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Prediction of Embolic Events in Infective Endocarditis Using Echocardiography

Luminita Iliuta

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Abstract

Aim: Defining the echographic parameters which can help in identifying the high-risk groups for embolic events (EE) in patients with infective endocarditis (IE). *Material and method:* 236 patients with IE followed up 3 years with ECO parameters measured on the vegetations (VEG). *Results:* (1) the incidence rate of the EE was 51.27% without any significant differences for EE occurrence from the point of view of clinical parameters. (2) There was a significant correlation between the embolia occurrence and IE with staphylococcus, IE of the right heart, the length and mobility of VEG. The only independent predictors for EE were: the maximum length >15 mm and the increased mobility of VEG with the maximal angle >60.7. (3) In 23.14% of the patients with big and very mobile, EE occurred after starting the antibiotic treatment. *Conclusions:* (1) the VEG dimension and mobility determined by TEE are important predictors for the prognostic and are correlated with the embolic risk. (2) Significant ECO predictors of the EE occurrence were: VEG length >15 mm, neck/thickness ratio >0.69, and maximal angle of displacement of VEG in the cardiac cycle >60.7. (3) During the antibiotic treatment, the embolic risk depends only on VEG mobility and dimension.

Keywords: infective endocarditis, transesophageal echocardiography, embolic events, echocardiography, vegetation

1. Introduction

In general population, the infective endocarditis incidence has been estimated between 2 and 6 cases per 100,000 patient years, but it is significantly higher in patients with valvular heart disease and those with intravenous drug abuse. In 22–50% of cases of IE occurs systemic embolization [1–4] and up to 65% of EEs involves the central nervous system which

are associated with a higher mortality rate. The incidence of embolic complications is higher in IE located on aortic and mitral valve and in IE due to *Staphylococcus aureus*, Candida species, HACEK and Abiotrophia organisms. The highest rate of embolic events is seen within the first 2–4 weeks of antimicrobial therapy [5], and it drops dramatically during the first 2 weeks of successful antibiotic therapy, from 13 to <1.2 embolic events per 1000 patient-days. Prediction of individual patient risk for embolization has proven extremely difficult. Echocardiography is the main investigation used in a lot of studies to identify a high-risk subset of patients with IE who might benefit from early surgery in order to avoid embolization. Higher embolic rates revealed by several studies using transthoracic echocardiography (TTE) and TEE were seen with the increase of the VEG dimensions [6]. Vegetation mobility has not been shown to be an independent risk factor for embolic events, probably because it is strongly correlated with VEG size [5]. In other studies, the embolic complications were by the infecting organism and the number of VEG, the number of valves involved and VEG characteristics.

That is why the first objective of our study was to identify the echographic parameters which were associated with the presence of an EE in patients with IE. Using these variables we tried to define the echographic parameters which can help in defining the high-risk groups for EE in IE patients and to evaluate the real value of the TEE for the EE prediction in these patients. Finally, we examined the relationship between the incidence of an EE occurrence during the antibiotic treatment and the type of antibiotherapy and the echographic predictors for a new EE during antibiotherapy.

2. Materials and method

A prospective study was performed on 236 consecutive patients diagnosed with IE according to Duke criteria [7] in our institute. The study protocol was approved by the institute management and Ethics Committee. All patients included in the trial gave written, informed consent. The study was in accordance with the Declaration of Helsinki regarding the human rights. The follow-up period was extended 3 years after randomization or until cardiac surgery whatever occurred the first and included clinical and echocardiographic examination for each visit.

The study protocol was completed with demographic data, the clinical status of the patient, VEG echographic parameters, EE occurrence, the antibiotic treatment efficacity and duration. The main echographic parameters measured on the VEG were: the maximum length (L), the maximum (tmax) and minimum (tmin) thickness, the narrowest diameter, the presence of the neck and its dimensions (lneck) and the mobility defined as the angle of displacement of long axis of vegetation throughout the cardiac cycle (**Figure 1**). The data base was done using Visual Fox Pro program.

The main prediction variables used were: NYHA class for heart failure, Duke criteria used for IE diagnosis (fever, new regurgitation murmur, blood cultures, inflammatory tests,

leukocytosis, anemia), type of IE (on native valve or prosthetic) and the type of the surgical intervention. The main outcome variables were: the presence and the type of EE, death occurrence and its causes.

