Clinical, Echocardiographic and Prognostic Profile of *Streptococcus viridans* Left-Sided Endocarditis

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Introduction and objectives. Published case series on *Streptococcus viridans* endocarditis are scarce and outdated. The aims of our study were multiple: to analyze the profile of the *Streptococcus viridans* endocarditis, to compare it with other types of left-sided endocarditis and with cases caused by *Staphylococcus aureus*, and to determine predictors of poor outcome in *Streptococcus viridans* endocarditis.

Patients and method. We analyzed 441 episodes of endocarditis: 330 left-sided and 54 caused by *Streptococcus viridans* (16%). We compared the 54 cases due to *Streptococcus viridans* with the remaining cases of left-sided endocarditis in our series, and also with cases caused by *Staphylococcus aureus*. We also analyzed the predictors of death and urgent surgery in *Streptococcus viridans* endocarditis.

Results. Left-sided endocarditis due to *Streptococcus viridans* led to a similar degree of valvular destruction, showed acute onset less frequently, and led to less renal failure, septic shock and mortality than the remaining cases of left-sided endocarditis in our series. The same differences were found in comparison to *Staphylococcus aureus* endocarditis. Prognostic factors for *Streptococcus viridans* left-sided endocarditis were heart failure and periannular complications.

Conclusions. Although *Streptococcus viridans* is a nonaggressive microorganism, valvular destruction is similar to that caused by other pathogens when it causes left-sided endocarditis. Nonetheless its prognosis is better, a feature which may be related to the fact that the systemic infectious syndrome can be treated more effectively. Prognostic factors in left-sided endocarditis due to *Streptococcus viridans* are heart failure and periannular complications.

Key words: *Endocarditis.* Streptococcus viridans. Staphylococcus aureus. *Prognosis. Transesophageal echocardiogram.*

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Perfil clínico, ecocardiográfico y pronóstico de las endocarditis izquierdas por Streptococcus viridans

Introducción y objetivos. Hay escasas y antiguas series en la literatura médica respecto de la endocarditis por *Streptococcus viridans*. Nuestro objetivo ha sido múltiple: analizar el perfil de la endocarditis por *Streptococcus viridans*, compararlo con el resto de las endocarditis izquierdas y con la endocarditis por *Staphylococcus aureus* y determinar los factores predictores de mal pronóstico en la endocarditis por *Streptococcus viridans*.

Pacientes y método. Hemos analizado 441 episodios de endocarditis: 330 izquierdas y 54 (16%) provocados por *Streptococcus viridans*. Hemos comparado las 54 endocarditis por *Streptococcus viridans* con las provocadas por el resto de las endocarditis izquierdas de nuestra serie y en un segundo análisis con las provocadas por *Staphylococcus aureus*. También hemos realizado un análisis de los factores predictores de muerte o cirugía urgente en la endocarditis por *Streptococcus viridans.*

Resultados. Las endocarditis izquierdas por *Streptococcus viridans* provocan una destrucción valvular similar, tienen menos frecuentemente un curso agudo, provocan menos insuficiencia renal, shock séptico y menor mortalidad que el resto de las endocarditis izquierdas de nuestra serie. Al compararlas con las endocarditis por *Staphylococcus aureus* se encontraron las mismas diferencias. Los factores determinantes del pronóstico en la endocarditis izquierda por *Streptococcus viridans* fueron la insuficiencia cardíaca y las complicaciones perianulares.

Conclusiones. Aunque *Streptococcus viridans* es un microorganismo poco agresivo, cuando provoca endocarditis izquierda da lugar a una destrucción valvular semejante a la del resto de las endocarditis. Sin embargo, el pronóstico es más favorable, lo que podría estar en relación con el hecho de que el síndrome infeccioso general se controla mejor. Los factores que determinan su pronóstico son la insuficiencia cardíaca y las complicaciones perianulares.

