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Asymptomatic and symptomatic embolic events in infective endocarditis: associated factors and clinical impact

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ABSTRACT

Background: Embolic complications of infective endocarditis are common. The impact of asymptomatic embolism is uncertain.
Objectives: To determine the frequency of emboli due to IE and to identify events associated with embolism.
Methods: Retrospective analysis of an endocarditis database, prospectively implemented, with a post hoc study driven by analysis of data on embolic events. Data was obtained from the International Collaboration Endocarditis case report forms and additional information on embolic events and imaging reports were obtained from the medical records. Variables associated with embolism were analyzed by the statistical software R version 3.1.0.
Results: In the study period, 2006–2011, 136 episodes of definite infective endocarditis were included. The most common complication was heart failure (55.1%), followed by embolism (50%). Among the 100 medical records analyzed for emboli in left-sided infective endocarditis, 36 (36%) were found to have had asymptomatic events, 11 (11%) to the central nervous system and 28 (28%) to the spleen. Cardiac surgery was performed in 98/136 (72%). In the multivariate analysis, splenomegaly was the only associated factor for embolism to any site ($p < 0.01$, OR 4.7, 95% CI 2.04–11). Factors associated with embolism to the spleen were positive blood cultures ($p = 0.05$, OR 8.9, 95% CI 1.45–177) and splenomegaly ($p < 0.01$, OR 9.28, 95% CI 3.32–29); those associated to the central nervous system were infective endocarditis of the mitral valve ($p < 0.05$, OR 3.5, 95% CI 1.23–10) and male gender ($p < 0.05$, OR 3.2, 95% CI 1.04–10). Splenectomy and cardiac surgery did not impact on in-hospital mortality.
Conclusions: Asymptomatic embolism to the central nervous system and to the spleen were frequent. Splenomegaly was consistently associated with embolic events.

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Introduction

Infective endocarditis (IE) is a severe infection of the heart, with in hospital mortality rate varying from 15 to 30%[1]; this results mainly from complications such as heart failure and embolic events.[1–3]

Embolic complications occur in 20–50%[1] of cases of IE, and are associated with increased mortality and morbidity. They can precede the diagnosis of IE in 25[1] to 60% of patients.[4,5] The most frequent sites of embolization are the central nervous system (CNS) and the spleen.[1] More than 50% of embolic events involve the CNS[6] and embolic events to the spleen occur in 19–36% of cases of IE.[7] There are a few well-established risk factors for embolic events, such as vegetation size and mobility, mitral valve (MV) involvement and some etiological agents (*Staphylococcus aureus*, *bovis* group streptococci, *Candida* spp.), previous embolism, multivalvular IE, and biological markers.[1,8,9]

Embolic events to the CNS are clinically apparent in 10 to 30% of patients with left-sided IE.[10] Imaging screening for emboli to the CNS using computed tomography (CT) scans or magnetic resonance imaging (MRI) have shown a significant frequency of asymptomatic or subclinical embolic events, of up to 71.5%.[9–11] There are fewer data about subclinical embolic events to the spleen, reported to occur in 26 to 38%.[11,12]

The primary objectives of this study were to analyze the frequency and severity of asymptomatic and symptomatic embolism secondary to IE and to identify factors potentially associated to embolic events.

Material and methods

This was a retrospective analysis of an endocarditis database, prospectively implemented, with a post hoc study driven by analysis of data of embolic events. It was conducted at Instituto Nacional de Cardiologia (INC), Rio de Janeiro, Brazil, a public cardiac surgery referral hospital. INC has been a collaborating site to the International Collaboration in IE (ICE) study since 2006. Annually, approximately 270 valve replacement surgeries are performed at INC and around 25 adults with definite IE are admitted.

Patients were prospectively and consecutively included after signing informed consent. Data from the ICE case report forms were plotted on datasheets. At INC, CT scans of the brain and abdomen are performed routinely in all patients with left-sided IE for whom cardiac valve replacement surgery is indicated. Additional information such as signs and symptoms suggestive of embolic events and imaging reports were obtained from the medical records. Splenomegaly was defined as a clinical and/or radiological finding. Acute IE was defined when signs and symptoms occurred in less than one month of the start illness, and subacute when they occurred between one and six months. Healthcare-associated IE consisted of either nosocomial or non-nosocomial acquired infection; IE was defined as nosocomial when occurring in a patient hospitalized for >48 h. Non-nosocomial healthcare-associated IE was defined if signs or symptoms consistent with IE developed before hospitalization in patients with extensive out-of-hospital contact with healthcare interventions, including (1) receipt of intravenous therapy, wound care, or specialized home nursing care within 30 days before the onset of IE; (2) visiting a hospital or hemodialysis clinic or receiving intravenous chemotherapy within 30 days before the onset of IE; (3) hospitalization in an acute care hospital for ≥2 days within 90 days before the onset of IE; or (4) residing in a nursing home or long-term care facility.[1]

The following clinical features were considered as suggestive of embolic events in IE: headache, back pain, seizure, focal deficit, visual changes, abdominal pain, and peripheral ischemia. Radiological tests used to investigate embolic lesions were brain and abdominal CT scans and abdominal ultrasound scans.

