ORIGINAL ARTICLE

Risk factors for systemic emboli in infective endocarditis

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ABSTRACT

A retrospective study was undertaken to analyse the risk factors for systemic emboli in infective endocarditis. Patients ($n = 80$; 70% males; mean age 65 years; range 20–91 years) with infective endocarditis, as defined by the Duke criteria and diagnosed using transoesophageal echocardiography during the period January 1995 to March 2001, were included. The average time between the start of the illness and the beginning of antibiotic treatment was 55 days (range 0–405 days). The pathogens identified were streptococci ($n = 47$), staphylococci ($n = 11$), enterococci ($n = 9$), and others ($n = 4$). In nine cases, blood cultures were sterile. Thirty patients with at least one embolic episode were compared with 50 control patients. According to univariate analysis, the main risk factor for systemic emboli was the size of the vegetation (12.4 mm vs. 7.8 mm; $p = 0.0005$). The risk of emboli was 57% when the vegetation measured >10 mm and only 22% when it was <10 mm ($p = 0.003$). The mobility of the vegetation 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 vegetations were not found to be risk factors. With multivariate analysis, only mobility was identified as a risk factor. Overall, mobile vegetations >10 mm in size were associated with an increased risk of embolic episodes in infective endocarditis.

Keywords Cardiac disease, emboli, endocarditis, mobility, size, vegetations

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INTRODUCTION

The prognosis of infective endocarditis, even with appropriate antibiotic therapy, is poor, with a 9–30% global mortality rate [1–4]. The complications leading to death are principally cardiac insufficiency, accounting for *c.* 40% of cases and 60% of mortality, strokes caused by emboli, rather than rupture of aneurysm, which account for 40% of reported cases and 20% of deaths, and persistent sepsis despite adequate antibiotic treatment [5,6], which is now rather rare. Emboli, seen in *c.* 40% of cases, regardless of location [5], may require surgery in cases of recurrence, notwithstanding appropriate treatment [7]. However, in cases of ischaemic cardiovascular accidents, surgery would carry a high risk of haemorrhage because of the anticoagulation measures needed for extracorporeal circulation [7]. Numerous authors have tried to establish the predictive factors for emboli, but their results are contradictory, particularly with regard to the embolic risk linked to a large, mobile vegetation. According to some, the larger the vegetation, the more frequent the embolic risk [8–11], but this opinion is not substantiated by others [1,3,4]. For this reason, a retrospective study was carried out to analyse the risk factors for systemic emboli (individual factors, cerebral localisation and type of valve, pathogen, treatment) and, in particular, the roles of both the size and mobility of the vegetation.

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PATIENTS AND METHODS

This was a retrospective study of 80 patients with infective endocarditis, hospitalised in either the infectious diseases, internal medicine or cardiology departments of the University Hospital of Saint Etienne or the Hospital of Roanne, France, between January 1995 and March 2001. Patients with at least one embolic episode were compared to those with no embolic history.

The diagnosis of infective endocarditis was made using the Duke criteria [12]. Only patients in whom transoesophageal echocardiography (TEE) showed a vegetation on a cardiac valve were retained in the study. The measurements taken during TEE were also the only ones taken into consideration.

The vegetations were measured in two orthogonal dimensions; one measurement was made perpendicular to the leaflet surface, and the second was parallel. Each measurement was made at the point of maximal thickness. A non-mobile vegetation was defined as a vegetation with no detectable independent motion, and a mobile vegetation was defined as a vegetation with a free mobile edge.

The following clinical and/or radiological localisations were considered to be embolic symptoms: cutaneous ischaemia (Janeway's lesions); and an infarct in any organ (principally in brain, spleen and kidney), but also pulmonary infarction in cases of right-sided infective endocarditis. Symptoms known to be of immunological origin (glomerulonephritis, aseptic arthritis, Osler's nodes), as well as secondary pyogenic localisations (spondylitis with discitis and abscesses), were excluded.

