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CLINICAL RESEARCH

Infective endocarditis without biological inflammatory syndrome: Description of a particular entity

Endocardite infectieuse sans syndrome inflammatoire biologique: description d'une entité particulière

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Abbreviations: CDRIE, cardiac device-related infective endocarditis; CRP, C-reactive protein; IE, infective endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC, white blood cell.

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KEYWORDS
Infective endocarditis;
Inflammation;
C-reactive protein;
Valvular regurgitation;
Heart failure

Summary
Background. — Bacterial infective endocarditis (IE) is rarely suspected in patients with a low C-reactive protein (CRP) concentration.
Aims. — To address the incidence, characteristics and outcome of left-sided valvular IE with low CRP concentration.
Methods. — This was a retrospective analysis of cases of IE discharged from our institution between January 2009 and May 2017. The 10% lowest CRP concentration (< 20 mg/L) was used to define low CRP concentration. Right-sided cardiac device-related IE, non-bacterial IE, sequelar IE and IE previously treated by antibiotics were excluded.
Results. — Of the 469 patients, 13 (2.8%; median age 68 [61—76] years) had definite ($n = 8$) or possible ($n = 5$) left-sided valvular IE with CRP < 20 mg/L (median 9.3 [4.7—14.2] mg/L). The median white blood cell count was 6.3 (5.3—7.5) G/L. The main presentations were heart failure ($n = 7$; 54%) and stroke ($n = 3$; 23%). Transthoracic echocardiography (TTE) showed vegetations ($n = 5$) or isolated valvular regurgitation ($n = 4$). Overall, eight patients (62%) had severe valvular lesions on transoesophageal echocardiography (TOE), and nine patients (69%) underwent cardiac surgery. All patients survived at 1-year follow-up. Bacterial pathogens were documented in eight patients (streptococci, coagulase-negative *Staphylococcus*, *Corynebacterium jeikeium*, HACEK group, *Coxiella burnetii*, *Bartonella henselae*) using blood cultures, serology or valve culture and/or polymerase chain reaction analysis.
Conclusions. — Left-sided valvular IE with limited or no biological syndrome is rare, but is often associated with severe valvular and paravalvular lesions. TOE should be performed in presence of unexplained heart failure, new valvular regurgitation or cardioembolic stroke when TTE is insufficient to rule out endocarditis, even in patients with a low CRP concentration.

MOTS-CLÉS
Endocardite infectieuse ;
Inflammation ;
Protéine C-réactive ;
Insuffisance valvulaire ;
Insuffisance cardiaque

Résumé
Contexte. — Le diagnostic d'endocardite infectieuse (EI) est rarement suspecté chez les patients avec protéine C-réactive (CRP) basse.
Objectifs. — Analyser l'incidence, les caractéristiques et le devenir des EI valvulaires du cœur gauche (EIVCG) à CRP basse.
Méthodes. — Une analyse rétrospective des cas d'EI entre janvier 2009 et mai 2017 a été réalisée. Les seuils 10 % plus bas (< 20 mg/L) ont été utilisés pour définir la CRP basse. Les EI du cœur droit sur matériel, non-bactériennes, séquellaires et patients avec antibiothérapie préalable ont été exclus.
Résultats. — Sur les 460 patients, 13 (2,8 %; 68 [61—76] ans) avaient une EIVCG certaine ($n = 8$) ou possible ($n = 5$) avec CRP < 20 mg/L (médiane 9,3 [2,4,7—14] mg/L). Le taux médian de leucocytes était 6,3 (5,3—7,5) G/L. Les principales présentations étaient l'insuffisance cardiaque ($n = 7$; 54 %) et les accidents vasculaires cérébraux (AVC) ($n = 3$; 23 %). L'échocardiographie transthoracique (ETT) mettait en évidence des végétations ($n = 5$) ou des insuffisances valvulaires ($n = 4$). Au total, 8 patients (62 %) avaient des lésions valvulaires sévères à l'échocardiographie transoesophagienne (ETO) et 9 patients (69 %) ont bénéficié d'une chirurgie cardiaque. Tous les patients avaient survécu à 1 an. Les bactéries ont été documentées chez 8 patients (streptococci, coagulase-negative *Staphylococcus*, *Corynebacterium jeikeium*, HACEK, *Coxiella burnetii*, *Bartonella henselae*) à l'aide d'hémocultures, de sérologies ou de culture/PCR des valves.
Conclusions. — Les EIVCG avec faible ou sans syndrome inflammatoire sont rares mais souvent associées à de sévères lésions valvulaires et para-valvulaires. L'ETO devrait être réalisée en présence d'insuffisance cardiaque inexpliquée, de nouvelle fuite valvulaire ou d'AVC cryptogénique lorsque l'ETT ne suffit pas à éliminer l'EI, même chez les patients avec CRP basse.