Inclusion criteria was definite diagnosis of IE by the modified Duke criteria[13] in patients aged ≥18 years who signed the informed consent form and who were treated for IE as inpatients at INC between 2006 and 2011.

Data were stored in an Excel Microsoft Office spreadsheet and the statistical tests used in univariate analysis were Chi-square, Fisher's and Student's *t*-test using the statistical program R version 3.1.0. Variables with $p < 0.25$ in univariate analysis were included in a multivariate logistic regression model to identify the variables independently associated with embolic events. A *p*-value less than 0.05 were considered significant.

Approval of INC in the ICE study was obtained under number 080/12.09.2005 and the present study was also approved by the Ethics Committee on 02/24/2014 under number 540.220. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

A total of 136 ICE forms were analyzed, and 134 patients included (two patients had two episodes of IE in the study period). The male:female ratio was 2:1, and the mean age ± SD was 45.2 ± 16.4 years. The clinical features and comorbidities are presented in Table 1 and the microbiological features in Table 2.

Episodes of IE were acute in 58% (72/124) of the patients and 42% were subacute; 56.7% (76/134) were referred from other hospitals, community-acquired in 65.4% (89/136), hospital-acquired in 29.4% patient, and healthcare associated in 5.1%. Native valve IE occurred in 88 patients and seven of these also had pacemaker involvement; prosthetic valve IE occurred in 37, and in two cases both native and prosthetic valves were involved. Other structures involved were a biventricular assist-device (BIVAD) in one patient, the myocardial wall and a pacemaker in one and a pacemaker alone in six patients.

Predisposing factors for IE were any valve predisposition in 51/119 (42.8%), rheumatic valve disease (RVD) in 51/127 (40.1%), previous IE in 21/136 (15.4%), congenital heart disease in 11 (8%), intravenous drug use in one (0.7%).

Transthoracic echocardiograms (TTE) were performed in 83.7% of patients, and transesophageal echocardiograms (TEE) in 83.5%; both TTE and TEE were performed in 65.4% (89/136) of patients. Only one patient had neither. Main echocardiographic findings were evidence of moderate to severe

Table 1 – Clinical and laboratory features and comorbidities in 136 episodes of infective endocarditis, 2006–2011, INC.

	n/N	%
Demographic features and comorbid conditions		
Age	45.26 (mean)	16.39 SD
Male gender	88/136	64.7%
Essential hypertension	31/118	26.2%
Diabetes mellitus	14/136	10.2%
COPD	6/136	4.4%
Coronary artery disease	11/136	8%
Atrial fibrillation	15/136	11%
Heart failure	43/136	31.6%
Cerebrovascular disease	7/136	5.1%
Chronic renal failure	24/136	17.6%
Clinical and laboratory features		
Fever	124/136	91.1%
Splenomegaly	35/132	26.5%
Embolic events	68/136	50%
New regurgitant murmur	73/119	61.3%
Worsening of previous cardiac murmur	29/99	29.2%
Haematuria	10/65	15.3%
High CRP	107/118	90.6%
High ESR	45/59	76.2%
Positive rheumatoid factor	4/19	21%
Janeway lesions	5/132	3.7%
Osler's nodes	5/131	3.8%
Splinter hemorrhages	4/131	3%
Conjunctival hemorrhage	2/132	1.5%

n/N, absolute number of findings/total number of patients with available data; %, percent; SD, standard deviation; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

regurgitation of the MV in 70/134 (52%) and of the aortic valve in 58 (43%). There was evidence of vegetations of the MV in 67/135 (49.6%), of the aortic valve in 55 (40.7%), of the tricuspid valve in 12 (8.8%) and of intracardiac devices in 14 (10.4%). The average size of the largest vegetation was 16 mm (SD 6 mm) in the 52 patients for whom this information was available.

Surgery was indicated for 114 of 136 patients (84%), and 98/136 (72%) patients actually had surgery. Overall in-hospital mortality was 33/135 (24%). Surgical indications were severe acute valvular regurgitation in 69/114 (60.5%) patients with surgical indication, heart failure in 50 (43.8%), size and mobility of vegetation in 37 (32.4%), emboli in 24 (21%), paravalvular abscess in 17 (14.9%), pathogen in 13 (11.4%), and persistent bacteremia in three (2.6%). Most patients had more than one indication for surgery.

The complications observed in the 136 cases of IE were: new onset or worsening of heart failure (55.1%), embolism to any site (50%), prosthetic valve perforation or dysfunction (28.9%), acute renal failure (27.8%), paravalvular abscess (19.2%), extra cardiac mycotic aneurysm (5.5%), persistent bacteremia (6.3%), prosthetic dehiscence (5.5%), and recurrent embolism (3.8%). Regarding the site of embolism, 23.5% of cases were to the CNS, 32.8% to the spleen, 7.3% to the kidneys, 6.1% to the lungs, 6% to the vascular periphery, and 1.5% to the liver.

