

## BRIEF REPORTS

# Influence of Sex on Left-Sided Infective Endocarditis

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In many cardiovascular and infectious diseases, there are clinical and prognostic differences between men and women. The aim of this study was to compare the presentation of left-sided infective endocarditis in the two sexes. A total of 621 episodes of left-sided infective endocarditis (395 in men, 226 in women) were studied. The comparative analysis considered epidemiological, clinical, microbiological, echocardiographic and prognostic variables. Despite marked epidemiological, echocardiographic and microbiological differences between men and women, clinical characteristics, treatment approaches and outcomes (in-hospital mortality: 28% in men and 35% in women;  $P=.1$ ) were similar in our patient series.

**Key words:** *Infective endocarditis. Sex. Prognosis.*

## Influencia del género en la endocarditis infecciosa izquierda

Las mujeres presentan diferencias clínicas y pronósticas en muchas enfermedades cardiovasculares e infecciosas respecto a los varones. El objetivo de este trabajo es comparar el perfil de la endocarditis infecciosa izquierda entre varones y mujeres. Se analizó un total de 621 episodios de endocarditis infecciosa izquierda (395 en varones, 226 en mujeres). Se realizó un análisis comparativo de variables epidemiológicas, clínicas, microbiológicas, ecocardiográficas y pronósticas. A pesar de notables diferencias epidemiológicas, ecocardiográficas y microbiológicas entre los dos sexos, las características clínicas, la estrategia de tratamiento y el pronóstico (mortalidad intrahospitalaria, el 28% en varones y el 35% en mujeres;  $p = 0,1$ ) fueron similares en nuestra serie.

**Palabras clave:** *Endocarditis infecciosa. Género. Pronóstico.*

## INTRODUCTION

Most cardiovascular and infectious diseases show relevant differences in the clinical profile and outcomes between men and women. In general, cardiovascular diseases appear later in women; therefore, females present associated comorbidities related to age most frequently than males.<sup>1</sup> Several studies have proven that women receive treatments following clinical guidelines less frequently and are less likely to undergo invasive procedures than men.<sup>2-4</sup> Moreover, mitral valvulopathy is more

common in women, whereas in men, aortic diseases predominate.<sup>5</sup> Some studies have also shown different features in infectious diseases in both sexes, regarding sepsis, lung and soft tissue infection.<sup>6,7</sup> All these facts make us speculate that infective endocarditis (IE) shows different characteristics in men than in women. However, this aspect is still a matter of debate because there are few studies that analyze the influence of sex in IE and they have contradictory results.<sup>8,9</sup> This study presents the largest series to date which analyzes the influence of sex on the most relevant variables in isolated left-sided IE.

## METHODS

Of 621 episodes of left-sided IE among 600 patients consecutively diagnosed in 3 tertiary centers between 1996 and 2007, 395 were males (64%) and 226 in females (36%). All patients occurred in subjected to an exhaustive diagnostic, therapeutic, and prognostic approach which has been previously reported in detail, as well as the definitions used in the description.<sup>10</sup> Surgery was considered as

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urgent if performed before antibiotic treatment had ended. Surgical indications were established by consensus of the researchers before the study began, and included heart failure refractory to medical treatment, fungal endocarditis, recurrent embolism with persistent vegetations in the echocardiogram, and uncontrolled infection defined as persistent bacteremia or fever persisting for more than 7 days despite appropriate antibiotic treatment, once other foci of infection had been ruled out. Surgery was defined as elective if performed after antibiotic treatment had ended. Once the antibiotic treatment was finished and the IE was healed, we followed the valvular disease guidelines for the indication of cardiac surgery. The clinical criteria to operate or not were the same in all groups. When a patient with surgical criteria did not undergo surgery, this was either because the patient rejected the intervention, surgical risk was too high, or because the patient was too fragile. In all cases the final decision was decided by a multidisciplinary team of cardiologists, cardiac surgeons, microbiologists and specialists in infective diseases.

