	5.55±0.94	5.70±0.83	0.511
LAA, cm^2	3.53±1.32	3.64±1.23	0.739
LAA emptying velocity, cm/s	0.35±0.14	0.28±0.13	0.028
LAA filling velocity, cm/s	0.40±0.18	0.23±0.16	0.019
LAA lateral wall velocity, cm/s	9.11±3.79	5.93±2.96	<0.001
Pulmonary vein S wave, cm/s	0.56±0.18	0.38±0.16	<0.001
Pulmonary vein D wave, cm/s	0.40±0.14	0.53±0.19	<0.001
Pulmonary vein S/D	1.52±0.60	0.82±0.58	<0.001
Mitral E velocity, cm/s	0.90±0.17	1.06±0.20	<0.001
Mitral Ea, m/s	0.15±0.08	0.08±0.02	<0.001
Mitral E/Ea	7.06±1.51	13.71±3.90	<0.001

*Pearson's chi-square, Fisher's exact test
D - diastolic; E - pulsed Doppler E velocity; Ea - tissue Doppler E velocity; EF - ejection fraction; Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction; LA - left atrium; LAA - left atrium appendix; LVED - left ventricle end-diastolic; LVES - left ventricle end-systolic; RA - right atrium; S - systolic

Table 3. The distribution of cases according to spontaneous echo contrast (SEC) level in left atrium and the frequency of thrombus

Variables	n=58		
SEC in left atrium	**Group N (n=28)**	**Group D (n=30)**	***P**
Absent	23 (82.1%)	2 (6.7%)	0,221
Grade 1	1 (3.6%)	7 (23.3%)	0,03
Grade 2	2 (7.1%)	9 (30%)	0,041
Grade 3	1 (3.6%)	3 (10%)	NS
Grade 4	1 (3.6%)	3 (10%)	NS
Thrombus in left atrium	-	6 (20%)	0,03

*Student -t test, Mann-Whitney U testi
Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction; NS - not significant

Table 4. Correlation coefficients and p values between clinical variables and spontaneous echo contrast (SEC) grading in left atrium

Variables	Left atrium SEC grading	
	*r	*P
Age	0.238	0.072
Body mass index	0.082	0.540
LA Size	0.220	0.097
RA maximum size	0.059	0.659
LAA	0.024	0.858
LAA emptying velocity	-0.438	<0.001
LAA filling velocity	-0.328	0.012
LAA lateral wall velocity	-0.447	<0.001
Pulmonary vein S	-0.240	0.070
Pulmonary vein D	-0.183	0.169
Pulmonary vein S/D	-0.233	0.078

*Spearman's correlation analysis
D - diastolic; E - pulsed Doppler E velocity; Ea - tissue Doppler E velocity; LA - left atrium; LAA - left atrium appendix; LVED - left ventricle end-diastolic; LVES - left ventricle end-systolic; RA - right atrium; S - systolic

Table 5. Echocardiographic measurements in SEC 1 and SEC 2-3-4 groups

Variables	Group SEC 1	Group SEC 2-3-4	*P
LAA emptying velocity, cm/s	0.39±0.11	0.26±0.10	0.003
LAA filling velocity, cm/s	0.42±0.17	0.21±0.15	0.029
LAA lateral wall velocity, cm/s	8.6±2.59	5.8±2.90	<0.002
Pulmonary vein S/D	1.3±0.41	0.80±0.48	<0.001

*Student t-test, Mann-Whitney U test
D - diastolic; LAA - left atrium appendix; S - systolic

In the study of Kamp et al. (17) LAA peak emptying velocity of lower than 20 cm/sec was found to be an independent predictor for thromboembolic event in nonvalvular AF cases. Özer et al. (18) demonstrated that in patients with stroke, LAA flow velocities were lower than normal in both patients with AF and sinus rhythm. In this study, LAA peak emptying velocity was lower in patients with diastolic dysfunction, and also, in patients with high grade SEC. Accordingly, we suggest that diastolic dysfunction may confer risk for SEC and stroke in patients with nonvalvular AF and preserved LV ejection fraction. Similarly, in a study carried out by Ito et al. (19) on 41 patients with dilated cardiomyopathy at sinus rhythm, in patients with stage 3 diastolic dysfunction, LAA flow velocity was found to be lower than those with stage 2 diastolic dysfunction (20, 21). But that study enrolled patients with systolic dysfunction and sinus rythm.