Left-sided IE occurred in 119 episodes. Medical records were reviewed in search for symptoms of embolism and screening images related to left-sided IE for 100 (84% of all left-sided IE episodes). Medical records were incomplete for 19 cases, and these were excluded from analysis; among these 19, only eight had documented embolism (42%). Table 3 shows the frequency of selected symptoms in patients with or without embolic events. Asymptomatic embolism occurred in 36 patients (36%); 11 patients had asymptomatic embolism to the CNS (11% of patients) and 28 patients had asymptomatic

Table 2 – Microbiological features in 136 episodes of IE, 2006–2011, Instituto Nacional de Cardiologia (INC).

Group	Pathogens	n	%
Viridans group streptococci		37	28.2
	Non-specified viridans streptococci	32	
	bovis group	3	
	S. pneumoniae	2	
Staphylococci		22	16.7
	S. aureus	13	
	S. epidermidis	6	
	Other	3	
Enterococci	*E. faecalis*	15	11.4
Non-HACEK Gram negatives		9	6.8
	Enterobacter sp.	2	
	Pseudomonas aeruginosa	2	
	Salmonella enteritidis	1	
	Serratia marcescens	1	
	Others	3	
HACEK		2	1.5
Candida sp.		7	5.3
Others		2	1.5
No pathogens grown in blood cultures		37	28.2
Total number of blood cultures		132	100

HACEK, *Haemophilus* spp. *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*.

Table 3 – Frequency of selected signs and symptoms related to embolism in 100 patients[a] with left-sided endocarditis, INC, 2006–2011.

Signs and symptoms	Associated with emboli	Not associated with emboli	*n* (%)
Headache	4	2	6 (6)
Seizure	2	2	4 (4)
Focal neurological deficit	7	3	10 (10)
Sleepiness or disorientation	5	3	8 (8)
Vertigo and postural instability	2	0	2 (2)
Behavioral changes	2	2	4 (4)
Abdominal pain	7	1	8 (8)
Back pain	3	2	5 (5)
Total records analyzed			100 (100)

[a] Analysis of the 100 patients with left-sided IE that had their records reviewed.

embolism to the spleen (28% of patients). Results of CT scans of embolic cases to the abdomen and to the CNS are shown in Table 4.

Among patients with embolism to the CNS, 18 had ischemia without hemorrhage, nine ischemia with hemorrhage, two hemorrhage, and in three the type of lesion was not specified. Seven patients had to be further investigated with an angio-CT or arteriography. Of the 32 patients with neurologic events, 18 (56%) eventually had cardiac surgery; further tests were necessary for 5/18 (28%), delaying the cardiac procedure (cerebral arteriography in four, brain angioCT scans in one). Cardiac surgery was further postponed in two (11%) of them, as the cerebral aneurysms disclosed had to be clipped before the cardiac procedure. Two patients died of hemorrhagic stroke before surgery, and a third also died for the same reason, but had no indication for cardiac surgery.

Twenty-one (21%) patients had splenectomy, 15 of whom had asymptomatic embolism (71%). Abscess or extensive infarction was found in the histopathological analysis of 19/21 (90%) of the removed spleens. All patients who had splenectomy were candidates for cardiac surgery and the splenic lesion was considered potentially deleterious (either as a potential residual focus of infection or risk for bleeding and rupture) and therefore splenectomy was recommended.

Other procedures performed were embolectomy, aneurysmectomy, and clipping, performed in six patients: clipping of cerebral aneurysm in two patients, clipping of a superior mesentery artery aneurysm in one patient, clipping of the hepatic artery and pseudo-aneurysm in femoral artery in one patient, clipping of a popliteal artery aneurysm in one patient, clipping and embolectomy of limb arteries in one patient, and partial pancreatectomy in one patient due to an aneurysm in the splenic artery being adhered to the pancreas.

Results of univariate analysis are shown in Table 5. The following features were associated with embolism to any site: splenomegaly ($p < 0.001$), MV IE ($p = 0.02$), cerebrovascular disease ($p = 0.01$), coronary artery disease ($p = 0.04$), male gender ($p = 0.04$), and atrial fibrillation ($p = 0.05$). Factors associated with embolism to the CNS were: splenomegaly ($p = 0.02$) and MV IE ($p < 0.01$). Factors associated with embolism to the spleen were: splenomegaly ($p < 0.01$), MV IE ($p = 0.01$), worsening of previous murmur ($p < 0.01$), and positive blood cultures ($p = 0.01$).

Mortality was 15.7% in patients who had cardiac surgery and 28.5% in those who did not (no statistical difference). Embolism to the CNS or to the spleen, symptomatic or asymptomatic, and cardiac surgery or splenectomy did not impact on mortality.

In multivariate analysis, splenomegaly ($p < 0.01$, OR 4.77, 95% CI 2.04–11) was the only factor independently associated with embolism to any site. Factors associated with embolism to the CNS were: MV IE ($p < 0.05$, OR 3.52, 95% CI 1.23–10) and male gender ($p < 0.05$, OR 3.29, 95% CI 1.04–10). Factors associated with embolism to the spleen were: splenomegaly ($p < 0.01$, OR 9.28, 95% CI 3.32–29) and positive blood culture ($p = 0.05$, OR 8.94, 95% CI 1.45–177).