### Statistics

Continuous variables are reported as mean (standard deviation) and compared with Student *t* test and Mann-Whitney *U* test for non-normaly distributed variables. Categorical variables are reported as absolute values and percentages and compared using  $\chi^2$  tests and Fisher's exact tests when appropriate. Differences were considered statistically significant at *P*-values below .05.

### RESULTS

The most relevant differences found between the sexes are summarized in Table 1. Women in this series were older and more likely to present diabetes mellitus, nosocomial endocarditis, and prosthetic valve endocarditis; they also had more rheumatic cardiopathy, whereas men were more likely to have endocarditis without predisposing cardiopathy. The only clinical difference was that women presented more septic shock at admission and developed more persistent infection during the clinical course of the disease.

Mitral mechanical prosthetic valve endocarditis was more common in women, whereas native aortic endocarditis was more common in men. Men were more likely to have pseudoaneurisms, valvular rupture, and significant valvular regurgitation.

The microbiological profile in both sexes is shown in Table 2. *Staphylococcus aureus* was the most frequent causal microorganism in both sexes

followed by *Streptococcus viridans* in men and coagulase-negative *Staphylococci* in women.

Both sexes received similar treatment strategies (medical or combined medical-surgical) and no significant differences in hospital mortality were found, although there was a trend towards higher mortality among women who received elective surgery. We followed our patients for a median of 111 months (interquartile range, 32-154). During the first year after discharge, the incidence of complications (defined as mortality, valvular surgery, relapse or reinfection) was 12% in men (14.5% among those patients medically treated, 16.4% in urgent surgery and 5.9% in elective surgery cases) and 8% in women (12.5% among those patients medically treated, 3.8% in urgent surgery and 4.8% in elective surgery cases), without significant differences between sexes, *P*=.3.

### DISCUSSION

Only 2 published studies have analysed the impact of sex on IE.<sup>8,9</sup> In both of them, women were less likely than men to undergo surgery, despite a similar clinical course in both sexes. Only in one, women presented higher in-hospital mortality,<sup>8</sup> although female sex was not an independent predictor of mortality in any of them. Both series included left and right-sided IE, entities with such important differences that in our opinion they must be analyzed separately. Another important limitation of these studies is the low use of transesophageal echocardiography, which can limit the echocardiographic findings. Our work is unique in several aspects: *a*) it is the series with the largest number of patients in which the influence of sex on IE is analyzed; *b*) it is the only one in which both sexes were treated equally; *c*) only episodes of left-sided IE were included; and *d*) transesophageal echocardiography was performed on every patient at least once.

Infective endocarditis is more frequent in men, with a male:female ratio of 2:1.<sup>11</sup> It had been proposed that hormonal factors could protect women from endothelial damage,<sup>12</sup> although the cause of this difference has not been well established yet. Our male to female ratio is similar to previous reports (1.7:1). In our series, women were older than men, which can explain the higher prevalence of comorbid conditions such as diabetes mellitus, strongly associated with increasing age.<sup>13</sup>

As expected, the disease was more often located in the mitral position in women (native or prosthetic valve) and in the aortic position in men; this pattern follows the distribution of the valvular disease according to sex.<sup>5</sup>

The microbiological profile is similar in both sexes. The higher incidence of *Streptococcus viridans* in men can be explained because they are more likely