Background

Infective endocarditis (IE) is a life-threatening disease with an incidence of 30—100 episodes per million patient-years [1]. The in-hospital mortality rate ranges from 16% to 25% [2], but may be reduced by structuring the care management to reduce the delay in diagnosis and surgery [3]. The diagnosis is commonly raised when fever and/or biological inflammatory profile is associated with a cardiac murmur or a systemic event. The current biological marker used to characterize inflammation is plasma C-reactive protein (CRP). CRP is a non-specific acute-phase serum protein secreted by the liver in response to inflammatory cytokines. CRP promotes early immune defence, activates complement and acts as an opsonin for various pathogens [4,5]. CRP is recommended for the diagnosis and monitoring of IE outcome [3], but may have reduced sensitivity in patients treated previously with antibiotics, and also in cardiac device-related IE (CDRIE) [6]. In left-sided valvular IE, limited studies have specifically addressed the clinical characteristics of patients with a low CRP concentration as a surrogate of inflammatory syndrome. This is an important topic because the diagnosis may be delayed or missed. The purpose of this study was to describe the incidence, clinical profile and outcome of these patients.

Methods

Population study

We retrospectively analysed all patients discharged from our institution with the diagnosis of IE between January 2009 and May 2017. The 10% lowest value of pooled CRP from all patients ($n = 442$) was used to define low CRP concentration. We included only left-sided IE. We excluded patients with sequelar IE (defined by endocarditis initially considered and treated as active, which was subsequently considered by the endocarditis team as sequelar to previously undiagnosed IE), isolated right-side IE, CDRIE and non-bacterial endocarditis (non-bacterial thrombotic, Libman-Sacks or marastic endocarditis). We also excluded patients treated previously with antibiotics, administered by a general practitioner, in our hospital or in other settings, during the month before the first CRP measurement. The study was approved by our local ethics committee. All patients provided informed consent to participate.

Clinical data and outcome

Clinical data were collected from electronic medical records. Fever was defined as body temperature $\geq 38\,^{\circ}C$. Echocardiographic data were stored digitally, and reviewed by two experts in endocarditis imaging. One-year mortality was obtained from medical records or by patient or family contact.

IE diagnosis

All medical records were reviewed retrospectively by the endocarditis team, and the diagnosis of IE was based on the European Society of Cardiology diagnostic criteria [3]. In patients undergoing cardiac surgery, excised cardiac valvular tissues were sent for pathological analysis. Histological criteria for endocarditis combined inflammatory and destructive tissue lesions with evidenced microorganism colonies on cultures. Culture of tissue biopsies was optimized by using the bead mill processing preanalytical method (Ultra-TurrAX®; Axon Lab AG, Reichenbach, Germany), several solid agar plates inoculated for aerobic and anaerobic culture and two blood culture vials per sample (bioMérieux, Marcy l'Étoile, France). Pathogen identification was done using matrix assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (Andromas; Beckman Coulter, Villepinte, France). Deoxyribonucleic acid extraction, broad-spectrum 16S ribosomal ribonucleic acid gene real-time polymerase chain reaction and sequence analysis were performed with the UMD-Universal kit according to the instructions of the manufacturer (Molzym GmbH & Co. KG, Bremen, Germany).