Discussion

The main focus of our study were the embolic events related to left-sided IE.

Univariate and multivariate analyses consistently showed splenomegaly and MV IE as factors associated to embolism. MV IE has an already well-established association with embolism but not splenomegaly. Splenomegaly has been classically associated to IE.[14] Lamas and Eykyn[15] proposed newly diagnosed splenomegaly as a minor criterion for IE (St Thomas' criteria), and in their study, it was found in 11% of patients. The reported frequency of splenomegaly varies (1–60%)[15,16] and it was present in 26.5% of our patients. This might reflect a more prolonged course of illness or diagnostic delay, but there was no statistical correlation between splenomegaly and time course (acute versus subacute).

Table 4 – Results of computed tomography (CT) scans in patients with IE and symptomatic or asymptomatic embolism.[a]

CT scans	Total	Overall positives for embolism[b]		Positive for asymptomatic embolism[c]		Positive for symptomatic embolism[c]	
		n	%	*n*	%	*n*	%
Abdominal CT scans	74	39	52.7	28	71.7	11	28.2
Brain CT scans	70	26	37	11	42.3	15	57.6

[a] Analysis of the 100 patients with left-sided IE that had their records reviewed.
[b] Relative number considering the total number of CT scans performed.
[c] Relative number considering the total number of CT scans positive for emboli.

Table 5 – Univariate analysis of features associated to endocarditis and embolism to any body site, to the CNS, and to the spleen in 136 episodes of IE, 2006–2011, INC.