The characteristics of the studied group were as follows:

- 58% male, the mean age was 47.8 ± 6 years;

- 77.12% of the patients were in NYHA class III;

- 86.96% of the patients had fever >38°C;

- a significant regurgitation murmur was present on 56.78% patients;

- 69.91% of the patients presented positive blood cultures (24.58% with *Staphylococcus aureus*);

- 38.14% of the patients presented anemia;

- 2.12% of the patients had prosthesis endocarditis;

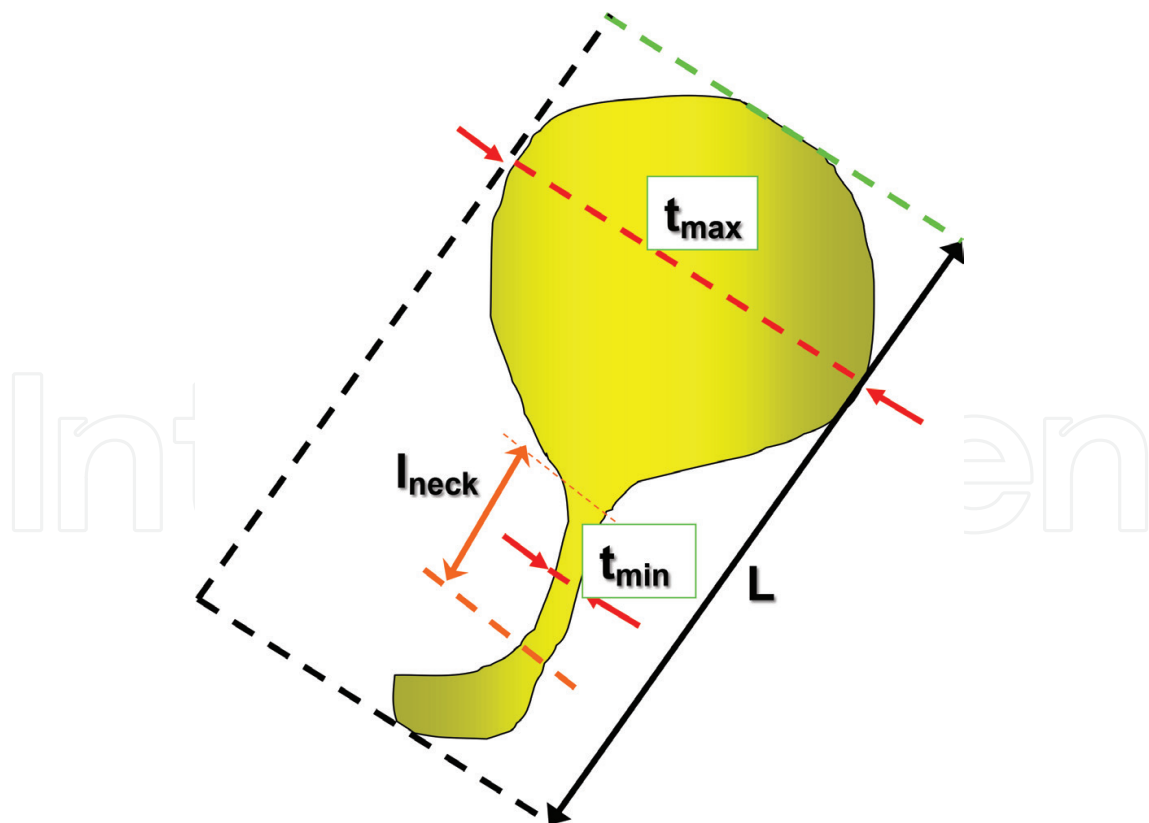- cardiac surgery was performed on 96.16% patients.

Figure 1. The echographic parameters measured on the vegetations.

The data collected represented the fields of a database in the Visual Fox Pro program. Data were processed using the Excel, Epi Info, Systat and SPSS programs for measurement of the power association between the prediction and outcome variables using the following tests:

a. for qualitative variables CHI square test or Fischer exact test (if expected cell size was less than 5)

b. for quantitative variables: T test (Student test), ANOVA test or U test depending on the samples volumes and Kruskal Wallis nonparametric tests.

The main methods of statistical correlation used in the study were the following:

- For quantitative variables analysis of simple linear and multivariate regression and correlation coefficient calculation;

- Relative risk calculation and the 95% confidence interval;

- Calculation of the positive and negative predictive value.

No sample size assumptions have been made. No confirmatory statistical hypothesis was pre-specified, but a detailed analysis plan was defined before the database was locked. Continuous data are expressed as mean ± SD. Discrete variables are expressed as counts (percentages).