CRP measurement

Plasma samples were collected from each patient on the day of admission, and were analysed in the biochemistry department. CRP was measured on a COBAS® 6000 analyzer series (Roche Diagnostics, Indianapolis, IN, USA) using the immunoturbidimetry technique. CRP concentration is expressed in milligrams per litre (mg/L).

Statistical analysis

Continuous variables are expressed as medians (interquartile ranges) because of the small population size. Nominal variables are expressed as numbers and percentages. Statistical analyses were performed using IBM SPSS® for Windows (IBM, Armonk, NY, USA).

Results

As shown in Fig. 1 , among the 469 patients admitted for IE between January 2009 and May 2017, CRP at admission was assessed in 442 patients and the median CRP concentration was 63.2 (28—129) mg/L. The 10% lowest value of CRP (CRP < 20 mg/L) included 43 patients. We excluded patients with sequelar ($n = 6$) or non-bacterial ($n = 3$) endocarditis, those previously treated by antibiotics ($n = 17$) and those with right-sided CDRIE ($n = 4$). Finally, 13 patients had left-sided bacterial IE with low CRP concentration (incidence of 2.8%).

Clinical presentation

The majority of patients (median age 68 [61—76] years; 77% men) did not have fever (85%, $n = 11/13$), and none had a history of immunodeficiency disease or long-term immunosuppressive therapy treatment. Relevant medical history included congenital heart disease ($n = 2$; one aortic bicuspid valve and one congenital aortic stenosis) and previous left-sided valvular surgery ($n = 5$). History of endocarditis was reported in 15% ($n = 2$), chronic kidney disease without dialysis in 23% ($n = 3$) and diabetes mellitus in 15% ($n = 2$) of patients. The main presentations were apyretic heart