Variables	Present (yes or no)	Embolism to any body site			Embolism to CNS			Embolism to spleen		
		No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value
Patients' features and previous medical history										
Age (mean (SD))	—	46.78 (17.81)	42.38 (14.10)	0.12	45.66 (16.85)	43.22 (14.67)	0.49	46.18 (17.27)	43.33 (14.72)	0.35
Male sex	Yes	40 (55.6)	44 (73.3)	**0.04**	67 (62.0)	21 (77.8)	0.17	55 (59.8)	32 (76.2)	0.08
	No	32 (44.4)	16 (26.7)		41 (38.0)	6 (22.2)		37 (40.2)	10 (23.8)	
Smoking	Yes	6 (35.3)	5 (25.0)	0.71	9 (30.0)	3 (37.5)	0.68	8 (33.3)	2 (16.7)	0.43
	No	11 (64.7)	15 (75.0)		21 (70.0)	5 (62.5)		16 (66.7)	10 (83.3)	
Native valve predisposition	Yes	27 (40.9)	23 (45.1)	0.70	39 (40.6)	12 (54.5)	0.24	31 (38.8)	19 (50.0)	0.31
	No	39 (59.1)	28 (54.9)		57 (59.4)	10 (45.5)		49 (61.3)	19 (50.0)	
LV ejection fraction <50%	Yes	19 (57.6)	15 (45.5)	0.46	27 (52.9)	7 (43.8)	0.57	21 (48.8)	11 (50.0)	1.0
	No	14 (42.4)	18 (54.5)		24 (47.1)	9 (56.2)		22 (51.2)	11 (50.0)	
Aspirin	Yes	3 (6.5)	5 (12.8)	0.46	7 (10.3)	1 (5.6)	1.0	4 (6.9)	4 (14.8)	0.25
	No	43 (93.5)	34 (87.2)		61 (89.7)	17 (94.4)		54 (93.1)	23 (85.2)	
Warfarin	Yes	11 (23.9)	6 (15.4)	0.41	14 (20.6)	4 (22.2)	1.0	15 (25.9)	2 (7.4)	0.07
	No	35 (76.1)	33 (84.6)		54 (79.4)	14 (77.8)		43 (74.1)	25 (92.6)	
Previous cardiac surgery	Yes	27 (38.6)	13 (21.7)	0.056	34 (32.1)	7 (25.9)	0.64	32 (35.6)	10 (23.8)	0.22
	No	43 (61.4)	47 (78.3)		72 (67.9)	20 (74.1)		58 (64.4)	32 (76.2)	
Previous IE	Yes	14 (19.4)	7 (11.7)	0.24	17 (15.7)	4 (14.8)	1.0	14 (15.2)	7 (16.7)	0.80
	No	58 (80.6)	53 (88.3)		91 (84.3)	23 (85.2)		78 (84.8)	35 (83.3)	
Mitral stenosis	Yes	7 (13.2)	4 (9.5)		10 (13.0)	1 (5.6)		5 (8.2)	5 (14.7)	
	No	46 (86.8)	38 (90.5)	0.75	67 (87.0)	17 (94.4)	0.68	56 (91.8)	29 (85.3)	0.48
	No	69 (95.8)	59 (98.3)		105 (97.2)	27 (100.0)		88 (95.7)	42 (100.0)	
Comorbidities										
Neoplasia	Yes	5 (6.9)	1 (1.7)	0.22	6 (5.6)	0 (0.0)	0.59	5 (5.4)	1 (2.4)	0.66
	No	67 (93.1)	59 (98.3)		102 (94.4)	27 (100.0)		87 (94.6)	41 (97.6)	
Congenital heart disease	Yes	5 (7.0)	6 (10.0)	0.75	10 (9.3)	1 (3.7)	0.46	9 (9.9)	2 (4.8)	0.50
	No	66 (93.0)	54 (90.0)		97 (90.7)	26 (96.3)		82 (90.1)	40 (95.2)	
Rheumatic valvulopathy	Yes	27 (40.9)	24 (42.1)	1.0	65 (63.7)	11 (45.8)	0.16	30 (35.7)	19 (46.3)	0.32
	No	39 (59.1)	33 (57.9)		37 (36.3)	13 (54.2)		54 (64.3)	22 (53.7)	
Liver cirrhosis	Yes	1 (1.4)	0 (0.0)	1.0	2 (1.9)	0 (0.0)	1.0	2 (2.2)	0 (0.0)	1.0
	No	70 (98.6)	60 (100.0)		105 (98.1)	27 (100.0)		89 (97.8)	42 (100.0)	
Coronary artery disease	Yes	8 (11.1)	1 (1.7)	**0.04**	11 (10.2)	0 (0.0)	0.12	9 (9.8)	2 (4.8)	0.50
	No	64 (88.9)	59 (98.3)		97 (89.8)	27 (100.0)		83 (90.2)	40 (95.2)	
Cerebrovascular disease	Yes	7 (9.9)	0 (0.0)	**0.01**	5 (4.7)	1 (3.7)	1.00	5 (5.4)	2 (4.9)	1.00
	No	64 (90.1)	60 (100.0)		102 (95.3)	26 (96.3)		87 (94.6)	39 (95.1)	
Diabetes mellitus	Yes	9 (12.9)	4 (6.7)	0.38	13 (12.3)	1 (3.7)	0.29	13 (14.3)	1 (2.4)	0.06
	No	61 (87.1)	56 (93.3)		93 (87.7)	26 (96.3)		78 (85.7)	40 (97.6)	
COPD	Yes	5 (6.9)	1 (1.7)	0.22	6 (5.6)	0 (0.0)	0.59	4 (4.3)	2 (4.9)	1.0
	No	67 (93.1)	58 (98.3)		102 (94.4)	26 (100.0)		88 (95.7)	39 (95.1)	
Atrial fibrillation	Yes	12 (19.4)	3 (5.8)	**0.05**	12 (12.6)	2 (9.5)	1.0	12 (15.6)	2 (5.3)	0.13
	No	50 (80.6)	49 (94.2)		83 (87.4)	19 (90.5)		65 (84.4)	36 (94.7)	
Essential hypertension	Yes	16 (25.8)	13 (24.5)	1.0	22 (23.2)	8 (36.4)	0.27	20 (25.6)	11 (28.9)	0.82
	No	46 (74.2)	40 (75.5)		73 (76.8)	14 (63.6)		58 (74.4)	27 (71.1)	
Heart failure	Yes	28 (38.9)	14 (23.3)	0.06	35 (32.4)	7 (25.9)	0.64	33 (35.9)	10 (23.8)	0.23
	No	44 (61.1)	46 (76.7)		73 (67.6)	20 (74.1)		59 (64.1)	32 (76.2)	
Chronic renal failure	Yes	15 (21.4)	7 (11.7)	0.16	19 (17.9)	5 (18.5)	1.0	17 (18.9)	7 (16.7)	0.81
	No	15 (21.4)	7 (11.7)		87 (82.1)	22 (81.5)		73 (81.1)	35 (83.3)	
Clinical features										
Splenomegaly	Yes	10 (14.1)	25 (43.9)	**<0.001**	24 (22.6)	12 (48.0)	0.23	13 (14.8)	22 (52.4)	**<0.001**
	No	61 (85.9)	32 (56.1)		82 (77.4)	13 (52.0)		75 (85.2)	20 (47.6)	

Table 5 – (*Continued*)

