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Clinical Research

Clinical Characteristics, Echocardiographic Feature, and Predictor of Embolic Events in Infective Endocarditis

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Background. There are many risk factors that are associated with embolic events in patients with Infective Endocarditis (IE) ranging from infecting organism, valve location, vegetation morphology, to age. Nevertheless, echocardiography role in predicting embolic events in patients with Infective Endocarditis remains controversial. Some studies reported an increased risk of embolism in patients with large and mobile vegetations, whereas other studies failed to demonstrate such a relationship.
Objectives. The aim of this study is to assess the risk factors that are associated with embolic events and to evaluate the role of transthoracic echocardiography (TTE) in predicting embolic events (EEs) in a small group of patients with definite endocarditis according to the Duke criteria.
Methods. Subjects more than 17 years of age, who were enrolled in National Cardiac Center Harapan Kita Infective Endocarditis Registry and who had complete TTE recording were selected for this study. Fourteenpatients with definite Infective Endocarditis according to the Duke Criteria who were hospitalised within 2010 – 2011 were examined with M-mode and two-dimension echocardiogram. The incidence of embolism was compared with the clinical and echocardiographic characteristics (localization and mobility) of the vegetations.
Results. Among 14 patients, 5 (35,7%) had one or more EEs. There were no difference between patients with and without embolism in terms of infecting organism, gender and vegetation mobility. Five out of 9 patients (55%) with mitral valve involvement vegetation had EE. No patients with only aortic and tricuspid valve vegetations had EEs. And all of the patents with EE had mitral valve involvement. Thus, there was a significant higher incidence of embolism was present in patients with mitral valve involvement of vegetation (100%, p = 0,038).
Conclusion. Our study shows that the involvement of mitral valve on TTE is predictive of embolism.

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Penelitian Klinis

Gambaran Klinis, Tampilan Ekokardiografi, dan Prediktor dari Kejadian Emboli pada Endokarditis Infektif

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Latar belakang. Terdapat banyak faktor risiko yang terkait dengan kejadian emboli (KE) pada pasien dengan Endokarditis Infektif (EI), seperti organisme penginfeksi, lolasi katup, morfologi vegetasi hingga usia. Akan tetapi, peranan ekokardiografi dalam memprediksi KE pada EI tetap menjadimhal yang kontroversial. Beberapa studi melaporkan peningkatan risiko KE pada pasien dengan vegetasi yang mobile,sementara studi lain gagal menunjukkan kaitan tersebut.
Tujuan. Tujuan dari studi ini adalah unuk menilai faktor risiko yang berhubungan dengan KE dan mengevaluasi peranan transthoracic echocardiography (TTE) dalam mempdiksi KE pada kelompok kecil pasien dengan diagnosis definite EI sesuai dengan kriteria Duke.
Metode. Subjek penelitian adalah pasien yang berusia > 17 tahun, yang termasuk ke dalam Registri Endokarditis Infektif Pusat Jantung Nasional Harapan Kita dan menjalani pemeriksaan TTE lengkap. Empat belas pasien dengan diagnosis definite EI sesuai kriteria Duke yang dirawat selama 2010 – 2011 diperiksa menggunakan ekokardiogram dua dimensi, dan M-Mode. Tampilan klinis dan fitur ekokardiografi dibandingkan pada kelompok yang dengan KE dan tanpa KE.
Hasil. Dari 14 pasien, 5 (35,7%) memiliki KE. karakteristik klinis dan ekokardiografi dibandingkan antara pasien dengan KE dan tanpa KE. Tidak terdapat perbedaam bermakna antara kedua kelompok dalam hal organisme penginfeksi, jenis kelamin, dan mobilitas vegetasi. Akan tetapi, 5 dari 9 pasien (55%) dengan keterlibatan katup mitral memiliki KE. Lebih lanjut lagi, tak ada pasien dengan keterlibatan katup aorta atau trikuspid saja yang mengalami KE. Semua pasien yang mendapatkan KE memiliki keterlibatan katup mitral. Maka dari itu, terdapat insidens KE yang lebih tinggi secara signifikan pada pasien dengan keterlibatsn katup mitral (100% , p = 0,038).
Kesimpulan. Studi kami menunjukkkan bahwa keterlibatan katup mitral merupakan prediktor dari KE.