According to the exposure level to the risk factors, data were grouped on the presence of an EE and the type of the treatment (surgical intervention or medical therapy). For each exposure level, there were introduced the number of patients with an EE (cases) and the number of patients without an EE (controls). The confounders were controlled by stratification.

Data interpretation was performed taking into account the following hypothesis:

- a relative risk >1 was considered unfavorable; for these patients, the occurrence of an EE was increased due to the presence of the group characteristic by the RR value;
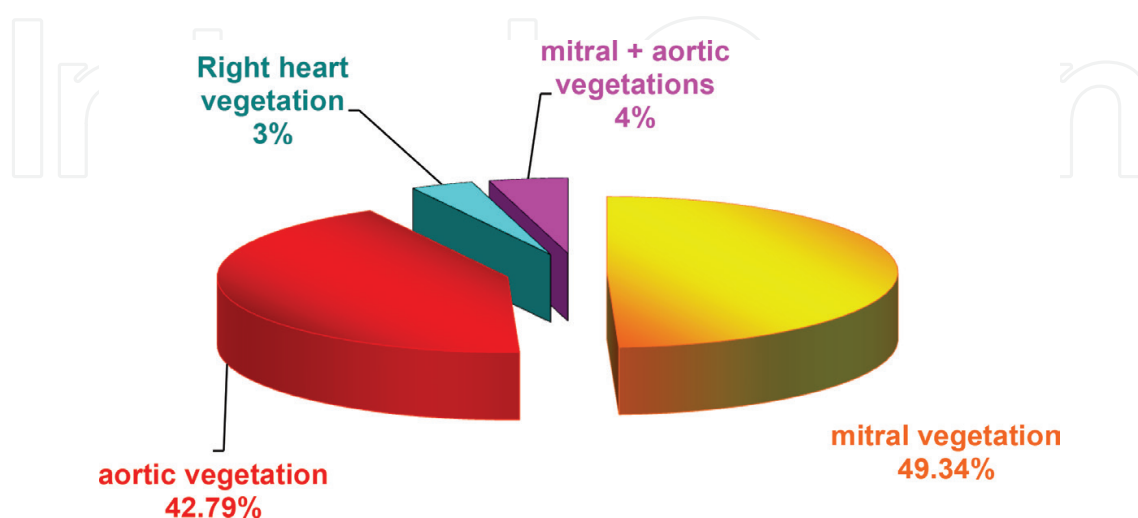

Figure 2. Patient distribution by vegetations site (229 patients).

- a relative risk = 1 included the patients subgroups classified as with no effect of the presence of group characteristic;

- a relative risk < 1 was considered favorable; for these patients, the occurrence of an EE was decreased due to the presence of the group characteristic by the RR value.

The patients were divided into two groups depending on the occurrence of the EE: group A—121 patients without an EE and group B—115 patients with an EE.

Depending on the VEG site, most of the patients (49.34%) had VEG on mitral valve, 42.79% on aortic valve, 4% both on mitral and aortic valve and 3% had right heart endocarditis (**Figure 2**).

3. Results

1. The incidence of the EE in patients with IE (diagnosed on Duke criteria) was 51.27% (121 patients). There were no significant differences for the occurrence of EE according to sex, age, fever presence, anemia, vegetation site or the presence of a significant regurgitation murmur (**Figure 3**).

2. The univariate analysis has shown a significant correlation between the EE presence and IE with staphylococcus, IE of the right heart, the length and mobility of vegetation. The only independent predictors for the EE revealed by the multivariate regression analysis were: the maximum length > 15 mm (RR = 4.92, p = 0.0001) and the increased mobility of the VEG with the maximal angle > 60.7 degree ± 12 (RR = 8.2, p = 0.003) (**Figure 4**). The univariate regression analysis has shown a significant correlation between the presence of an EE and the following parameters:

- IE with Staphylococcus (R^2 = 0.71, p < 0.0001);

- right heart IE (R^2 = 0.43, p < 0.0001);

- the maximum length of the vegetation (R^2 = 0.921, p < 0.01);

- the mobility of the vegetation (R^2 = 0.48, p < 0.001).

The multivariate regression analysis showed that the only echographic independent predictors of the EE were:

- the maximum length of the vegetation > 15 mm (RR = 4.92, p = 0.0001);

- the increased mobility of the vegetation—estimated as "the maximal angle of displacement of long axis of the vegetation throughout the cardiac cycle" more than 60.70 ± 12 (RR = 8.2, p = 0.003).