Variables	Present (yes or no)	Embolism to any body site			Embolism to CNS			Embolism to spleen		
		No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value
Fever >38° C	Yes	64 (88.9)	58 (96.7)	0.11	97 (89.8)	26 (96.3)	0.45	81 (88.0)	41 (97.6)	0.10
	No	8 (11.1)	2 (3.3)		11 (10.2)	1 (3.7)		11 (12.0)	1 (2.4)	
New regurgitant murmur	Yes	39 (61.9)	31 (59.6)	0.84	59 (62.8)	14 (60.9)	1.0	52 (64.2)	20 (57.1)	0.53
	No	24 (38.1)	21 (40.4)		35 (37.2)	9 (39.1)		29 (35.8)	15 (42.9)	
High CRP	Yes	55 (88.7)	49 (96.1)	0.18	86 (90.5)	21 (100.0)	0.36	70 (89.7)	37 (97.4)	0.26
	No	7 (11.3)	2 (3.9)		9 (9.5)	0 (0.0)		8 (10.3)	1 (2.6)	
Worsening of a previous heart murmur	Yes	17 (30.9)	14 (35.0)	0.82	23 (29.1)	8 (44.4)	0.26	16 (22.9)	15 (53.6)	**0.007**
	No	38 (69.1)	26 (65.0)		56 (70.9)	10 (55.6)		54 (77.1)	13 (46.4)	
Splinter hemorrages	Yes	0 (0.0)	3 (5.4)	0.08	2 (1.9)	1 (4.2)	0.46	3 (3.4)	0 (0.0)	0.55
	No	72 (100.0)	53 (94.6)		103 (98.1)	23 (95.8)		85 (96.6)	40 (100.0)	
Elevated ESR	Yes	25 (75.8)	21 (80.8)	0.75	40 (80.0)	8 (72.7)	0.68	24 (70.6)	23 (88.5)	0.12
	No	8 (24.2)	5 (19.2)		10 (20.0)	3 (27.3)		10 (29.4)	3 (11.5)	
Aspects of IE episode										
Acute IE	Yes	39 (60.9)	30 (52.6)	0.36	56 (58.3)	15 (55.6)	0.82	52 (61.9)	18 (47.4)	0.16
	No	25 (39.1)	27 (47.4)		40 (41.7)	12 (44.4)		32 (38.1)	20 (52.6)	
Community-acquired	Yes	46 (63.9)	41 (68.3)	0.71	70 (64.8)	21 (77.8)	0.25	60 (65.2)	29 (69.0)	0.69
	No	26 (36.1)	19 (31.7)		38 (35.2)	6 (22.2)		32 (34.8)	13 (31.0)	
Hospital-acquired	Yes	22 (30.6)	15 (25.0)	0.56	31 (28.7)	5 (18.5)	0.33	27 (29.3)	10 (23.8)	0.54
	No	50 (69.4)	45 (75.0)		77 (71.3)	22 (81.5)		65 (70.7)	32 (76.2)	
Referred from another hospital	Yes	38 (53.5)	34 (57.6)	0.72	59 (55.7)	17 (63.0)	0.52	54 (60.0)	20 (47.6)	0.19
	No	33 (46.5)	25 (42.4)		47 (44.3)	10 (37.0)		36 (40.0)	22 (52.4)	
Time for referral (median. days)	—	14	20.5	0.32	13	22	0.25	12	22	0.16
Etiologic agent	*Candida*	1 (1.9)	5 (10.4)	0.33	4 (4.9)	2 (8.7)	0.52	3 (4.3)	3 (8.6)	0.11
	Enterococcus	10 (18.9)	6 (12.5)		12 (14.8)	4 (17.4)		10 (14.3)	7 (20.0)	
	Staphylococcus	12 (22.6)	8 (16.7)		18 (22.2)	2 (8.7)		14 (20.0)	6 (17.1)	
	None	9 (17.0)	5 (10.4)		11 (13.6)	5 (21.7)		15 (21.4)	1 (2.9)	
	Others	6 (11.3)	9 (18.8)		13 (16.0)	2 (8.7)		8 (11.4)	7 (20.0)	
	Viridans strep	15 (28.3)	15 (31.2)		23 (28.4)	8 (34.8)		20 (28.6)	11 (31.4)	
Aortic valve IE	Yes	27 (37.5)	25 (42.4)		42 (39.3)	14 (51.9)		38 (41.8)	17 (40.5)	
	No	45 (62.5)	34 (57.6)	0.59	65 (60.7)	13 (48.1)	0.27	53 (58.2)	25 (59.5)	1.0
	No	72 (100.0)	58 (98.3)		106 (99.1)	27 (100.0)		91 (100.0)	41 (97.6)	
Mitral valve IE	Yes	30 (41.7)	37 (62.7)	**0.02**	48 (44.9)	21 (77.8)	**0.002**	40 (44.0)	28 (66.7)	**0.01**
	No	42 (58.3)	22 (37.3)		59 (55.1)	6 (22.2)		51 (56.0)	14 (33.3)	
Tricuspid valve IE	Yes	6 (8.3)	6 (10.2)	0.76	11 (10.3)	1 (3.7)	0.45	11 (12.1)	1 (2.4)	0.10
	No	66 (91.7)	53 (89.8)		96 (89.7)	26 (96.3)		80 (87.9)	41 (97.6)	
Size of vegetation (mm. mean, (SD))	—	15.16 (6.40)	16.43 (7.17)	0.494	15.82 (DP 6.53)	15.94 (DP 7.63)	0.95	14.52 (6.65)	17.91 (6.93)	0.07
Duration of antibiotics prior to surgery (median, days)	—	13	14.5	0.371	13	22	0.25	14.00	13.00	0.71
Complications										
Paravalvular abscess	Yes	15 (21.1)	10 (16.7)	0.65	21 (19.6)	6 (22.2)	0.79	20 (22.0)	7 (16.7)	0.64
	No	56 (78.9)	50 (83.3)		86 (80.4)	21 (77.8)		71 (78.0)	35 (83.3)	
Persistent bacteremia	Yes	2 (3.4)	5 (10.0)	0.24	5 (5.6)	2 (10.0)	0.61	3 (4.2)	4 (11.1)	0.21
	No	56 (96.6)	45 (90.0)		84 (94.4)	18 (90.0)		69 (95.8)	32 (88.9)	
LVF due to acute aortic regurgitation	Yes	41 (56.9)	31 (51.7)	0.6	57 (52.8)	18 (66.7)	0.27	49 (53.3)	25 (59.5)	0.57
	No	31 (43.1)	29 (48.3)		51 (47.2)	9 (33.3)		43 (46.7)	17 (40.5)	
Prosthetic perforation or dysfunction	Yes	23 (34.3)	13 (22.0)	0.16	33 (32.7)	5 (18.5)	0.23	27 (31.4)	11 (27.5)	0.83
	No	44 (65.7)	46 (78.0)		68 (67.3)	22 (81.5)		59 (68.6)	29 (72.5)	

CNS, central nervous system; SD, standard deviation; IE, infective endocarditis; LV, left ventricular; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LVF, left ventricular failure.
P values less than 0.05 were highlighted in bold.