Palabras clave: *Endocarditis.* Streptococcus viridans. Staphylococcus aureus. *Pronóstico. Ecocardiograma transesofágico.*

ABBREVIATIONS

IE: infective endocarditis.
MIC: minimum inhibitory concentration.
NYHA: New York Heart Association.
S aureus: *Staphylococcus aureus.*
S viridans: *Streptococcus viridans.*

INTRODUCTION

Infective endocarditis (IE) was first described 3 centuries ago and has remained a major challenge for the clinician, due to its high morbidity and mortality. Although advances in antibiotic therapy and surgical techniques have improved the prognosis of endocarditis,[1] the mortality rate in recent decades has held steady at 15% to 50%.[2-11] Improving this prognosis will require identifying patients at higher risk who could benefit from more aggressive therapy, as well as understanding the profile of the most frequent types of endocarditis.

Although almost any type of microorganism has been cited as a possible cause of endocarditis, the bacteria isolated in 90% of the cases belong to one of three main groups, all of which have the capacity to adhere to the endocardium: staphylococci, streptococci, and enterococci.[12-16] The literature contains numerous studies that describe the unique clinical and prognostic characteristics of patients with *Staphylococcus aureus* endocarditis, which has a virulent clinical course and is associated with an elevated mortality when the left side of the heart is affected.[2,17-21] Nevertheless, few studies report on endocarditis caused by *Streptococcus viridans.* Our study had several objectives: *a)* to analyze the profile of left-sided endocarditis caused by *S viridans; b)* to compare the profile of left-sided *S viridans* endocarditis with that of left-sided *S aureus* endocarditis; *c)* to compare the profile of left-sided *S viridans* endocarditis with other cases of left-sided endocarditis (excluding *S aureus* endocarditis); and *d)* to determine the predictive factors of events in *S viridans* endocarditis.

PATIENTS AND METHODS

Study Group

A total of 441 episodes of infective endocarditis were analyzed in 411 consecutive patients diagnosed with endocarditis, in accordance with the Duke diagnostic criteria, at 5 tertiary centers from 1996 to 2004.[22] Among the 330 cases of endocarditis located in the left-sided heart valves, 54 (16%) were caused by *S viridans* and were analyzed in our study. Nine patients with polymicrobial endocarditis in which one of the organisms was *S viridans* were not included in the study. The number of cases per hospital ranged from 22 to 144 and the percentage of *S viridans* endocarditis was between 10% and 18%.

A total of 69 variables were obtained prospectively: 9 demographic, 23 clinical, 10 analytical, 3 radiological, 3 electrocardiographic, 16 echocardiographic, and 5 on clinical evolution. The patients were included consecutively and underwent at least 1 physical examination, 1 electrocardiogram, 1 chest x-ray, 1 urine analysis, 3 blood cultures at admission, another 3 at 48 h and 1 transthoracic and transesophageal echocardiography. The echocardiographic definitions of vegetation, abscess, pseudoaneurysm, and fistula have already been described.[23,24] Antibiotic therapy was initiated after blood cultures were taken, and specific serology was obtained if the blood cultures were negative after 72 h. Surgical indications included New York Heart Association (NYHA) Class III or IV heart failure, fungal endocarditis, and uncontrolled infection (persistent bacteremia with fever lasting more than 7 days despite appropriate antibiotic therapy). Echocardiographic evidence of a periannular complication was not necessarily considered an indication for surgery. However, these are only some examples of the indications, as all the factors potentially influencing the therapeutic decision cannot be described.

Statistical Analysis

The continuous variables are expressed as mean ± standard deviation, and the categorical variables as absolute value and percentage. Student's *t* test was used to compare continuous variables, and the χ^2 and Fisher exact text (when appropriate) were used for the categorical variables.

Multivariate analysis with backward stepwise logistic regression was performed to predict an event in the group of patients with *S viridans*. The variables with a *P*-value <.10 in the univariate analysis were included in the model. The adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated for each variable. Significance was set at a *P*-value <.05. The data were analyzed using SPSS version 11.0.