The maximum length of the VEG more than 15 mm increased the embolic risk by 4.92 times and its value between 10 mm and 15 mm by 1.84 times. Values less than 10 mm of the maximum length of the VEG turned out to be protective for EE, the associated RR being 0.92.
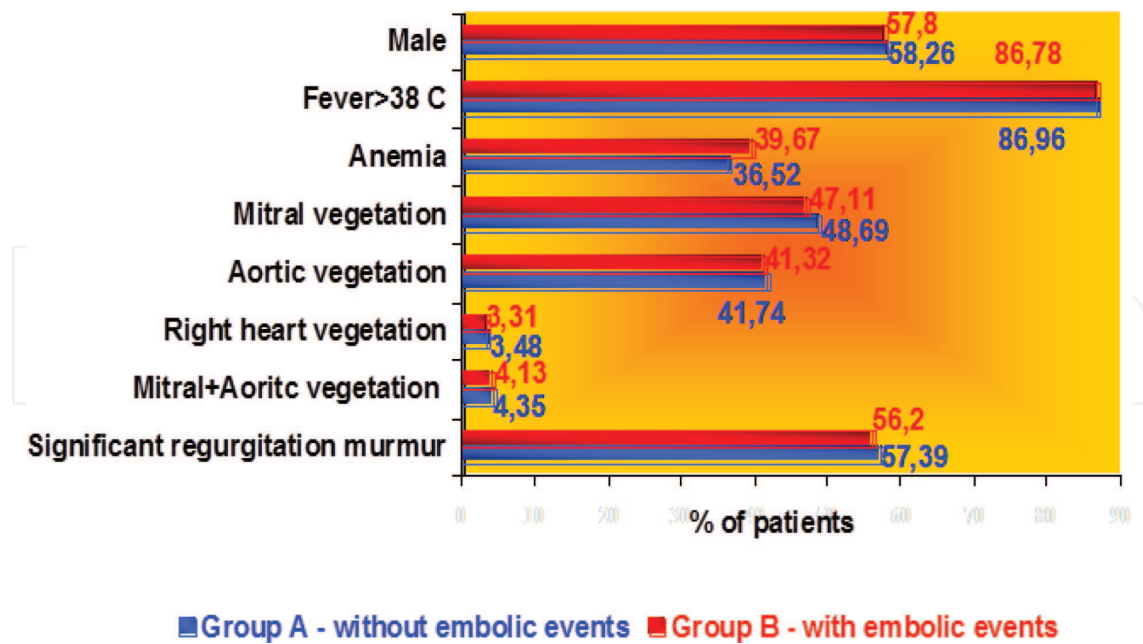
Figure 3. The occurrence of an embolic event depending on clinical parameters. Mean age: group A—48.7 ± 5 years; group B—46.9 ± 6 years.
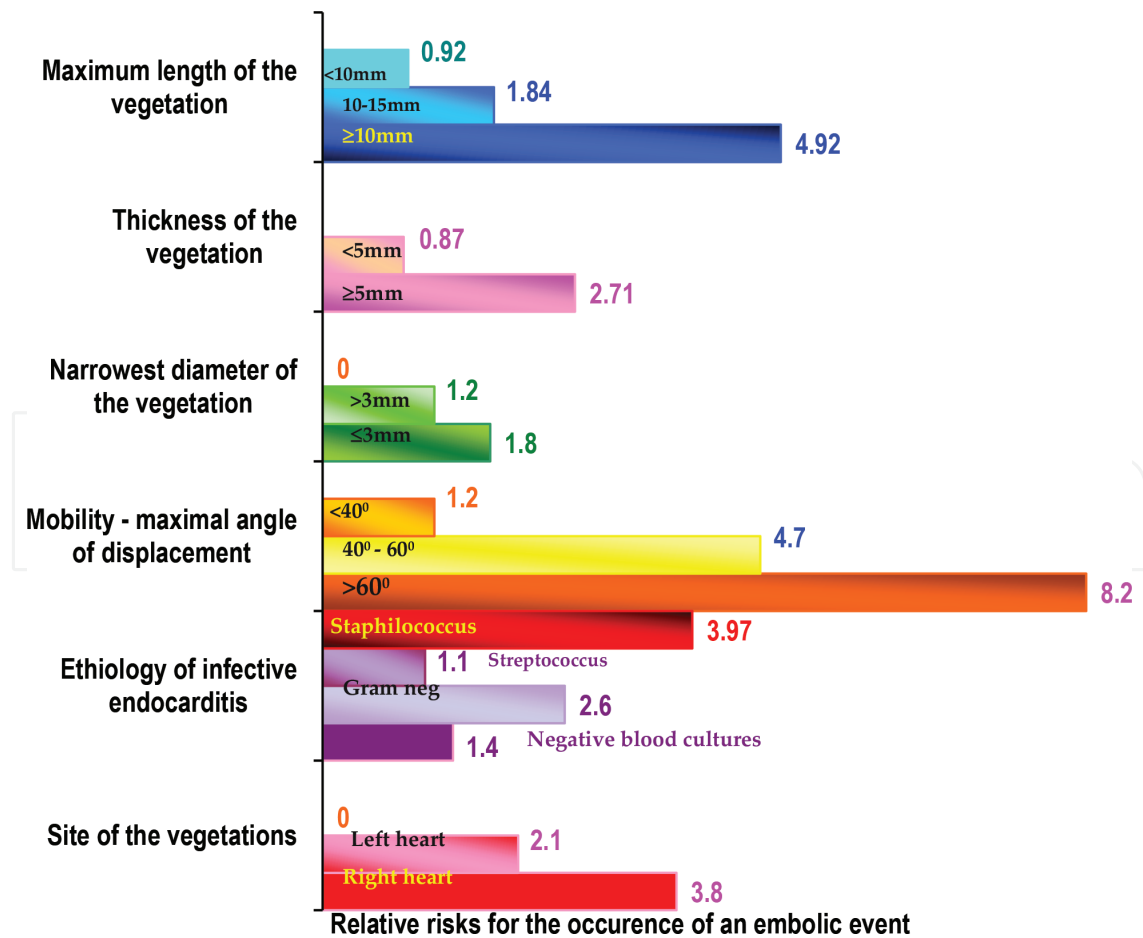