The antibiotic treatment was considered to be adequate when given in accordance with the recommendations of the American Heart Association, as closely followed by French practitioners [13]. The starting point of the illness was defined by interrogating the patient about his first symptoms (e.g., fever, emboli or pain resulting from an embolic episode).

The chi-square test was used for qualitative comparisons, and ANOVA for quantitative variables. The 95% confidence intervals for odds ratios were calculated by the Cornfield method. The actuarial survival curves were created with the log-rank and Breslow–Gehaan–Wilcoxon tests. The software used was Epi-info v.6.0 (Centers for Disease Control, Atlanta GA, USA) and StatView v.5 (SAS Institute; Cary, NC, USA).

The association of emboli and above-average vegetation size was tested as described previously [9]. TEE measurements were used to determine the sensitivity, specificity, and the positive predictive values (PPVs) and negative predictive values (NPVs), according to the following definitions: sensitivity = number of patients with an embolus and a vegetation of greater than mean size ÷ total number of patients with an embolic episode; specificity = number of patients with no embolus and a vegetation of less than mean size ÷ total number of patients without an embolic episode; PPV = number of patients with an embolus and a vegetation of greater than mean size ÷ total number of vegetations of greater than mean size; NPV = number of patients with no embolus and a vegetation of less than mean size ÷ total number of vegetations of less than mean size.

RESULTS

Characteristics of patient population

Eighty patients (30% female; mean age 65 years; range 20–91 years) with infective endocarditis and positive findings on echocardiography were studied. The average time lapse between the presumed onset of the disease and the start of antibiotic treatment was 45 days (median, 22 days), and 55 days (median, 23 days) were needed for adequate antibiotic treatment.

In 72 (90%) patients, the infective endocarditis appeared on a native valve, in seven (9%) patients on a mechanical prosthesis, and in one (1%) patient on a homologous graft. Thirty (38%) patients experienced at least one embolic episode.

The average size of the vegetations was 9.5 mm, which was rounded up to 10 mm. The size of the vegetation in the seven (9%) patients who died was greater than in patients who survived, although there was no statistical correlation between death and the size of the vegetation. Among the seven patients who died, six experienced at least one systemic embolus. The deaths were mostly caused by cardiogenic shock ($n = 4$) (Table 1).

Thirty patients had undergone valve replacement surgery. Fourteen cases required surgery because of extensive valve destruction, including multiple emboli ($n = 6$), cardiogenic shock ($n = 5$), a large vegetation ($n = 3$), and other factors ($n = 2$).

Site and timing of emboli

The brain was the site most frequently affected by emboli (34%), followed by spleen (27%), skin (22%), kidney (7%), coronary artery (5%) and lungs (5%). Emboli occurred within 10 days of the start of the disease (40%) and before the start of any antibiotic treatment (73%) (Fig. 1).

Pathogens

Table 2 shows the pathogens that were responsible for infective endocarditis. The most frequent were streptococci (59%) and staphylococci (14%). There was no correlation between the type of pathogen and the occurrence of embolic episodes; of those

Table 1. Comparison of size of the vegetations and emboli in patients who died or survived

	Died	Survived	
Mean size of the vegetation (mm)	15.9	8.9	p = 0.015
Size of the vegetation			
> 10 mm	5 (14%)	30 (86%)	p: NS
< 10 mm	2 (4%)	43 (96%)	
Emboli	6 (86%)	24 (33%)	p = 0.019
No emboli	1 (14%)	49 (67%)	OR 12.2 (1.3–28.5)
Causes of death			
Four deaths from cardiogenic shock			
One death from septic shock			
Two unexpected deaths			

NS, not statistically significant; OR, odds ratio.