RESULTS

Patient Characteristics With *S viridans* Endocarditis

The mean patient age was 55±17 years, and 43 were men. Thirty patients had a history of heart disease: 9 patients with prosthetic valves, 7 with degenerative heart disease, 5 with rheumatic heart disease, 4 congenital heart disease, and 5 with myxomatous mitral valve prolapse. Of the 54 episodes, 7 were nosocomial, 3

TABLE 1. **Comparison of Patient Characteristics With Left-Sided Endocarditis Caused by S viridans Versus *S aureus****

Variables	*S viridans*	*S aureus*	*P*
Patients, n	54	60	–
Nosocomial	7 (13%)	21 (38%)	.007
Previous heart disease	30 (58%)	29 (50%)	.54
Trigger: dental procedure	9 (17%)	3 (5%)	.08
Trigger: intravascular catheter	0 (0%)	9 (15%)	.003
Trigger: prior surgery	0 (0%)	7 (12%)	.01
Onset of symptoms <15 days	13 (26%)	40 (67%)	<.001
Cutaneous manifestations	7 (13%)	19 (32%)	.02
Fever	45 (83%)	52 (87%)	.81
Heart failure	25 (46%)	33 (55%)	.35
Renal failure	10 (19%)	34 (57%)	<.001
Septic shock	0 (0%)	18 (30%)	<.001
Acute CVA	6 (11%)	17 (28%)	.04
Systemic embolism	11 (20%)	22 (37%)	.06
Echocardiography Prosthetic	6 (11%)	18 (30%)	.03
Native aortic valve	24 (44%)	20 (33%)	.03
Mechanical aortic valve	0	9 (15%)	.003
Vegetations	46 (89%)	49 (85%)	.74
Periannular complications	18 (33%)	23 (43%)	.43
Urgent surgery	12 (22%)	14 (23%)	.89
Elective surgery	19 (35%)	15 (25%)	.24
Medical treatment	23 (43%)	31 (52%)	.33
Mortality, urgent surgery group	2 (17%)	5 (36%)	.52
Mortality, elective surgery group	5 (28%)	4 (27%)	.75
Mortality, medical treatment group	3 (14%)	22 (71%)	<.001
In-hospital mortality	8 (15%)	31 (52%)	<.001

*Includes variables that were statistically significant and those of interest from a clinical standpoint. CVA indicates cerebrovascular accident; *S aureus*, *Staphylococcus aureus*; *S viridans*, *Streptococcus viridans*.

patients were intravenous drug abusers, and 7 had a prior history of endocarditis. Evidence of a triggering factor was found in 19 patients: 6 local infections, 3 procedures involving the genitourinary tract, 9 dental procedures, and 1 gastrointestinal procedures. Lastly, 10 patients had predisposing diseases: 4 cases of chronic anemia, 4 of diabetes mellitus, and 2 of cancer.

The most common symptom at the time of presentation was fever, followed by dyspnea. The initial symptom was stroke in 5 patients (3 ischemic and 2 hemorrhagic). In 7 patients, the usual cutaneous manifestations of endocarditis appeared.

By definition, blood cultures were positive for *S viridans* in all patients. Positive results persisted in 10 patients at 48 h from admission. In 90% of the cases, *S viridans* was sensitive to penicillin (minimum inhibitory concentration [MIC] <0.1 mg/L), whereas in the remaining 10% the sensitivity was lower (MIC between 0.1 and 1 mg/L) although there were no cases of resistance to this antibiotic.

Endocarditis affected native valves in 47 patients (29 native aortic and 29 native mitral valves) and prosthetic valves in 6 (3 mechanical mitral, 2 biological aortic, and 1 biological mitral valve). In 15 patients, two valves were affected. All cases of prosthetic valve endocarditis appeared one year after surgery. The mortality of native valve endocarditis caused by *S viridans* was 19% (9 patients) and 17% (1 patient) in the cases of prosthetic valve endocarditis. The transesophageal echocardiogram showed vegetations in 46 patients. A total of 25 periannular complications were observed in 18 patients (10 abscesses, 7 pseudoaneurysms, and 8 fistulae).

Over the clinical course, 3 patients had heart failure, 1 stroke, and 11 systemic embolism; there were no cases of septic shock. Urgent surgery (before completing the course of antibiotic) was necessary in 12 patients, 2 of whom died. The indication for urgent surgery was heart failure (n=10) and uncontrolled infection (n=2). Among the 42 patients who initially received medical treatment, 19 required elective surgery, 6 died during their hospital stay, and 2 died during follow-up (1 from prostate cancer and 1 from respiratory failure). The overall in-hospital mortality was 15% (8 patients).