Figure 4. The relative risks for the occurrence of an EE depending on different echo parameters.

Values more than 5 mm of the maximum thickness of the VEG have increased the risk of the EE occurrence among our patients by 2.71 times. For thinner VEG, under 5 mm, the risk for EE was significantly reduced. The narrowest diameter (respectively the neck thickness—l_{neck}) less than 3 mm increased the risk for EE by 1.8 times. Regarding the mobility of the VEG, it significantly influenced the frequency of EE occurrence. Thus, the maximal angle of the VEG displacement between 400 and 600 increased by 4.7 times the risk for EE and for its values more than 600, by 8.2 times. The analysis by etiologic agent of IE showed a higher risk of EE in IE with *Staphylococcus aureus* and with Gram-negative bacteria. As other studies also showed, the likelihood of EE occurrence is higher in IE on right heart, the presence of infectious process on the tricuspid valve increasing the risk for EE by 3.8 times.

3. The differences between the patients with and without EE according to echocardiographic parameters of VEG are shown in **Table 1**.

Thus, the maximum length of the VEG was nearly twice in patients who suffered an EE compared with patients without an EE (about 12.6 mm and respectively about 6.2 mm).

In addition, the maximum thickness of the VEG measured by TEE was higher with about 3.3 mm in patients in group B. The ratio between the thickness of the VEG neck and the maximum thickness of the VEG was higher in patients without an EE (0.78 in group A respectively 0.42 in group B). In the same way, the VEG mobility (which was estimated by the measurement of the maximal angle of displacement of the vegetation was about three times bigger in patients who suffered an EE (25.1 degrees in group A and respectively 71.8 degrees in group B).

4. The rate of the EE occurred after starting the antibiotic treatment was 23.14% (28 patients) and simple linear and multivariate regression analysis found only in two independent predictors. These independent predictors for the occurrence of the EE, once antibiotic treatment has been started were the length of the VEG more than 15 mm and a high mobility of the VEG with maximal angle of displacement of long axis during the cardiac cycle >65 degrees (**Figure 5**). Thus, the maximum length of the VEG more than 15 mm increased the risk for EE occurrence by 7.1 times, the maximum width more than 5 mm increased the EE risk by 3.2 times and a neck/thickness ratio < 0.5 increased the EE risk by 3.5 times. Regarding the VEG mobility, the maximal angle of displacement values between 40 and 60 degrees increased the risk of the EE occurrence by 4.1 times and for its values >650, by 9.2 times. The IE due to a staphylococcal infection was associated with a more frequent EE occurrence, but the VEG localization on the right or left heart do not influence at the same level the EE risk as before the beginning the antibiotic treatment.

