Microvascular Research 118 (2018) 61–68

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

Evaluation of microvascular endothelial function and capillary density in patients with infective endocarditis using laser speckle contrast imaging and video-capillaroscopy

Amanda Barcelos[a], Eduardo Tibirica[a,d,*], Cristiane Lamas[a,b,c]

[a] National Institute of Cardiology, Ministry of Health, Rio de Janeiro, Brazil
[b] National Institute of Infectious Diseases Evandro Chagas, Oswaldo Cruz Institute, Rio de Janeiro, Brazil
[c] UnigranrioUniversity, Rio de Janeiro, Brazil
[d] Laboratory of Cardiovascular Investigation, Oswaldo Cruz Institute, Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Infective endocarditis
Microcirculation
Microvascular dysfunction
Capillary density
Speckle contrast imaging
Skin video-capillaroscopy

ABSTRACT

Objective: To evaluate the systemic microcirculation of patients with infective endocarditis (IE).
Methods: This is a comparative study of patients with definite IE by the modified Duke criteria admitted to our center for treatment. A reference group of sex- and age-matched healthy volunteers was included. Microvascular flow was evaluated in the forearm using a laser speckle contrast imaging system, for noninvasive measurement of cutaneous microvascular perfusion, in combination with skin iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) to test microvascular reactivity. Microvascular density was evaluated using skin video-capillaroscopy.
Results: We studied 22 patients with IE; 15 were male and seven female. The mean age and standard deviation (SD) were 45.5 ± 17.3 years. Basal skin microvascular conductance was significantly increased in patients with IE, compared with healthy individuals (0.36 ± 0.13 versus 0.21 ± 0.08 APU/mmHg; $P < 0.0001$). The increase in microvascular conductance induced by ACh in patients was 0.21 ± 0.17 and in the reference group, it was 0.37 ± 0.14 APU/mmHg ($P = 0.0012$). The increase in microvascular conductance induced by SNP in patients was 0.18 ± 0.14 and it was 0.29 ± 0.15 APU/mmHg ($P = 0.0140$) in the reference group. The basal mean skin capillary density of patients (135 ± 24 capillaries/mm^2) was significantly higher, compared with controls (97 ± 21 capillaries/mm^2; $P < 0.0001$).
Conclusions: The main findings in the microcirculation of patients with IE were greater basal vasodilation and a reduction of the endothelium-dependent and -independent microvascular reactivity, as well as greater functional skin capillary density compared to healthy individuals.

1. Introduction

Infective endocarditis (IE) is a disease which may result in severe complications and with a high mortality rate. Its clinical presentation is dynamic and variable; depending on patient age, the presence of co-morbidities (especially underlying valvular heart disease), the causative microorganism and the presence of complications (Baddour et al. 2015). In recent years, there has been a change in its epidemiological profile, especially in developed countries. Although younger patients with rheumatic valve disease were the predominant population affected by IE, in the last two decades, older individuals and healthcare-associated infections (including those related to intracardiac devices, valve prosthesis and hemodialysis) and a staphylococcal etiology has become more frequent (Baddour et al. 2015; Habib et al. 2015; Murdoch et al. 2009). However, in developing countries, patients with rheumatic valve disease account for a third of all IE cases, and *viridians* group streptococci are the causative agents in a third of all IE cases (Brandao et al. 2017).

Infective endocarditis is a systemic disease involving the vascular system and is often accompanied by bacteremia or fungaemia. Therefore, it results in a septic state. In addition, acute heart failure or acute-on-chronic heart failure commonly complicates left-sided IE due to valve destruction, which leads to acute valvular regurgitation. Indeed, the most common indication for valve replacement surgery is severe heart dysfunction not amenable to pharmacologic intervention (Baddour et al. 2015; Habib et al. 2015; Murdoch et al. 2009).

* Corresponding author at: Av. Brasil 4365, 21045-900, Rio de Janeiro, Brazil.
E-mail address: etibi@ioc.fiocruz.br (E. Tibirica).

https://doi.org/10.1016/j.mvr.2018.02.007
Received 21 November 2017; Received in revised form 26 February 2018; Accepted 27 February 2018
Available online 06 March 2018
0026-2862/

Considering the severity and increasing incidence of IE, it is important to understand further the pathophysiology of the endocarditis syndrome. The use of noninvasive techniques in the early diagnosis of IE and its complications may prove useful. In fact, the evaluation of systemic microvascular reactivity has proven to be very helpful in the investigation of the pathophysiology of cardiovascular and metabolic disorders (Rizzoni et al. 2011; Struijker-Boudier et al. 2007) as well as sepsis (Vincent and Taccone, 2016).

Abnormalities in the microcirculation have been demonstrated through microvascular rarefaction to be present in diseases such as arterial hypertension, diabetes, obesity and metabolic syndrome (De Boer et al. 2012; Francischetti et al. 2011; Kaiser et al. 2013; Karaca et al. 2014; Struijker-Boudier et al. 2007; Tibirica et al. 2007). Moreover, impaired systemic microvascular function, characterized primarily by capillary rarefaction in the skin, has been demonstrated in individuals with increased coronary artery disease risk (IJzerman et al. 2003; Souza et al. 2014).