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Kata kunci: endokarditis infektif, emboli

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Embolic events (EEs) are a frequent and life-threatening complication of Infective Endocarditis (IE)[1]. Therefore, an accurate prediction of embolic risk in IE is mandatory.

Chan et. al[1] have clearly studied risk factors that are associated with EEs in patients with IE. He found

that infecting organism, vegetation morphology, and vegetation location are predictors of EEs in IE. Furthermore, other researchers have tried to determine which echocardiographic feature is helpful to evaluate the risk of embolism in patients with IE. Unfortunately, the value of echocardiography in predicting EEs remains controversial. Several investigators do not consider the presence of a vegetation as a specific marker for increased risk of embolism,[2] and the significance of some vegetation characteristics, such as mobility, is still unclear. Some studies reported an increased risk of embolism in patients with mobile vegetations,[3,4] whereas other studies failed to demonstrate such a relationship.[2,5] The causes of these conflicting outcome are multiple, ranging from the use of TTE versus transesophageal echocardiography (TEE), various diagnostic criteria for IE to the inclusion or exclusion of patients with subclinical EEs preceding the echocardiographic study.

The aim of our study is to assess risk factors associated with EEs such as vegetation location, and mobility, and infecting organism. Byusing transthoracic echocardiography (TTE) in analysing vegetation characteristics, this research also studied the role TTE in predicting embolic events (EEs) in a small group of patients with definite endocarditis according to the Duke criteria by using multiplane TTE.[6-9]

Methods

Design. This is a retrospective and descriptive analysis statistics. Data were taken from medical records.

Patients. Subjects were taken from National Cardiac Center Harapan Kita Infective Endocarditis Registry. Within 2010 – 2011, seventy patientswere referred to our center for suspected Infective Endocarditis. 26 patients had definite IE and 14 had possible IE. Inclusion criteria is patients above 17 years of age with diagnosis of definite IE according to the Duke criteria.[6-8] Fourteen patients (9 men and 5 women, mean age 41,7 ± 9,7) fulfilled the inclusion criteria. Those 14 patients were examined with M-mode and two-dimension echocardiogram.Blood cultures (BC) were collected from 13 patients (92,9%) of which 10 patients had positive results. One patient which didn't had blood cultures was already referred to our center with definite IE.

Bacteriologic and clinical characteristics of the patients are summarized in Table 1 and Table 2. Infective Endocarditis involved a native valve in all of the patients. In-hospital death occured in 1 patient (7,1%). Descriptive characteristics of samples are showed in Table 3.

Patients were excluded from this study when diagnosed with possible and rejected IE.

Table 1. Occurence of Different Pathogens and Relationship with Embolic Events

	Total Group (n = 14)	Embolism Group (n = 5)	No Embolism Group (n=9)	*p* Value*
Streptococci	5 (35,7%)	2 (14,3%)	3 (21,4%)	0,803
Staphylococci	3 (21,4%)	1 (7,1%)	2 (14,3%)	0,923
Negative blood cultures	3 (21,4%)	1 (7,1%)	2 (14,3%)	0,923
Others	2 (14,3%)	1 (7,1%)	1 (7,1%)	0,649

Others: *Serratia marcesens*; Data as presented as number (%) of patients; * comparison between groups with and without embolism

Table 2. Clinical Features of Patients With and Without Embolic Events

	Total Group (n = 14)	Embolism Group (n = 5)	No Embolism Group (n=9)	*p* Value *
Mean age (years)	41,7 ± 9,7	40,1 ± 10,9	42,3 ± 9,6	0,842
Men	9 (64,3%)	3 (21,4%)	6 (42,9%)	0,803
Surgical therapy	9 (64,3%)	3 (21,4%)	6 (42,9%)	0,803
In-hospital death	1 (7,1%)	1 (7,1%)	0	0,164

*Comparison between patients with embolic events and patients without embolism; Data are presented as the mean value ± SD or as number (%) of patients

Surgical management. Surgerywas performed in 9 patients (64,3%). The surgical procedure was valve replacement in 5 patients (35,7%), including a bioprosthesis in 7,1%, and a mechanical valve in 28,6%; valve repair in 2 patients (14,3%); and 1 other (VP shunt). One patient (7,1%) underwent surgery within the first 24 hours (emergency), and 8patients after 2 weeks of antibiotics treatment (elective). The indications for emergencyoperation is because of hydrocephalus in 1 patient(7,1%).

