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## Original article

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

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## ABSTRACT

**Background:** Embolic complications of infective endocarditis (IE) 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 (ICE) 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 IE 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 IE, 36 (36%) were found to have had asymptomatic events, 11 (11%) to the central nervous system (CNS) 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 CNS were IE 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 CNS 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%<sup>1</sup>; this results mainly from complications such as heart failure and embolic events.<sup>1–3</sup>

Embolic complications occur in 20–50%<sup>1</sup> of cases of IE, and are associated with increased mortality and morbidity. They can precede the diagnosis of IE in 25<sup>1</sup> to 60% of patients.<sup>4,5</sup> The most frequent sites of embolization are the central nervous system (CNS) and the spleen.<sup>1</sup> More than 50% of embolic events involve the CNS<sup>6</sup> and embolic events to the spleen occur in 19–36% of cases of IE.<sup>7</sup> 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.<sup>1,8,9</sup>

Embolic events to the CNS are clinically apparent in 10 to 30% of patients with left-sided IE.<sup>10</sup> 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%.<sup>9–11</sup> There are fewer data about subclinical embolic events to the spleen, reported to occur in 26 to 38%.<sup>11,12</sup>

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.<sup>1</sup>

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<sup>13</sup> 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

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