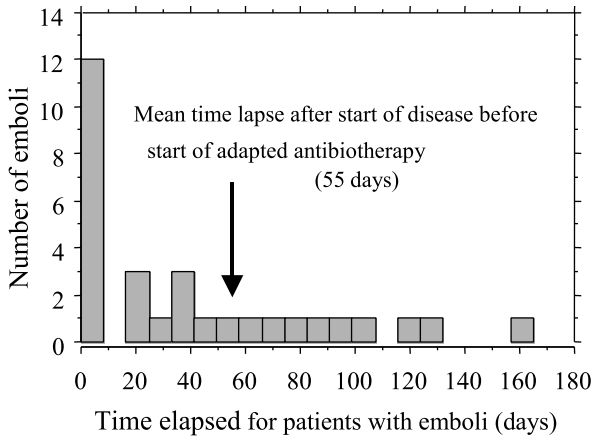

Fig. 1. Time elapsed before occurrence of emboli.

patients infected by enterococci, 33% had emboli, compared with 36% of patients with staphylococci, 45% of patients with streptococci, and 22% of patients with sterile blood cultures (p = 0.35).

Risk factors for emboli

Factors that could predict the onset of an embolic episode were investigated. In the present series, the age, sex, location and type of valve affected, initial antibiotic treatment, evolution of the vegetation and its size 4 weeks after the initial echocardiography and the number of vegetations did not appear to be risk factors for an embolic episode (Table 3).

However, vegetation size (Fig. 2) and mobility did appear to be risk factors for emboli (Table 3). The most mobile vegetations were also the largest; the average size of the mobile vegetations was 11.4 mm vs. 4.54 mm for the non-mobile vegetations (p < 0.0001).

When a threshold figure of 10 mm above which patients were at high risk of systemic emboli was fixed, the following values were obtained: sensitivity 67%; specificity 70%; PPV 57%; and NPV 78% (Table 4). In relation to mobile vegetations >10 mm in size, the values were: sensitivity 71%; specificity 60%; PPV 63%; and NPV 69%.

Embolic episodes are often indicators of infective endocarditis, and the first TEE is therefore often performed rather belatedly. If the 17 patients who underwent TEE after the occurrence of the embolic episode were excluded, then mobility and vegetation size remained risk factors (Table 5).

Table 2. Distribution of bacteria isolated in infective endocarditis

Organism	No.	%
Streptococcus	47	59
Streptococcus bovis	23	
Streptococcus oralis	7	
Streptococcus mitis	3	
Streptococcus agalactiae	3	
Streptococcus sanguis	3	
Streptococcus mutans	2	
Streptococcus gordonii	2	
Streptococcus anginosus	1	
Streptococcus constellatus	1	
Streptococcus defectivus	1	
Streptococcus spp.	1	
Staphylococcus	11	14
Staphylococcus aureus, methicillin-resistant	1	
Staphylococcus aureus, methicillin-sensitive	5	
Staphylococcus epidermidis	3	
Staphylococcus lugdunensis	1	
Staphylococcus warneri	1	
Corynebacterium	1	1
Escherichia coli	1	1
Enterococcus	9	11
Erysipelothrix rhusiopathiae	1	1
Propionibacterium acnes	1	1
Sterile blood culture	9	11
Total	80	

Table 3. Risk factors for the occurrence of an embolic episode

	Emboli	No emboli	
Sex			
Female	10 (42%)	14 (58%)	NS
Male	26 (46%)	30 (54%)	
Age at start of illness	64 years	65 years	NS
Initial antibiotherapy			
Adapted	25 (38%)	41 (62%)	NS
Not adapted	5 (36%)	9 (64%)	
Time lapse before start of adapted antibiotherapy			
Mean	66 days	48 days	NS
Median	33 days	26 days	NS
Affected valves			
Aortic	8 (26%)	23 (74%)	NS
Mitral	15 (40%)	23 (60%)	
Tricuspid	2 (50%)	2 (50%)	
Mitral + aortic	5 (72%)	2 (28%)	
Valve type			
Native	25 (35%)	47 (65%)	NS
Prosthesis	5 (62%)	3 (38%)	
Evolution of the size of the vegetation 4 weeks later			
Increased	4 (67%)	2 (33%)	NS
Decreased	11 (48%)	12 (52%)	
Stable	8 (32%)	17 (68%)	
Number of vegetations			
1	19 (33%)	39 (67%)	NS
2	5 (42%)	7 (58%)	
> 3	6 (60%)	4 (40%)	
Mobility of vegetation			
Mobile	28 (48%)	30 (52%)	$p = 0.003$
Fixed	2 (9%)	20 (91%)	OR = 9.3 (1.8–63.7)
Mean size of vegetation (mm)	12.4	7.8	$p = 0.005$
Size of vegetation			
> 10 mm	20 (57%)	15 (43%)	$p = 0.003$
< 10 mm	10 (22%)	35 (78%)	OR = 4.7 (1.6–13.9)