Study of limitations

The most important limitation of our study was the number of patients to be less. Although a common arrhythmia is atrial fibrillation society, difficult to find that the working conditions of the patient. Another limitation of our study was the lack of homogeneity in the SEC's groups. But you would not know in advance because groups's $CHADS_2$ scores were similar.

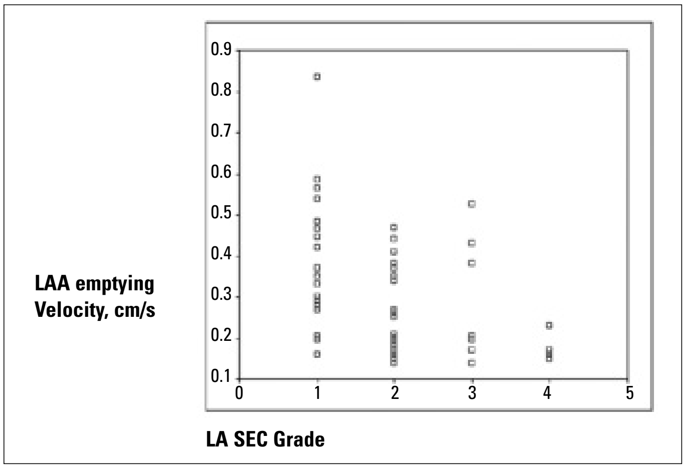

Figure 1. Distrubition graphic of spontaneous echo contrast (SEC) grade in left atrium (LA) and left atrium appendage (LAA) emptying velocity

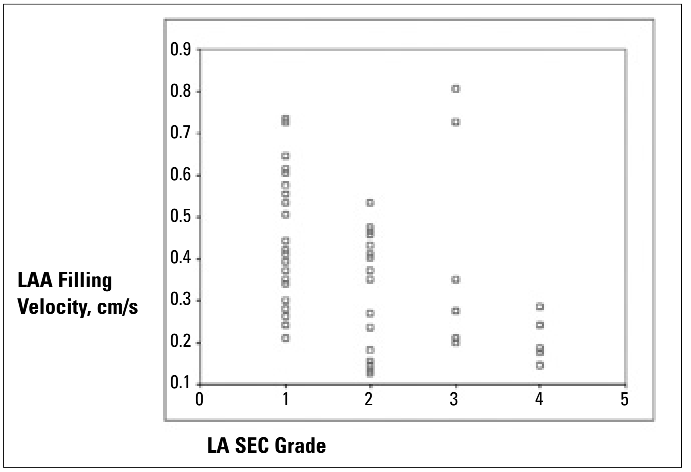

Figure 2. Distrubition graphic of spontaneous echo contrast (SEC) grade in left atrium (LA) and left atrium appendage (LAA) filling velocity

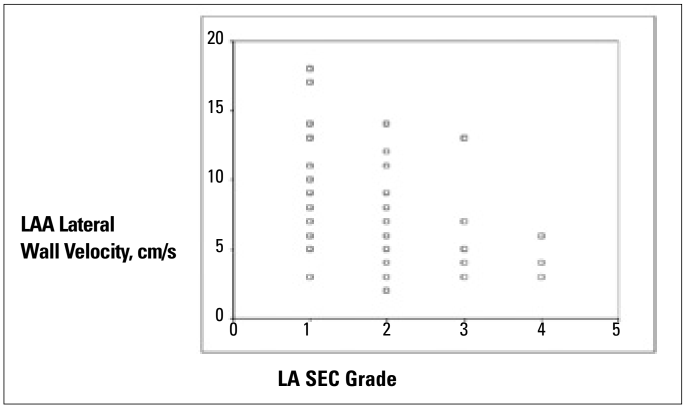

Figure 3. Distrubition graphic of spontaneous echo contrast (SEC) grade in left atrium (LA) and left atrium appendage (LAA) lateral wall velocity

Conclusion

LAA functions decrease and SEC grading increases in patients with nonvalvular AF, preserved LVEF and diastolic dysfunction. Decreased LAA flow velocities may be useful in predicting embolic complications in these patients. Thus, diastolic dysfunction contributes to the detection of subgroups carrying risk for embolic events in a disease that influences public health considerably such as AF. It is our contention that evaluation of diastolic dysfunction in patients with nonvalvular AF will elucidate the approach to anticoagulants in clinical practice.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - M.B.D., H.Ç.; Design - M.B.D.; Supervision - M.B.D., M.Ç.; Materials - M.B.D., Ö.U., H.Ç.; Data collection&/or processing - M.Ç., M.D.; Analysis &/or interpretation - M.B.D., Ö.U., H.Ç.; Literature search - M.B.D., M.Ç., M.D.; Writing - M.B.D., M.D.; Critical review - Ö.U., H.Ç.