Laser speckle contrast imaging, which is used to assess skin microvascular reactivity, allows for innovative and reproducible noninvasive evaluation of tissue flow with high real-time spatial resolution in patients with cardiometabolic diseases (Millet et al. 2011; Roustit and Cracowski, 2013)and critically ill patients (De Backer et al. 2013; De Backer et al. 2010). Moreover, cutaneous microvascular reactivity has been correlated to microvascular function in different vascular beds, both in intensity and regarding the underlying mechanisms (Holowatz et al. 2008).

Although IE is the prototype of a septic condition that results in acute heart dysfunction, only one study has addressed microcirculation in a series of patients with infective endocarditis (Piette et al. 1989), and thus far, none have utilized laser speckle contrast imaging or functional skin video-capillaroscopy. Studies have shown microvascular changes in sepsis, in which abnormalities are found in early phases even before the deterioration of hemodynamic parameters (Kiss et al. 2015). These studies show the relationship of microcirculatory changes with organ failure and mortality, which are independent of the systemic hemodynamic variables (Kiss et al. 2015). It is probable that in acute staphylococcal endocarditis, findings similar to those in the studied sepsis models may be encountered (De Backer et al. 2013; Edul et al. 2012).

The goal of this study is to assess microvascular reactivity and density in patients with acute and subacute endocarditis using laser speckle contrast imaging and intravital video-microscopy, respectively.

2. Methods

2.1. Study design and place

This is a comparative study that included patients with a confirmed diagnosis of infective endocarditis who were admitted to the National Institute of Cardiology (NIC) at the Ministry of Health in Rio de Janeiro, Brazil. The NIC is a national reference center for the treatment and research of cardiovascular diseases. Its staff is composed of cardiologists, cardiothoracic surgeons, infectious diseases' specialists, specialized nursing staff, physiotherapists and pharmacists as well as technical staff. The investigative resources include echocardiography, computed tomography, magnetic resonance imaging and scintigraphy. The NIC has outpatient units, four intensive care units and operating theatres where approximately 1300 cardiac surgeries are performed yearly.

2.2. Study participants and recruitment

The present study was conducted in accordance with the Declaration of Helsinki 1975, which was revised in 2000, and was approved by the Institutional Review Board (IRB) of the National Institute of Cardiology in Rio de Janeiro, Brazil under protocol # CAAE 52871216.0.0000 and registered at ClinicalTrials.gov (NCT02940340).Study participants were informed on the nature of the protocol and gave written consent.

The eligibility criteria were as follows: i) confirmed IE according to the modified Duke criteria (Li et al. 2000); ii) inpatient treatment at the NIC; iii) clinical stability at the time of the intervention as evaluated by the investigator; iv) age ≥ 18 years and v) cardiac surgery performed > 15 days prior to the protocol date (Boralessa et al. 1986; Wan et al. 1997). The exclusion criterion was a confirmed previous diagnosis of *diabetes mellitus*.

2.3. Study variables

The variables included were as follows: demographic data (sex and age), medical conditions prior to the diagnosis of IE (systemic arterial hypertension, renal failure on conservative or dialytic treatment, smoking, chronic valvular disease, cardiac surgery or percutaneous procedures), predisposing conditions to IE (previous episode of IE, rheumatic valve disease, congenital heart disease, intravenous drug use, valve prosthesis and intracardiac devices), medications in use (angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), statins, betablockers, diuretics), data referring to the episode of IE, such as timing of presentation (acute IE was defined as the presentation of signs and symptoms within one month of diagnosis, and subacute IE as that presenting for more than one month at the time of diagnosis), mode of acquisition (community-acquired and health care-related; the second defined as IE occurring > 72 h following hospital admission or acquired within two months of an invasive procedure), etiologic agents. These latter were divided into four groups for analysis: i) viridans group streptococci, including those with blood culture negative, since we have previously shown by PCR of excised valves that viridians streps are the most frequent agents in our scenario IE (Lamas et al. 2016); ii) aggressive staphylococci (including *Staphylococcus aureus* both methicillin susceptible and resistant and *S. lugdunensis*; iii) coagulase negative staphylococci and iv) enterococci. We also evaluated affected structures and left ventricular function, evaluated as normal or moderately to severely compromised at the time of diagnosis of IE; left ventricular ejection fraction was not used as a parameter for heart dysfunction as it is often overestimated in moderate to severe valvular regurgitation, the predominant lesion in IE. Other variables studied were pulmonary artery systolic pressure (PASP), as an indirect measure of myocardial dysfunction, embolic and non-embolic complications (paravalvular abscess, prosthetic dehiscence, atrioventricular block, new cardiac failure, new renal failure); antibiotic and surgical treatment and laboratory data (C-reactive protein levels, CRP, hemoglobin, hematocrit, leukocyte count, and serum creatinine levels). For complete data describing clinical characteristics of patients see Tibirica et al. (2018).

2.4. Intervention

The evaluation of microvascular endothelial function in patients with infective endocarditis was performed using laser speckle contrast imaging. These results were compared to those previously obtained from age and sex-matched healthy volunteers (Souza et al. 2014). The systemic microvascular data obtained from this group of healthy volunteers were used as reference microcirculatory values of individuals free of systemic diseases. The healthy volunteers did not present with arterial hypertension, diabetes, dyslipidemia or any other systemic pathology.

2.5. Evaluation of microcirculatory reactivity

The microcirculatory tests were performed in the morning between 8 A.M. and 12 P.M. in an undisturbed, quiet room with a defined stable temperature (23 ± 1 °C), following a 20-min rest period in the supine