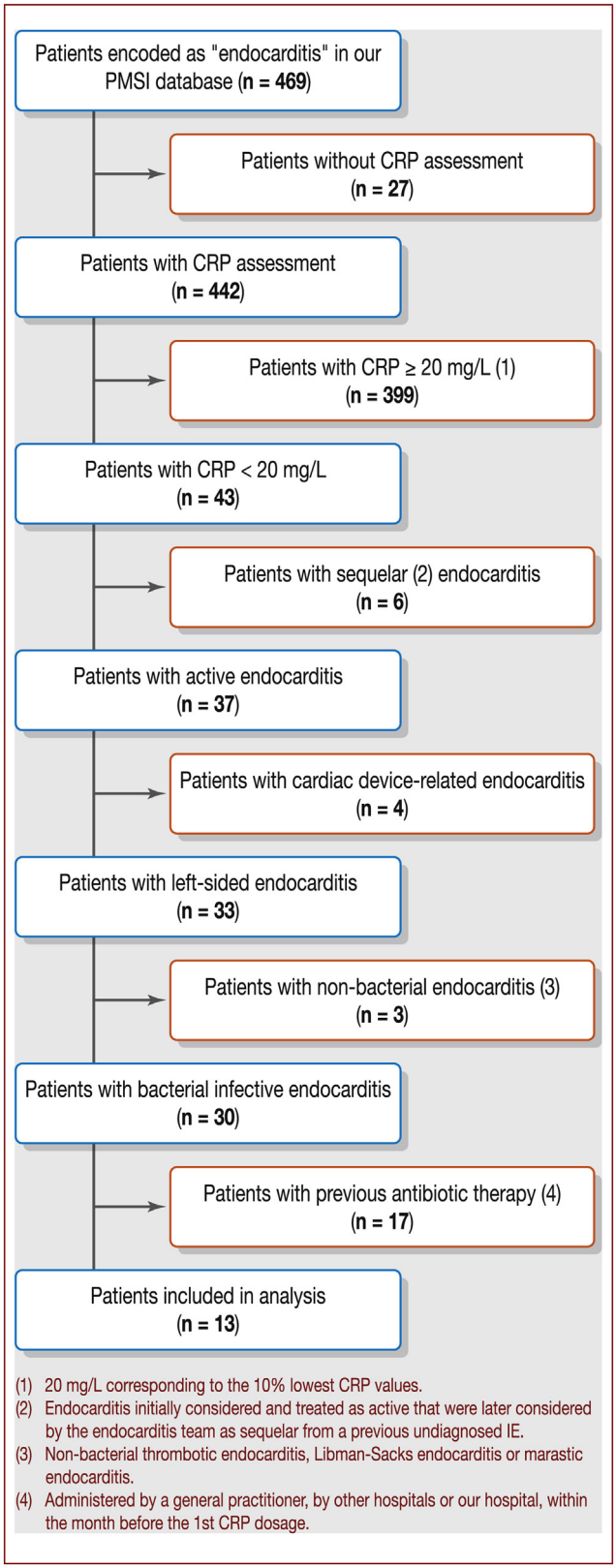

Figure 1. Flow chart. CRP: C-reactive protein; PMSI: Programme de Médicalisation des Systèmes d'Information. [a] 20 mg/L corresponding to the 10% lowest CRP values. [b] Endocarditis initially considered and treated as active, which was subsequently considered by the endocarditis team as sequelar to previously undiagnosed infective endocarditis. [c] Non-bacterial thrombotic endocarditis, Libman-Sacks endocarditis or marastic endocarditis. [d] Administered by a general practitioner, by other hospitals or in our hospital, within the month before the first CRP measurement.

failure ($n = 7$, 54%) and stroke ($n = 3$, 23%). The time interval between onset of symptoms and IE diagnosis was < 1 month for eight patients and > 1 month for five patients (Table 1 and Table A.1).

Echocardiographic data

Transoesophageal echocardiography (TOE) was indicated because transthoracic echocardiography (TTE) showed vegetations ($n = 5$) and/or severe valvular regurgitation ($n = 4$). For the remaining patients, TOE was performed to investigate the cause of systemic embolization ($n = 1$), positive *Coxiella burnetii* serology ($n = 1$) or bacteraemia (*Streptococcus*; $n = 1$). One patient had IE diagnosed during cardiac surgery. Endocarditic lesions were located on the aortic valve for five patients, on the mitral valve for four patients and on both valves for four patients. Most patients had severe valvular lesions (62%, $n = 8$), which included paravalvular abscess ($n = 4$), severe valve regurgitation ($n = 7$) and valvular perforations ($n = 2$).

Biological and microbiological analysis

All patients had a white blood cell (WBC) count ≤ 10 G/L (median 6.3 [5.3—7.5] G/L), with a median neutrophil count of 4.2 (2.6—5.9) G/L. The median CRP concentration on admission was 9.3 (4.7—14.2) mg/L. Blood cultures were positive for four patients, but two were considered to be contaminations (Table 2 and Table 3). One patient had positive serology for *C. burnetii*, and five patients were considered to have culture-negative IE. Valve culture was performed in eight of nine patients who underwent cardiac surgery. Valve culture was positive for four patients, and the microorganisms identified were *Corynebacterium jeikeium* ($n = 2$), *Bartonella henselae* ($n = 1$) and *Staphylococcus hominis* ($n = 1$); the last of these was considered as a potential contamination. Finally, 16S ribonucleic acid detection using polymerase chain reaction was positive in three patients, enabling identification of *Cardiobacterium hominis*, *B. henselae* and *C. jeikeium*, respectively. Overall, 10 patients had microbiological documentation (Table 2 and Table 3).

Treatment and outcome

IE diagnosis was considered as definite for eight patients: three with two major criteria [3] and five confirmed by explanted cardiac valve analysis (Table 4). For the remaining five patients, the diagnosis of IE was considered as possible by the endocarditis team. Empirical antimicrobial therapy was administered after blood culture samples in all cases; the antibiotics were then adapted to the microbiological findings (Table A.2). Systemic embolic events were reported in six patients during hospitalization (Table 1). Major neurological sequelae were reported in the three patients with cerebral embolisms. No patient experienced haemodynamic

Table 1 Patient characteristics ($n = 13$).