Echographic parameters	Embolic event		p value
	No	Yes	
Maximum length (mm)	6.2 ± 0.03	12.6 ± 0.04	<0.001
Maximum thickness (mm)	3.9 ± 0.01	7.2 ± 0.02	<0.003
Neck/thickness ratio	0.78 ± 0.2	0.42 ± 0.2	<0.001
Maximal angle of displacement of the vegetation	25.1 ± 10	71.8 ± 14	<0.0001

Table 1. Echographic differences between patients with IE who suffered or without EE.
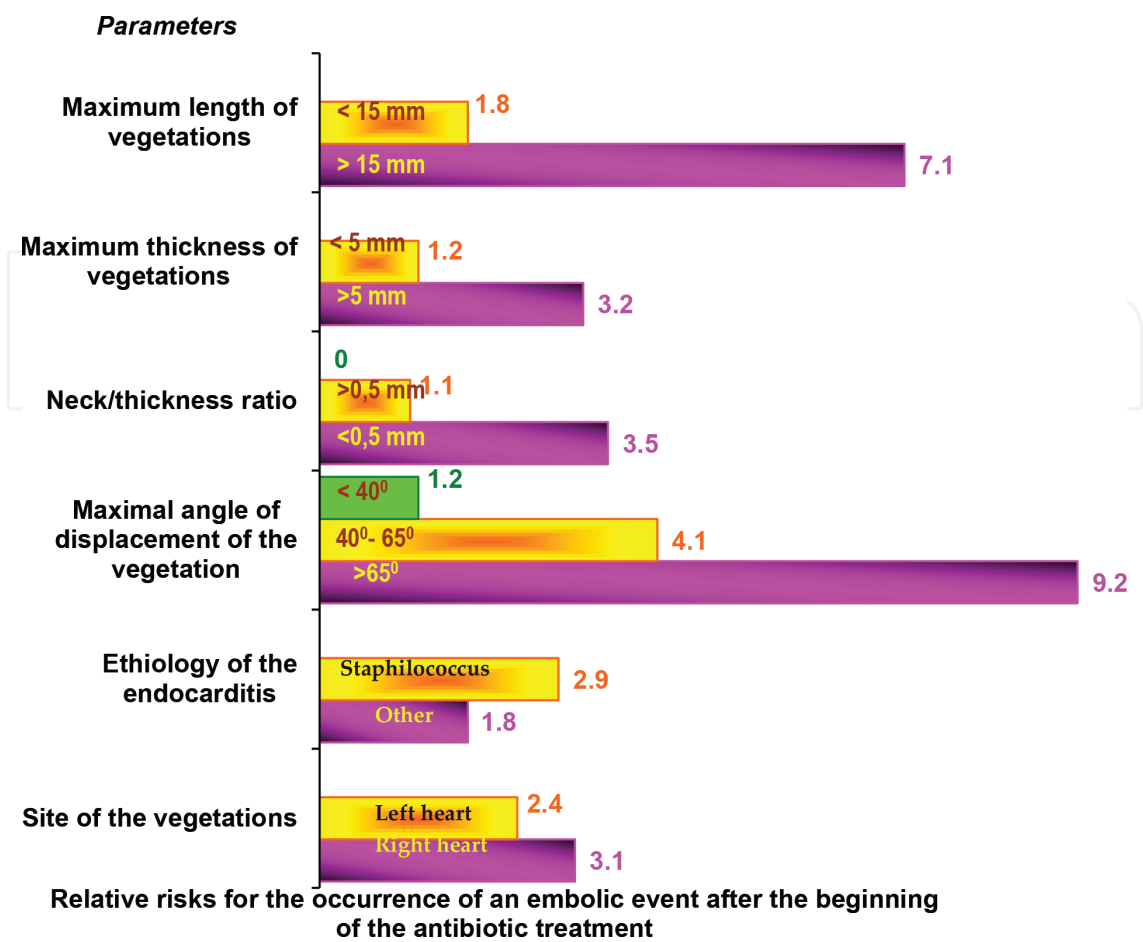
Figure 5. Correlation between clinical and echo parameters and the appearance of the embolic events after the antibiotic treatment has been started.