References

1. Seet RC, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation 2011; 124: 477-86. [CrossRef]
2. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation 2009; 119: 62-70. [CrossRef]
3. Manning WJ, Leeman DE, Gotch PJ, Come PC. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. J Am Coll Cardiol 1989; 13: 617-23. [CrossRef]
4. Kusunose K, Yamada H, Nishio S, Tomita N, Niki T. Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. JACC Cardiovasc Imaging 2009; 10: 1147-56. [CrossRef]
5. Mazzone C, Pandullo C, Scardi S, Salvi R, Miccio M, Cattarini G, et al. Left atrial and appendage mechanical function after pharmacological or electrical cardioversion in patients with chronic atrial fibrillation: a multicenter, randomized study. Ital Heart J 2000; 1: 128-36.
6. Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993; 22: 1359-66. [CrossRef]
7. Chimowitz MI, DeGeorgia MA, Poole RM, Hepner A, Armstrong WM. Left atrial spontaneous echo contrast is highly associated with previous stroke in patients with atrial fibrillation or mitral stenosis. Stroke 1993; 24: 1015-9. [CrossRef]
8. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994; 23: 961-9. [CrossRef]
9. Black IW, Chesterman CN, Hopkins AP, Lee LC, Chong BH, Walsh WF. Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 1993; 21: 451-7. [CrossRef]
10. Yang Y, Grosset DG, Li Q, Lees KR. Identification of echocardiographic "smoke" in a bench model with transcranial Doppler ultrasound. Stroke 2000; 31: 907-14. [CrossRef]
11. Agarwal AK, Venugopalan P. Left atrial spontaneous echo contrast in patients with rheumatic mitral valve stenosis in sinus rhythm: relationship to mitral valve and left atrial measurements. Int J Cardiol 2001; 77: 63-8. [CrossRef]
12. Black IW. Spontaneous echo contrast: where there's smoke there's fire. Echocardiography 2000; 17: 373-82. [CrossRef]
13. Tsai LM, Lin LJ, Teng JK, Chen JH. Prevalence and clinical significance of left atrial thrombus in nonrheumatic atrial fibrillation. Int J Cardiol 1997; 58: 163-9. [CrossRef]
14. Cemri M, Timurkaynak T, Özdemir M, Boyacı B, Yalçın R, Çengel A, et al. Effects of left ventricular systolic dysfunction on left atrial appendage and left atrial functions in patients with chronic nonvalvular atrial fibrillation. Acta Cardiol 2002; 57: 101-5. [CrossRef]
15. Ito T, Suwa M, Kobashi A, Yagi H, Hirota Y, Kawamura K. Influence of altered loading conditions on left atrial appendage function in vivo. Am J Cardiol 1998; 81: 1056-9. [CrossRef]
16. Tabata T, Oki T, Fukuda N, Iuchi A, Manabe K, Kageji Y, et al. Influence of left atrial pressure on left atrial appendage flow velocity patterns in patients in sinus rhythm. J Am Soc Echocardiography 1996; 9: 857-64. [CrossRef]
17. Kamp O, Verhost PMJ, Welling RC, Visser CA. Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation. Eur Heart J 1999; 20: 979-85. [CrossRef]
18. Özer N, Tokgözoğlu L, Övünç K, Kabakçı G, Aksöyek S, Aytemir K, et al. Left atrial appendage function in patients with cardioembolic stroke in sinus rhythm and atrial fibrillation. J Am Soc Echocardiography 2000; 13: 661-5. [CrossRef]
19. Ito T, Suwa M, Otake Y, Moriguchi A, Hirota Y, Kawamura K. Left ventricular Doppler filling pattern in dilated cardiomyopathy relation to hemodynamics and left atrial function. J Am Soc Echocardiography 1997; 10: 518-25. [CrossRef]
20. Iwakura K, Okamura A, Koyama Y, Date M, Higuchi Y, Inoue K, et al. Effect of elevated left ventricular diastolic filling pressure on the frequency of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. Am J Cardiol 2011; 107: 417-22. [CrossRef]
21. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. J Am Coll Cardiol 1994; 23: 599-607. [CrossRef]