Men	10 (77)
Age (years)	68 (61—76)
History of IE	2 (15)
Congenital aortic valve disease	2 (15)
Previous left-sided valvular surgery	5 (38)
Stroke	3 (23)
Diabetes mellitus	2 (15)
Chronic kidney disease	3 (23)
Symptoms and clinical features	
Time interval between symptoms and IE diagnosis < 1 month	8 (62)
Time interval between symptoms and IE diagnosis > 1 month	5 (38)
Fever	2 (15)
Heart failure	7 (54)
Stroke	3 (23)
Extracardiac signs of IE	3 (23)
Biological data	
C-reactive protein (mg/L)	9.3 (4.7—14.2)
White blood cells (G/L)	6.3 (5.3—7.5)
Polymorphonuclear leukocytes (G/L)	4.2 (2.6—5.9)
Transoesophageal echocardiography findings	
Paravalvular abscess	4 (31)[a]
Severe valvular regurgitation	7 (54)
Valve perforation	2 (15)
Vegetations	7 (54)
Left ventricular ejection fraction	55 (50—60)
Native valve endocarditis	7 (54)
Aortic IE	5 (38)
Mitral IE	4 (31)
Polyvalvular IE	4 (31)
Embolic lesions	
Cerebral	4 (31)
Renal	1 (8)
Splenic	1 (8)
Cardiac surgery	
All	9 (69)
Valve replacement	7 (78)
Valve repair	2 (22)
Time from diagnosis to surgery (days)	6.8 (0—24)
Outcome	
Neurological sequelae[b]	4 (31)
One-year mortality	0

Data are expressed as number (%), median (interquartile range) or mean (range). IE: infective endocarditis.
[a] Two diagnosed by TOE and two discovered during cardiac surgery.
[b] Three patients had sequelae from stroke and one from epileptic seizures caused by hydroxychloroquine.

instability. All patients with a surgical indication ($n = 10$) were operated on, except for one who was deemed to be at prohibitive surgical risk. The median EuroSCORE II was 3.8% (2.5—6.4%). Valvular replacement was performed in 78% of patients, and mitral valve repair was performed in 22%. No patient died or relapsed after the 1-year follow-up (Table A.2).

Discussion

This study is, to our knowledge, the first published description of patients with IE associated with low inflammatory syndrome. This study has demonstrated that IE with low CRP concentration is relatively rare (2.8%), but is often associated with severe valvular destruction. The diagnosis is often challenging, because the WBC count is normal, fever is often missing and blood cultures are negative.

Biological inflammation and fever are the basic signs that raise suspicion of IE. Despite the exclusion of patients previously treated by antibiotics and patients with non-bacterial endocarditis [7] we found that a very small proportion of patients can have left-sided valvular endocarditis with only limited inflammation (CRP concentration < 20 mg/L) and a normal WBC count. IE diagnosis in this setting is challenging, because the presence of fever is rare (15%) and blood

Table 2 Characteristics of individual patients with definite infective endocarditis according to European Society of Cardiology criteria.