Blood cultures. Blood cultureswere retrieved from 13 patients (93,3%). Major bacteriologic criteria were BCs positive for typical endocardial pathogens or persistently positive for a microorganism consistent with IE.[10,11] Minor bacteriologic criteria were positive BCs but not meeting major criteria as described earlier.[10,11] Blood cultures were positive in 11 patients (73,3%), with *Streptococcus sp.* being the most frequent (5patients, 35,7%) isolated pathogen (Table 1).

Echocardiography. Transthoracic echocardiography (TTE) was performed on all patients at least once. All echocardiographic studies were performed during the acute phase of IE, without any complications. One experienced echocardiographer independently reviewed the TTE studies without knowledge of the patients' clinical history or subsequent clinical course. Echocardiographic data were classified by using the Duke echocardiographic criteria.[7,12] Major echocardiographic findings included vegetation, abscess, new partial dehiscence of the prosthetic valve and valvular perforation.[12-14] As recommended by Durack et al.,[9] prosthetic dehiscence and regurgitant murmur had to be documentedas new to constitute a major criterion for IE. The usual definitions of perivalvular abscesses were used.[9,14,15]

Assessment of vegetations. Vegetation was defined as a fixed or oscillating mass adherent to a leaflet or other cardiac structure with a distinct echogenic structure and independent motion.[14] Vegetation is called mobile when it has detectable independent motion.[3,14,16]

Definition of EEs. Embolism is a dreaded complication in patients with IE, as it is a major contributor to mortality and morbidity in these patients. Cerebral embolism accounts for the majority of systemic embolic events and most commonly affects the territory of the middle cerebral artery resulting in severe disability.[1] The diagnosis of embolism was based on clinical signs and data derived from noninvasive diagnostic procedures. The diagnosis of cerebral EE, in all cases, was made by an experienced neurologist.

Statistical analysis. Factors associated with embolism (univariate analysis) were determined using the chi-square test. Data are expressed as the mean value ± SD or as number (%) of patients. Statistical significance was established at $p < 0.05$

Results

Echocardiographic data. Echocardiography was positive for IE in all patients, showing vegetations in those patients. Echocardiographic comparison between group with and without EEsis shown in Table 4.

Embolic events. Of 14patients, 5 patients (35,7%) had one or more EEs. All of the site for EEs was the central nervous system (n=5). The diagnosis of EEs was made from an experienced neurologist.

There was no statistical difference between patients with and those without embolism in terms of gender, blood cultures, the need for operation, and mortality (Table 1 and Table 2). But, there was a significant relation regarding the involvement of the mitral valve and embolic events.

Involvement of mitral valve. From 5 patients (35,7%) with EEs, there is a significant statistical difference (p 0,038) between those who had mitral valve involved (64,3%) and those who hadn't (35,7%). Moreover, 5 out 9 patients (55%) with mitral valve involvement vegetation had EE. Furthermore, no patients with only aortic and tricuspid valve vegetations had EEs. And all of the patents with EE had mitral valve involvement. Thus, there was a significant higher incidence of embolism was present in patients with mitral valve involvement of vegetation (100%, p = 0,038).

Influence of vegetation mobility. Ten patients (71,4%) had mobile vegetations, while 4 patients (28,6%) had fixed vegetations. Of 5 patients with EEs, 4 of them had mobile vegetations, although it didn't reach statistical significant (p = 0,597).

Table 3. Samples Descriptive Characteristics

Sex	Men	9 (64,3%)
	Women	5 (35,7%)
Age (years)		41,7 ± 9,7
IE localization	Native valve	14 (100%)
Valve involvement	Mitral	9 (64,3%)
	Aorta	4 (28,6%)
	Trikuspid	1 (7,1%)
Port d'entree	Dental	7 (50%)
	Urogenital	3 (21,4%)
	Unknown	4 (28,6%)
New York Heart Association	I	2 (14,3%)
(NYHA) Class	II	4 (28,6%)
	III	2 (14,3%)
	IV	6 (42,9%)
Symptoms	Fever > 38°C during hospitalisation	4 (28,6%)
	History of recurrent fever	1 (7,1%)
	Dyspnea	7 (50%)
	Myalgia	2 (14,3%)
Physical examinations	Pulmonary rales	5 (35,7%)
	New onset murmur	8 (57,1%)
	S3 gallop	1 (7,1%)
In-hospital mortality		1 (7,1%)
Underlying disease	Rheumatic valve disease	3 (21,4%)
	Congenital heart disease	3 (21,4%)
	Ventricular Septal Defect (VSD)	3 (21,4%)
	Degenerative	8 (57,1%)
Major arterial embolism	Cerebral	5 (35,7%)