**TABLE 1. Clinical, Echocardiographic, and Prognostic Features of Left-Sided IE in Both Sexes**

	Men, n (%)	Women, n (%)	P
Age, mean (SD), y	59 (15)	63 (15)	<.01
Nosocomial endocarditis; n (%)	103 (26)	79 (35)	.03
Diabetes mellitus	67 (17)	59 (26)	<.01
Diagnosis delay (days)	10.1	8.1	.07
Previous cardiopathy	263 (67)	174 (78)	<.01
Rheumatic	28 (7)	28 (13)	.03
Degenerative	39 (10)	31 (14)	.1
Prosthetic valve	145 (37)	105 (47)	.01
None	119 (30)	45 (20)	<.01
Endocarditis location			
Aortic native valve	172 (37)	49 (18)	<.01
Mitral native valve	138 (29)	95 (35)	.09
Aortic mechanical prosthesis	58 (12)	31 (12)	.7
Mitral mechanical prosthesis	57 (12)	74 (28)	<.01
Echocardiographic data			
Periannular complications	95 (24)	42 (19)	.1
Abscess	57 (14)	28 (12)	.5
Pseudoaneurysm	44 (11)	13 (6)	.03
Fistula	10 (2.5)	9 (4)	.3
Valvular rupture	36 (9)	10 (4.5)	.03
Severe valvular regurgitation	259 (67)	106 (48)	<.01
Clinical course			
Heart failure	64 (27)	46 (34)	.1
Renal failure	84 (25)	60 (31)	.1
Septic shock	35 (9)	26 (13)	.2
Stroke	31 (9)	14 (8)	.5
Persistent infection	125 (32)	91 (40)	.03
Systemic embolism	110 (28)	68 (30)	.5
Treatment			.08
Medical treatment	153 (39)	108 (48)	
Urgent surgery	112 (28)	54 (24)	
Elective surgery	130 (33)	64 (28)	
In-hospital mortality	112 (28)	78 (35)	0.1
Mortality (urgent surgery)	37 (33)	16 (30)	.6
Mortality (elective surgery)	25 (19)	20 (31)	.06
Mortality (medical treatment)	50 (33)	42 (39)	.3

**TABLE 2. Microbiological Profile**

	Men, n (%)	Women, n (%)	P
<i>Streptococcus bovis</i> ; n (%)	16 (4)	9 (4)	.9
<i>Streptococcus viridans</i>	66 (17)	24 (11)	.04
<i>Enterococci</i>	38 (10)	13 (6)	.09
<i>Staphylococcus aureus</i>	71 (18)	44 (20)	.6
Coagulase-negative Staphylococci	63 (16)	40 (18)	.5
Gram-negative bacilli	10 (2.5)	19 (8)	.001
Fungus	4 (1)	6 (3)	.2
HACEK group	3 (0.8)	1 (0.4)	.9
Polymicrobial endocarditis	21 (5)	17 (7.5)	.3
Negative cultures	63 (16)	31 (14)	.4

HACEK: *Haemophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.

to present native valve endocarditis. On the other hand, women present a higher rate of Gram negative bacilli infection, as they suffer more frequently from genitourinary infections.

The echocardiographic studies showed minor differences; men presented a slightly higher rate of significant valvular regurgitation, which can be explained because they present more native

IE and pseudoaneurysms; however, this did not achieve remarkable clinical differences.

In-hospital mortality is high and similar in both sexes. When different treatment groups were analyzed, there was a trend towards higher in-hospital mortality in women compared to men who underwent elective surgery. This finding can be explained because of the higher age (61 [13] vs 56 [14];  $P=.013$ ) and higher proportion of reinterventions (58% vs 40%;  $P=.019$ ) in women. Both facts increase the risk of surgery substantially. There were no other differences in mortality between other groups of treatment. It is known that females have higher mortality than males in coronary surgery and female sex is considered a risk factor in prognostic scores like EuroSCORE.<sup>14</sup> However, our data suggest that female sex is not related to a higher mortality in IE, regardless of whether surgery is needed or not. The clinical relevance of this paper lies in that it is the first work to date in IE in which women receive the same treatment as men with no differences in in-hospital or long-term prognosis. Although randomized trials are needed to determinate the optimal treatment in IE, our data suggest that women should be treated equally.

Although in our series women have a worse epidemiological profile, the clinical features are quite similar and there are no significant differences in the treatment strategy or in-hospital prognosis between men and women with left-sided IE.

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