NS, not statistically significant; OR, odds ratio.

If the eight patients with valve prostheses were excluded, the risk factors for systemic emboli were identical. However, there was still no evidence that the diseased valve was a risk factor (Table 6).

Actuarial survival

When actuarial survival was considered, the size of the vegetation was a risk factor for an embolic episode. This occurred both more frequently and sooner in cases where the vegetation was >10 mm in size (Fig. 3).

Multivariate analysis

With multivariate analysis, only the mobility of the vegetation appeared to be a risk factor for an embolic episode, with an odds ratio of 10.39 (1.20–89.8), $p = 0.003$.

DISCUSSION

Even though the antibiotic treatments for infective endocarditis are well-documented [13], the indications for and the timing of surgery still pose problems. The principal dilemma is whether to operate early to limit the risk of emboli and/or to avoid eventual severe cardiac insufficiency, or to delay surgical intervention after the episode of infection to reduce the risks of surgery. Moreover, replacement of valves implies anticoagulation for life as well as the risk of a further infective episode involving the mechanical valve.

In some previous reports, the size of the vegetation was a risk factor for embolic episodes regardless of aetiology [10], while in others this was only true when the microorganism was a streptococcus [8]. Others have stated that there is

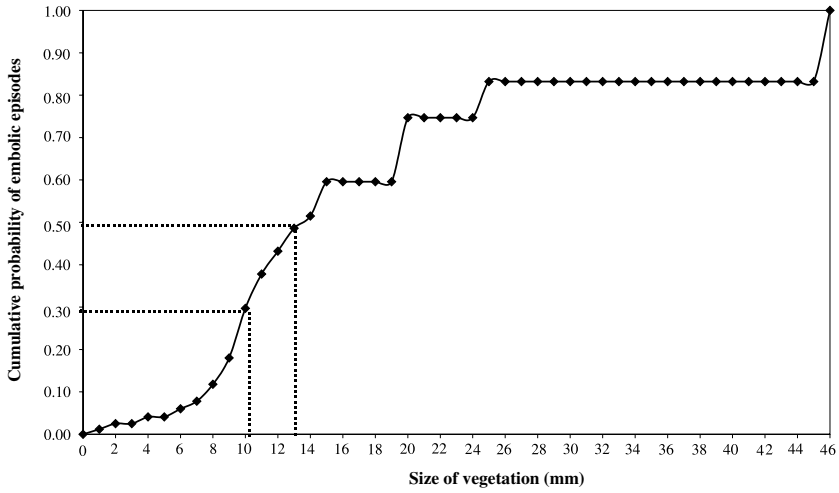

Fig. 2. Cumulative probability of embolic episodes in the studied population (including the 17 patients who had emboli before the first TEE).

no correlation between the size of the vegetation and the embolic risk [1,3,4,14,15]. All these studies only used transthoracic echocardiography; however, Mügge *et al.* [9] found a significant statistical correlation between a vegetation >10 mm in size on the mitral valve and embolic risk by measuring the vegetations using TEE. Other authors have also found a similar correlation using transthoracic echocardiography [16–18], and these results have been confirmed by a meta-analysis [19]. Lancellotti *et al.* [20] reported that the embolic risk was increased only for vegetations >14 mm in size, but the study included only 45 patients.