Patient number	Age (years)	Admission symptoms & signs	IE	Cardiac history	Admission CRP; WBCs (mg/L; G/L)	Indication for TOE after TTE	TOE findings	Surgery findings	Microbiology	Blood cultures	Valve culture	16S RNA	Histology findings	Antibiotics
1[a]	65	Apyrexia; HF	Aortic NVE	None	4.7; 8.7	Valvular regurgitation	Severe AR; septal abscess	Aortic vegetation & abscess	−ve	−ve	−ve	−ve	+ve	Amoxicillin + amoxicillin & clavulanic acid + gentamicin
2[a]	33	Apyrexia; HF	Aortic NVE	Aortic bicuspid valve	12.8; 7.2	Vegetation	Aortic vegetation & abscess; severe AR	Aortic valve abscess	*Cardiobacterium hominis*	−ve	−ve	+ve	+ve	Amoxicillin & clavulanic acid + gentamicin
3[a]	65	Fever; HF	Aortic/mitral/ tricupsid NVE	None	19.7; 3.7	Vegetation	Aortic & tricuspid vegetations; severe MR	Aortic valvular abscess & tricuspid vegetations	*Bartonella henselae*	−ve	ND	+ve	+ve	Doxycycline + gentamicin
4	21	Fever	Mitral NVE	Aortic stenosis	10.4; 5.5	*Streptococcus* bacteraemia	Mitral vegetation	Not operated	*Streptococcus viridans*	×2 (first 33/37 h; second 27/41 h)	−ve	ND	−ve	Amoxicillin + gentamicin
5[a]	68	Apyrexia; HF	Mitral PVE (annuloplasty)	Mitral annuloplasty	4.2; 6.3	ND	Mitral valve stenosis	Incidental mitral abscess	*Corynebacterium jeikeium*	−ve	+e	+ve[b]	ND	Vancomycin + rifampicin + gentamicin
6[a]	76	Apyrexia; stroke	Mitral PVE (annuloplasty)	IE; mitral annuloplasty	2.9; 7.5	Vegetation	Mitral vegetation	Mitral vegetations & abscess	*Corynebacterium jeikeium*	−ve	+ve	ND	+ve	Amoxicillin + cefazoline + gentamicin
7	75	Apyrexia; purpura; polyarthralgia	Aortic PVE (bioprosthesis)	Aortic bioprosthesis	14.4; 3.9	Vegetation	Aortic & mitral vegetations	Not operated	*Staphylococcus epidermidis*	×3 (22−27 h)	−ve	ND	−ve	Vancomycin + gentamicin
8	76	Apyrexia; purpura	Aortic PVE (mechanical Bentall)	None	9.3; 4.3	Positive *Coxiella* serology	Periaortic haematoma	Not operated	*Coxiella burnetii*	Positive serology[c]	−ve	ND	−ve	Doxycycline + hydroxychloroquine

−ve: negative; +ve: positive; AR: aortic regurgitation; CRP: C-reactive protein; HF: heart failure; IE: infective endocarditis; MR: mitral regurgitation; ND: Not done; NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; RNA: ribonucleic acid; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography; WBC: white blood cell.

[a] Definite IE with histological confirmation.

[b] Polymerase chain reaction (Unyvero; Curetis, Holzgerlingen, Germany).

[c] Immunoglobulin G phase 1: 65536.

Table 3 Characteristics of individual patients with possible infective endocarditis according to European Society of Cardiology criteria.

Patient number	Age (years)	Admission symptoms & signs	IE	Cardiac history	Admission CRP; WBCs (mg/L; G/L)	Indication for TOE after TTE	TOE findings	Surgery findings	Microbiology	Blood cultures	Valve culture	16S RNA	Histology findings	Antibiotics
9	61	Apyrexia; TIA	Mitral PVE (annuloplasty)	IE; mitral annulo-plasty	4.2; 6.5	Vegetation	Mitral vegetation	Not operated	−ve	−ve	−ve	−ve	−ve	Vancomycin + gentamicin
10	17	Apyrexia; cerebral haemorrhage	Aortic/mitral PVE	Mitral annu-loplasty; aortic mechanical prosthesis	7.6; 5.3	Stroke	Severe MR	Periaortic abscess	−ve	−ve	−ve	−ve	−ve	Cefotaxime + vancomycin + gentamicin
11	78	Apyrexia; HF	Mitral NVE	None	14.2; 8	Valvular regurgita-tion	Mitral valve perforation & vegetation; severe MR	Posterior mitral destruction	*Staphylococcus capitis (considered as a contamination)*	×1 (15 h)	+ve	ND	−ve	Vancomycin + gentamicin
12	81	Apyrexia; HF	Mitral NVE	None	17.1; 10.5	Valvular regurgita-tion	Severe MR; mitral chordae rupture	Posterior mitral prolapse	*Streptococcus gallolyticus spp. pasteurianus*	×2 (12 h)	−ve	−ve	ND	Penicillin G + gentamicin
13	73	Apyrexia; HF	Aortic/mitral NVE	None	4.7; 6.1	Valvular regurgita-tion	Mitral perforation; severe MR	Mitral-aortic abscess	*Staphylococcus hominis (considered a contamination)*	−ve	+ve	−ve	ND	Amoxicillin + amoxicillin & clavulanic acid + gentamicin

−ve: negative; +ve: positive; CRP: C-reactive protein; HF: heart failure; IE: infective endocarditis; MR: mitral regurgitation; ND: Not done; NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; RNA: ribonucleic acid; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography; WBC: white blood cell.