There was no association between embolic events and specific microorganisms responsible for IE, but positive blood cultures overall were associated to embolism to the spleen. *S. aureus* is classically associated with embolic events,[4,17] but not in our study, possibly due to a relatively small number of patients.

The frequency of embolism (50%) was similar to that reported in the literature. Embolism to the CNS, in 23.5%, was within the 20–40% range reported in the literature,[5,18–21] and the 32.8% embolism to the spleen was within the 19–36% range reported in the literature.[7,11]

The importance of asymptomatic embolic events is still not clear. It appears to be safe to operate on patients with asymptomatic embolism.[19,22] In fact, Rossi et al.[22] analyzed 20 papers addressing the question whether there is an optimal timing for surgery in IE with cardiovascular complications, and they have found that the optimal timing for valve replacement depends on the type of neurological complication and the urgency of the operation.

Asymptomatic embolism to the CNS were seen in 9.8% of the patients in this study. Thuny et al., who utilized CT scans as screening method, found 3.8%,[19] and Cooper et al., 2009, who utilized MRI, found nearly 50% of subclinical embolism,[10] while Hess et al. found 71%.[5] Iung et al. analyzed 120 patients and found ischemic lesions in 64 patients, of whom only 15 had neurological symptoms.[23] Another study by Iung et al.[12] analyzed 58 patients and diagnosed 81% of cerebrovascular complications by MRI, but only 8.5% of this patients had neurological symptoms. In this last study, based only on MRI results, the Duke classification was upgraded and/or the treatment plan was modified in 28% of the patients.

There are fewer data regarding asymptomatic embolism to the spleen. Our rate of splenic embolic events overall was 25%. Ting et al.[11] found a 38% rate of embolic lesions to the spleen when systematic screening was done with CT, while Luaces-Mendez et al.[24] found only a 10% rate when only patients with symptoms were studied by US or CT. Trouillet et al.[25] found 35/135 (25.9%) of embolic events to the spleen; and only 9% were diagnosed by US, while 35% were diagnosed by CT. Iung et al.[12] did abdominal MRI in 58 patients and found at least one IE-related lesion in 34%, all asymptomatic; the spleen was the most affected organ (26% of the patients had ischemic lesions, 3% had hemorrhagic lesions and 3% splenic abscess). It has been recognized that the imaging technique (ultrasound scanners, CT or MRI) and systematic screening vs symptom-oriented diagnostic tests influence the rate of splenic lesions found in endocarditis series. Very few of the patients in these series had histopathological documentation of removed spleens. The rate of abscess and/or very large splenic infarcts was high in the histopathological analysis in our study. These histological findings confirmed the clinical suspicion of a complicated splenic lesion that indicated splenectomy in the first place, in the scenario of emergent cardiac surgery as was the case for most patients in the present study.

The mean size of the vegetation was large (16 ± 6 mm), but there was no association between vegetation size and embolic events, possibly because in less than half the patients vegetation size was documented. Published studies have found 10 mm as the cutoff size associated with higher embolization risk.[8,9,18,24] Rizzi et al. have found a cutoff of 13 mm,[17] and Iung et al. found a 10% increase in the rate of ischemic cerebral lesions at each millimeter increase in vegetation size.[23]

A high percentage of patients had cardiac surgery (74.2%), higher than the 50% described in the literature.[2] This was essentially due to referral bias, as our institution is a referral center for cardiac surgery.

The mortality in this study was 24.2%, which is within the reported range of 9.6–26%.[16,18,26,27] The presence of embolism to the CNS and/or to the spleen did not show an impact on mortality, which contradicts previous studies.[9,18,19]

Considering surgery in patients with cardiovascular complications, some studies have shown to be safe to perform valve replacement surgery in patients with silent stroke; however, other investigators such as Misfield et al.[28] who had analyzed 1571 patients with acute IE, found that survival after surgery is significantly impaired by cerebral embolism, both symptomatic and asymptomatic, concluding that CT scans should be performed in all patients.

Most of the symptoms related to embolic events were nonspecific, and they were infrequent both in patients with or without embolism. Therefore, this reinforces the concept that screening for embolic events should not be based on symptoms. Screening for asymptomatic embolism may be helpful in establishing a definite diagnosis of IE and it may also influence clinical management plans.[12,29] The identification of recent embolic events or infectious aneurysms by imaging only (silent events) should be considered a minor criterion according to the 2015 ESC guidelines, which is an important recognition of their relevance.[1]

Study limitations

This is a single center retrospective study, and therefore results may not be extrapolated to other centers. Data on imaging of the CNS and abdomen were obtained retrospectively through patients' notes.