In the present study, all the vegetations were measured using TEE, and an increased risk of emboli was identified when the vegetation was >10 mm in size, regardless of the aetiology or the valve involved. From the actuarial survival curve, it appeared that the embolic risk is both greater and occurs earlier for vegetations >10 mm in size than for those <10 mm. It would

Table 4. Association between embolic episodes and vegetation size >10 mm

	Total population	**Patients without embolic episodes before the echocardiography**
Emboli with vegetation >10 mm	20	9
No emboli with vegetation >10 mm	15	15
No emboli with vegetation <10 mm	35	35
Emboli with vegetation <10 mm	10	4
Sensitivity	67%	69%
Specificity	70%	70%
Positive predictive value	57%	38%
Negative predictive value	78%	90%

Table 5. Risk factors of systemic emboli after exclusion of the 17 patients who presented with an embolus before the initial transoesophageal echocardiography

	Emboli	**No emboli**	
Mobility of vegetation			
Mobile	13 (30%)	30 (70%)	p = 0.022
Fixed	0 (0%)	20 (100%)	OR = 8.7 (1.02–191.3)
Mean size of vegetation (mm)	12.1	7.8	p = 0.017
Size of vegetation			
> 10 mm	9 (38%)	15 (62%)	p = 0.022
< 10 mm	4 (10%)	35 (90%)	OR = 5.25 (1.2–24.5)

OR, odds ratio.

Table 6. Risk factors for systemic emboli in patients with infective endocarditis affecting native valves

	Emboli	No emboli	
Affected valve			
Aortic	7 (25%)	21 (75%)	NS
Mitral	11 (33%)	22 (67%)	
Tricuspid	2 (50%)	2 (50%)	
Mitral + aortic	5 (72%)	2 (28%)	
Mobility of vegetation			
Mobile	23 (44%)	29 (56%)	p = 0.020
Fixed	2 (10%)	18 (90%)	OR = 7.1 (1.4–49.7)
Mean size of vegetation (mm)	11.2	8.4	p = 0.031
Size of vegetation			
> 10 mm	17 (53%)	15 (47%)	p = 0.007
< 10 mm	8 (20%)	32 (80%)	OR = 4.5 (1.43–14.77)

NS, not statistically significant; OR, odds ratio.

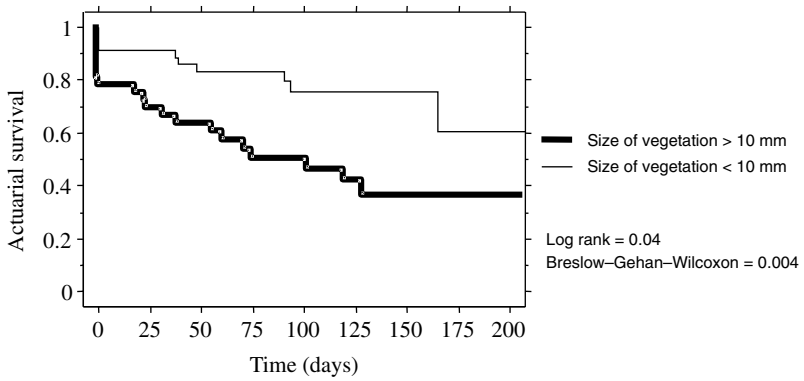

Fig. 3. Actuarial survival: embolic risk according to the size of the vegetation.

be interesting to determine a threshold value above which the embolic risk becomes very important, but the sizes of the vegetations seen in the present study did not extend over a sufficient range and were not sufficiently homogeneous to allow us to analyse the data [21]. Therefore, the threshold was fixed at 10 mm, as this was the average size of all the vegetations. In defining this threshold for detecting patients with a high risk of systemic emboli, it was found that the sensitivity, specificity, PPV and NPV figures were similar to those reported by Mügge *et al.* [9], even after excluding the 17 patients whose disease was revealed by the embolic episode and for whom TEE was therefore only performed after the embolic episode.