Table 4 Confirmation of diagnosis of infective endocarditis.

Diagnosis confirmation	Number of patients
Definite IE[a]	
Two major criteria	3
One major criterion and three minor criteria	0
Five minor criteria	0
Possible IE[a], but histological confirmation	5
Possible IE[a]	
One major criterion and one minor criterion	5
Three minor criteria	0

IE: Infective endocarditis.
[a] According to the European Society of Cardiology criteria.

cultures are often negative (77%). The mechanism of low CRP concentration is probably related to microorganism patterns, as no patient had documented immunodeficiency or liver dysfunction. The majority of microorganisms found in this study may potentially be associated with an attenuated inflammatory response. Typically, during the chronic phase of infection with *C. burnetii* [8], the patient presents with a normal WBC count and a low inflammatory response [9]. Similarly, the inflammatory response may be attenuated in *B. henselae* infection by an overproduction of interelukin-10 [10], Toll-like receptor 4 inhibition [11] and endothelial cell function subversion [12]. *C. hominis* and *Staph. epidermidis* are generally associated with insidious presentation, with a delayed diagnosis because of their slow-growing nature [13]. *Staph. epidermidis* is able to maintain a low level of virulence and to subsist chronically [14] by synthetizing a protective biofilm. Similarly, *Strep. viridans* [15] can also develop a protective biofilm [16] and attenuate the immune response. Finally, in a systematic review of *C. jeikeium* IE published in 2006 [17], Mookadam et al. demonstrated that 78% of patients included for analysis had fever on admission. These infections mainly concerned patients with prosthetic material (74% of prosthetic valvular IE in this study), with a mortality rate of 30—40%, depending on the study. This bacterium is mainly known for being related to nosocomial infection. Both of our patients with *C. jeikeium* IE fitted the profile (except for their absence of fever), as they both had prosthetic valve infections and a paravalvular abscess discovered by surgery. CRP concentrations were not stated in this study, and there seems to be few mentions of CRP concentrations in *Corynebacterium*. IE in the literature. In a report of five cases published in 1989 [18], however, there was allusion to a ''pronounced inflammatory syndrome'' in one patient.

The severe and rapid progression of the endocarditic process in this population is intriguing, given the low inflammatory process and the bacterial profile. This contrasts with previous published studies reporting a correlation between the severity of inflammation and the importance of valvular destruction and embolic complications [19—25]. This was probably related to a population selection bias in these studies, because TOE was only performed in symptomatic patients with unexplained severe valvular lesions or with systemic embolic events. Then, it is probable that some IE without severe valvular lesions may be underdiagnosed because of the low inflammatory profile. This study underlines the need to perform TOE in the presence of unexplained heart failure, new valvular regurgitation or cardiac embolism when TTE is insufficient to rule out endocarditis.

Study limitations

One-year survival was excellent despite destructive valvular lesions, probably because most patients were referred to cardiac surgery (69%), and because the population was relatively young with a low operative risk [26]. It is tempting to hypothesize that low inflammation may have a protective role, but the population size was too small to further support this assumption. A large prospective multicentre study may be of value in addressing this particular entity specifically.

Conclusions

IE with low inflammatory profile is rare, but may be associated with severe and destructive valvular lesions. This entity is challenging, because fever is rarely present and blood cultures are often negative. TOE should be performed systematically in the presence of unexplained heart failure, new valvular regurgitation or cardioembolic stroke when TTE is insufficient to rule out infective endocarditis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2019.02.005.

Disclosure of interest

The authors declare that they have no competing interest.

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