Conclusions

Asymptomatic embolism to the CNS and especially to the spleen are common in IE. Our data reinforces the importance of routine screening for embolic events in all patients, since nearly one-tenth had asymptomatic embolism to the CNS and one quarter had asymptomatic embolism to the spleen.

Splenomegaly was consistently associated with embolic events.

Embolic events did not have an impact on mortality. However, the detection of embolic events had an impact on the decision-making process regarding the best timing for cardiac surgery and the decision to perform splenectomy.

Therefore, routine screening for embolism by CT scans in patients with IE seems to be justified, especially in those that will undergo cardiac surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:3075–128.
2. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435–86.
3. Mocchegiani R, Nataloni M. Complications of infective endocarditis. Cardiovasc Hematol Disord-Drug Targets. 2009;9:240–8.
4. Hoen B, Duval X. Infective endocarditis. N Engl J Med. 2013;368:1425–33.
5. Hess A, Klein I, Iung B, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. Am J Neuroradiol. 2013;34:1579–84.
6. Lester SJ, Wilansky S. Endocarditis and associated complications. Crit Care Med. 2007;35 Suppl.:S384–91.
7. Naito R, Mitani H, Ishiwata S, et al. Infective endocarditis complicated with splenic abscess successfully treated with splenectomy followed by double valve replacement. J Cardiol Cases. 2010;2:e20–2.
8. Deprèle C, Berthelot P, Lemetayer F, et al. Risk factors for systemic emboli in infective endocarditis. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2004;10:46–53.
9. Mangoni ED, Adinolfi LE, Tripodi M-F, et al. Risk factors for "major" embolic events in hospitalized patients with infective endocarditis. Am Heart J. 2003;146:311–6.
10. Cooper HA, Thompson EC, Laureno R, et al. subclinical brain embolization in left-sided infective endocarditis results from the evaluation by mri of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. Circulation. 2009;120:585–91.
11. Ting W, Silverman NA, Arzouman DA, Levitsky S. Splenic septic emboli in endocarditis. Circulation. 1990;82 Suppl.:IV105–9.
12. Iung B, Klein I, Mourvillier B, et al. Respective effects of early cerebral and abdominal magnetic resonance imaging on clinical decisions in infective endocarditis. Eur Heart J-Cardiovasc Imaging. 2012;13:703–10.
13. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–8.
14. Von Reyn CF, Arbeit RD. Case definitions for infective endocarditis. Am J Med. 1994;96:220–2.
15. Lamas CC, Eykyn SJ. Suggested modifications to the duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. Clin Infect Dis. 1997;25:713–9.
16. Math RS, Sharma G, Kothari SS, et al. Prospective study of infective endocarditis from a developing country. Am Heart J. 2011;162:633–8.
17. Rizzi M, Ravasio V, Carobbio A, et al. Predicting the occurrence of embolic events: an analysis of 1456 episodes of infective endocarditis from the Italian Study on Endocarditis (SEI). BMC Infect Dis. 2014;14:230.
18. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009) The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J. 2009;30:2369–413.
19. Thuny F, Avierinos J-F, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J. 2007;28:1155–61.
20. Chaudhary G, Lee JD. Neurologic complications of infective endocarditis. Curr Neurol Neurosci Rep. 2013;13:380.
21. Derex L, Bonnefoy E, Delahaye F. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. 2010;257:315–21.
22. Rossi M, Gallo A, Silva RJD, Sayeed R. What is the optimal timing for surgery in infective endocarditis with cerebrovascular complications? Interact Cardiovasc Thorac Surg. 2012;14:72–80.
23. Iung B, Tubiana S, Klein I, et al. Determinants of cerebral lesions in endocarditis on systematic cerebral magnetic resonance imaging: a prospective study. Stroke J Cereb Circ. 2013;44:3056–62.
24. Luaces Méndez M, Vilacosta I, Sarriá C, et al. Hepatosplenic and renal embolisms in infective endocarditis. Rev Esp Cardiol. 2004;57:1188–96.
25. Trouillet JL, Hoen B, Battik R, et al. Splenic involvement in infectious endocarditis. Association for the study and prevention of infectious endocarditis. Rev Med Interne. 1999 Mar;20:258–63.
26. Letaief A, Boughzala E, Kaabia N, et al. Epidemiology of infective endocarditis in Tunisia: a 10-year multicenter retrospective study. Int J Infect Dis. 2007;11:430–3.
27. Tariq M, Alam M, Munir G, Khan MA, Smego RA Jr. Infective endocarditis: a five-year experience at a tertiary care hospital in Pakistan. Int J Infect Dis. 2004;8:163–70.
28. Misfeld M, Girrbach F, Etz CD, et al. Surgery for infective endocarditis complicated by cerebral embolism: a consecutive series of 375 patients. J Thorac Cardiovasc Surg. 2014;147:1837–44.
29. Duval X, Iung B, Klein I, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med. 2010;152:497–504. W175.