In the present study, the mobility of the vegetation was also a risk factor for emboli, but this was closely correlated with size, since the largest vegetations are also the most mobile. These results are in agreement with those published previously [11,22]. As this was a retrospective study and the evaluation criteria had not been decided in advance, it was not possible to evaluate the risk of emboli as a function of the surface area of the vegetation, a risk factor documented by Cabell *et al.* [23].

In the literature, the development of the size of the vegetation over time seemed to be a prognostic factor for the severity of infective endocarditis [8,24]. This risk factor was not identified in the present series, but only 54 (68%) patients had a TEE control performed 4 weeks later. This number was probably too small to show a significant statistical difference.

There was a high (38%) level of emboli in the present series compared with those reported in the literature (19–30%) [3,4,10]. This was probably because only those patients with at least one vegetation on TEE were included in the present study, whereas numerous other studies included patients with no visible vegetations on echocardiography. If, in these studies, the rate of emboli in the subgroups with visible vegetations is analysed, then similar rates of 40–50% are calculated [1,8,15].

Depending on the study, there either exists [1,19] or does not exist [4,9,10] a correlation between the size of the vegetation and mortality. A correlation was identified in the present study between a higher mortality rate and increased vegetation size. On the other hand, when the threshold level was set at 10 mm for systemic emboli, no correlation was found, but this is based on only seven deaths. Contrary to some previous studies [8–10], but in agreement with Steckelberg *et al*. [15], the present study did not find any significant statistical correlation between embolic risk and the valve involved. Similarly, in contrast to some studies [1,3,15], no correlation was observed between the infecting microorganism and embolic risk. Antibiotic treatment seemed to influence the size of the vegetation [24], but in the present retrospective study it was not possible to analyse this aspect.

In agreement with most other studies [8,9,15], there was a strong prevalence of emboli occurring within 15 days of the onset of disease, often leading to the diagnosis of infective endocarditis. This could represent a biased result, as the first echocardiography was often performed after the embolic episode, and the size of the vegetation may have been underestimated. For this reason, the statistical calculations for the subgroup of patients who had an embolic episode after echocardiography were repeated, but the size of the vegetation and its mobility were still identified as risk factors for systemic emboli.

The sensitivity and specificity of TEE for identifying valve vegetations vary in the cited studies from 82–100% and 91–100%, respectively, to 10–63% and 91–98% [25–27] for transthoracic echocardiography. Only TEE was used in the present study, decreasing the risk of biased results through incorrect estimation of the vegetation size. However, one of the limitations of this type of retrospective study is the inter- and intra-observer variability in the measurement of vegetation size and mobility. Furthermore, numerous asymptomatic embolic episodes, particularly those affecting the spleen, have not been taken into account in the retrospective studies. Only a prospective study, using systematic clinical research and medical imaging of the emboli, particularly splenic and renal emboli, could eliminate bias in the final data. Finally, 24 patients had early valve replacement surgery for reasons unconnected with the emboli, which probably decreased their risk of a later embolic episode.

A multivariate analysis according to the Cox model was not carried out. This is only possible where the risk to the patient remains proportional over time, which was not the case in the present study, since the risk of emboli is at a maximum during the first 2 weeks [8,9,15]. With the use of logistic regression, only the mobility of the vegetation, and not its size, appeared as a risk factor for emboli. This result may be explained by an insufficient number of patients to allow identification of size as an independent risk factor for embolic episodes.

Many (40%) emboli began within 10 days of the onset of symptoms, and 75% occurred before the onset of therapy. Embolisation became less frequent with longer duration of therapy, as previously reported [8,15,28]. According to Mügge [29], it appears that early diagnosis with initiation of adequate antibiotic therapy is still the best way to prevent embolic complications.

The present study confirmed that a mobile vegetation >10 mm in size, measured using TEE, puts the patient at increased risk from embolic episodes. In view of the accumulation of data establishing this risk factor, it seems urgent to undertake a prospective study to evaluate the connection between the gains and risks of surgical intervention vs. early antibiotic therapy in cases where the vegetation falls within this category.

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