4. Discussions

The prediction of individual patient risk for embolization has proven extremely difficult. Many studies have attempted to use echocardiography to identify a high-risk subset of IE patients who might benefit from early surgery to avoid embolization [5, 6, 8–16]. In several studies using TTE was shown a trend toward higher embolic rates with VEG more than 1 cm in diameter located on the left heart [6]. In our study, the VEG dimension associated with a higher EE rate was about 15 mm probably because of a more precise measurement by TEE. Regarding the VEG diameter, in another study based on TEE, mitral VEG diameter more than 1 cm was associated with the highest incidence of embolism [6]. The association was strengthened when analysis was limited to those patients who had not yet experienced a clinical EE. Among such patients, the predictive accuracy for embolism with large mitral VEG was nearly 100% and in our study that value was about 94%. Mugge et al. had found particularly for patients with mitral valve IE, a VEG diameter greater than 10 mm was highly sensitive in identifying patients at risk for EE. On the other hand, VEG size was not significantly different in patients with and without severe heart failure

or in patients surviving or dying during acute IE. In addition, no significant correlation was found between VEG size and IE location or type of infective organism. VEG with a maximal diameter of >10 mm were associated with a 50% incidence of EE, compared with a 42% incidence of emboli in patients with VEG measuring less or equal to 10 mm. Inter observer variability was higher with respect to vegetation shape, mobility, and attachment characteristics. Echocardiographic VEG characteristics were not helpful in defining the risk of embolic complications in patients with IE [5].

Heinle et al. found that patients with a maximum VEG diameter > 10 mm had a significantly higher incidence of EE than those with < or = 10 mm (p < 0.05). There were no significant differences in the frequency of emergent valve replacement between patients with aortic value and mitral valve IE. The maximum size and total score reflecting mobility, extent and consistency of VEG using two-dimensional echocardiography provide useful information to predict the occurrence of EE in patients with IE [6].

Another prospective TEE study, however, found no clear correlation of VEG size with embolization, and transthoracic and TEE characteristics of VEG were not helpful in defining embolic risk in patients with IE [8].

De Castro used multivariate analysis and identified echocardiographic accessible risk factors for subsequent embolism a VEG size of more than 10 mm and mitral valve involvement [8]. Risk factors associated with in-hospital increased mortality rate were embolism, a vegetation size of more than 10 mm, and *Staphylococcus aureus* IE. Also, precise echocardiographic visualization of VEG helps to stratify patients into a high-risk sub-group, needing early prophylactic surgical intervention.

Overall, these data are compatible with previous observations that in general, mitral VEG, regardless their size, are associated with higher rates of embolization (25%) than aortic VEG (10%) [10]. On the other hand, the highest embolic rate (37%) has been seen in the subset of patients with mitral VEG attached to the anterior rather than the posterior mitral leaflet. In particular, mobile VEG attached to the mitral valve with a maximal diameter > 10 mm may be prone to EE [10]. In a retrospective study, Deprele et al. analyzed the risk factors for systemic emboli in IE [13]. They found that the risk of emboli was 57% when the VEG measured >10 mm and only 22% when it was <10 mm (p = 0.003). The mobility of the VEG was also a risk factor: 48% if the vegetation was mobile; and 9% if fixed (p = 0.003). Sex, age, pathogen, antibiotic treatment, type of valve and the number and position of the VEG were not found to be risk factors. With multivariate analysis, only mobility was identified as a risk factor.

The effect of VEG size on embolic potential was specific to the infecting organism, with large VEG independently predicting EE only in the setting of streptococcal IE [13, 17–19]. In contrast, staphylococcal or fungal IE appears to carry a high risk of embolization that is independent of the VEG size.

The evolution of VEG size revealed by TEE appears to predict EE; however an increase in VEG size revealed by TEE over 4–8 weeks of antibiotic therapy. In patients with IE and increasing VEG size, the EE rate among was twice that of patients with static or decreasing VEG size. In

addition, a second peak of late EE occurred at 15–30 weeks after diagnosis of IE, and it was associated with failure of a VEG to stabilize or diminish in size as defined by echocardiography [5, 6].

Because of the known decrease in embolic risk over the first 2 weeks of antibiotic therapy, the benefit of surgery in avoiding catastrophic embolic events is the greatest early in the course of the IE. Early surgical intervention may preclude a primary or recurrent major EE but exposes the patient to both the immediate and the life-long risks of valve replacement. That is why, the strategy for surgical intervention to avoid systemic embolization in IE still remains specific to the individual patient, benefit being the greatest in the early phase of IE when embolic rates are the highest and when other predictors of a complicated course are present (i.e., recurrent embolization, congestive heart failure aggressive, antibiotic-resistant organisms or prosthetic-valve IE). Surgical options must be considered when large VEG are detected on the mitral valve, particularly the anterior leaflet. Failure of a VEG to stabilize or diminish in size on TEE during clinically adequate therapy may also predict later EE.

5. Conclusions

1. The unfavorable prognostic in IE is predicted by the VEG dimension and mobility measured by TEE and is correlated with the EE.

2. The most important echographic predictors of the EE occurrence were: VEG length > 15 mm, neck/thickness fraction > 0.69, maximal angle of displacement of VEG throughout of the cardiac cycle > 60.7 degrees.