Data are presented as the mean value ± SD or as number (%) of patients

Table 4. Vegetation Characteristics Comparison Between Groups With and Without EEs

	Total Group (n = 15)	Embolism Group (n = 5)	No Embolism Group (n=10)	*p* Value *
Mobile	10 (71,4%)	4 (28,6%)	6 (42,9%)	0,597
Mitral valve involvement	9 (64,3%)	5 (35,7%)	4 (28,6%)	0,038

*Comparison between patients with embolic events and patients without embolism. Data are presented as the mean value ± SD or as number (%) of patients

Discussion

To the best of our knowledge, this study is the first research in Indonesia assessing the risk factors of EEs and the value of TTE in predicting EEs in a group of patients with definite Infective Endocarditis according to the Duke Criteria. The main result was that the risk of EEs was not related to infecting organism, and vegetation mobiility. But, there are a significant relationship between EEs and mitral valve involvement (p = 0,038).

Embolic events in IE. The rate of systemic embolization in IE is estimated to be between 10% and 50%.[11] Our incidence is 5 patients (35,7%), which is similar to some references.[1,17] Furthermore, 1 patients (7,1%) undertook surgery within the first 10 days of treatment after the diagnosis of IE had been established and this approach could have prevented clinical EEs .

Embolic events and vegetation characteristics: report of previous studies. The main result of our study is that there are no significant relationships between EEs, infecting organism, and vegetation mobility. Nevertheless, the rate of EEs was higher on patients with mitral valve involvement compared to those with didn't (100% of patents with EEs had mitral valve involvement; p 0,038). These findings are consistent with previous reports. Rohmann et.al,[4] managed to found a significant relationship between EEs and mitral valve involvement.However, there are results from this study which contradict to those of earlier published studies. Di Salvo et al. detailed that EEs was higher in patients with mobile vegetation.[16] On the other hand, in a prospective study of 118 patients which undertook TEE, Rohmann et al.[4] found that, on a multivariate analysis, that the risk factors for EEs was mitral valve involvement.

Explanations of contradicting results are because of unclear standards in diagnosing IE, suboptimal images collected from TTE in earlier studies and small samples size.

Results of present study. This study didn't overcome all limitations of previous studies; small sample size (n = 14), and the use of TEE in only 4 patients (28,6%). But, we firmly believe that this study define the incidence of EEs in the era of early surgery. Moreover, this study use of strict diagnosis criteria of only includes patients with diagnosis of definite IE overcome one issue of earlier studies which is unclear standards in diagnosing IE.

Our study shown significant relationship between mitral valve involvement and EEs (100% of patients with EEs had mitral valve involvement, p 0,038). That result matches earlier studies from Mugge et.al.[18] and Rohmann et.al[4] which establish significant connection between EEs and mitral valve involvement. The mechanism proposed was that a great movement of the mitral valve could destabilize attached vegetations.[4] Other reference[1] hypothesized that thehigher rates of embolic events associated withmitral valve endocarditis might be due to theassociated enlarged left atrium with lower flowleading to a more congenial environment forproduction of more friable vegetations.

Study limitations. This study has few limitations. First, the subjects size was small (n=14). The use of larger number of subjects might identify more relations between echocardiographic vegetations characteristics and EEs. Second, TEE was not performed on all subjects. TEE was only made in 4 patients (28,6%). The use of TEE could identify vegetations characteristics more clearly.[11]

Clinical implications. Our study clearly shows that the involvement of mitral valve in TTE is a predictor of embolic events. Thus, the use of TTE could predict EEs in IE. However, the results of our study which contradict with earlier reports could be used as suggestions for further studies to include larger size of samples, and the use of TEE in all patients in order to establish the relationship between vegetation echocardiography characteristic and embolic events.

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