3. During the antibiotic treatment, the embolic risk depends only on the VEG mobility and dimension, and it does not depend on infectious agent and on the VEG site.

4. Early TEE in IE can identify the patients with high risk for an EE and who are candidates for the early surgical treatment (patients with very mobile VEG and with VEG length > 15 mm).

Conflict of interest

There is no conflict of interest.

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References

[1] Bayer AS. Infective endocarditis. Clinical Infectious Diseases. 1993;**17**:313-320

[2] Francioli P. Central nervous system complications of infective endocarditis. In: Scheld WM, Whiteley RJ, Durack DT, editors. Infections of the Central Nervous System. New York, NY: Raven Press; 1991. pp. 515-559

[3] Lerner P. Neurologic complications of infective endocarditis. The Medical Clinics of North America. 1985;**69**:385-398

[4] Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliercio CP, Giuliani ER, Wilson WR. Emboli in infective endocarditis: The prognostic value of echocardiography. Annals of Internal Medicine. 1991;**114**:635-640

[5] Mugge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: Reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. Journal of the American College of Cardiology. 1989 Sep;**14**(3):631-638

[6] Heinle S, Wilderman N, Harrison JK, Waugh R, Bashore T, Nicely LM, Durack D, Kisslo J. Value of transthoracic echocardiography in predicting embolic events in active infective endocarditis. Duke Endocarditis Service. American Journal of Cardiology. 1994;**74**(8):799-801

[7] Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. The American Journal of Medicine. 1994;**96**:200-209

[8] Koie S, Iwase M, Hasegawa K, Matsuyama H, Yamamoto H, Takeda K, Kato C, Kimura M, Hishida H, Kamiya H, Ohno M. Echocardiographic prediction of risk for embolism in patients with infective endocarditis. Journal of Cardiology. 1997;**29**(Suppl 2):117-122

[9] De Castro S, Magni G, Beni S, Cartoni D, Fiorelli M, Venditti M, Schwartz SL, Fedele F, Pandian NG. Role of transthoracic and transesophageal echocardiography in predicting embolic events in patients with active infective endocarditis involving native cardiac valves. The American Journal of Cardiology. 1997;**80**(8):1030-1034

[10] Rohmann S, Erbel R, Gorge G, Makowski T, Mohr-Kahaly S, Nixdorff U, Drexler M, Meyer J. Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. European Heart Journal. 1992;**13**(4):446-452

[11] Mugge A, Daniel WG. Echocardiographic assessment of vegetations in patients with infective endocarditis: Prognostic implications. Echocardiography. 1995;**12**(6):651-661

[12] Daniel WG, Mugge A, Grote J, Hausmann D, Nikutta P, Laas J, Lichtlen PR, Martin RP. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. The American Journal of Cardiology. 1993;**71**:210-215

[13] Deprele C, Berthelot P, Lemetayer F, Comtet C, Fresard A, Cazorla C, Fascia P, Cathebras P, Chaumentin G, Convert G, Isaaz K, Barral X, Lucht F. Risk factors for systemic emboli in infective endocarditis. Clinical Microbiology and Infection. 2004;**10**(1):46-53

[14] Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. Journal of the American College of Cardiology. 1991;**18**:391-397

[15] Lutas EM, Roberts RB, Devereux RB, Prieto LM. Relation between the presence of echocardiographic vegetations and the complication rate in infective endocarditis. American Heart Journal. 1986;**112**:107-113

[16] Sanfilippo AJ, Picard MH, Newell JB, Rosas E, Davidoff R, Thomas JD, Weyman AE. Echocardiographic assessment of patients with infectious endocarditis: Prediction of risk for complications. Journal of the American College of Cardiology. 1991;**18**:1191-1199

[17] Fowler VG Jr, Li J, Corey GR, Boley J, Marr KA, Gopal AK, Kong LK, Gottlieb G, Donovan CL, Sexton DJ, Ryan T. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: Experience in 103 patients. Journal of the American College of Cardiology. 1997;**30**:1072-1078

[18] Fowler VG, Sanders LL, Kong LK, et al. Infective endocarditis due to Staphylococcus aureus. Clinical Infectious Diseases. 1994;**28**:106-114

[19] Bayer AS, Lam K, Ginzton L, Norman DC, Chiu CY, Ward JI. Staphylococcus aureus bacteremia: Clinical, serologic and echocardiographic findings in patients with and without endocarditis. Archives of Internal Medicine. 1987;**147**:457-462