Comparison of *S viridans* Endocarditis, Other Types of Edocarditis, and S aureus Endocarditis

We performed an initial analysis (Table 1) to compare the characteristics of left-sided *S viridans* endocarditis (n=54) with all the other cases of left-sided endocarditis in our series, excluding *S aureus* endocarditis (n=216). In a second analysis, we compared left-sided endocarditis caused by *S viridans* to *S aureus* endocarditis (n=60) (Table 2). The results were similar in both comparisons: *S aureus* endocarditis and all other left-sided endocarditis cases were more frequently of nosocomial origin than *S viridans* endocarditis, a finding explained by a higher incidence of intravascular stents and prior surgery as triggering factors of the infection in these two groups. As expected, *S viridans* endocarditis was most commonly of subacute onset. Prosthetic valves were less frequently affected in this group. There were no statistically significant differences in radiographic or electrocardiographic data between the groups compared. The analytical data from both comparisons showed a higher incidence of kidney disease and a higher level of leukocytosis in *S aureus* endocarditis and other left-sided IE. *S aureus* endocarditis and all other left-sided IE are more aggressive than IE caused by *S viridans*, as indicated by the higher incidence of renal failure and septic shock as well as higher mortality.

TABLE 2. **Comparison of Patient Characteristics With Left-Sided Endocarditis Caused by *S viridans* Versus Other Cases of Endocarditis (*S aureus* Endocarditis Not Included)***

Variables	*S viridans*	Other left-sided IE	*P*
Patients, n	54	216	–
Male	43 (80%)	136 (63%)	.02
Nosocomial	7 (13%)	62 (30%)	.01
Previous heart disease: prosthetic	9 (17%)	100 (47%)	<.001
Trigger: dental procedure	9 (17%)	18 (8%)	.12
Trigger: intravascular catheter	0 (0%)	20 (9%)	.02
Trigger: prior surgery	0 (0%)	32 (15%)	.005
Onset of symptoms <15 days	13 (26%)	91 (44%)	.02
Fever	45 (83%)	175 (81%)	.81
Heart failure	25 (46%)	117 (56%)	.22
Renal failure	10 (19%)	78 (36%)	.01
Septic shock	0 (0%)	24 (11%)	.01
Acute CVA	6 (11%)	38 (18%)	.04
Systemic embolism	11 (20%)	62 (29%)	.06
Echocardiography Multivalve	15 (28%)	29 (13%)	.02
Prosthetic	6 (11%)	91 (42%)	<.001
Native mitral valve	23 (43%)	57 (26%)	.02
Mechanical aortic valve	0	29 (13%)	.009
Mechanical mitral valve	3 (6%)	46 (21%)	.01
Urgent surgery	12 (22%)	49 (23%)	.89
Elective surgery	19 (35%)	74 (34%)	.85
Medical treatment	23 (43%)	93 (43%)	.95
Mortality, urgent surgery group	2 (17%)	21 (43%)	.18
Mortality, elective surgery group	5 (28%)	18 (24%)	.99
Mortality, medical treatment group	3 (14%)	31 (33%)	.07
In-hospital mortality	8 (15%)	68 (32%)	.02

*Includes variables that were statistically significant and those of interest from a clinical standpoint.
CVA indicates cerebrovascular accident; *S aureus*, *Staphylococcus aureus*; *S viridans*, *Streptococcus viridans*..

Analysis of Predictive Factors of Events in Left-Sided Endocarditis Caused by *S viridans*

We performed a univariate analysis (Table 3) of *S viridans* endocarditis to identify statistically significant factors in the onset of events in this group, with events considered to be in-hospital mortality or urgent surgery (before completion of the antibiotic cycle). When only in-hospital death was considered an event, the results of the univariate analysis were very similar (Table 4). Significant variables were used to perform a multivariate analysis. The predictive factors for an event (when considered to be both types) were heart failure and periannular complications. When only in-hospital mortality was considered an event, the only predictive factor was the presence of periannular complications (Table 5).

TABLE 3. **Univariate Analysis for In-Hospital Mortality or Need for Urgent Surgery as an Event in Left-Sided Endocarditis Caused by *S viridans****

Variables	No Event	Event	*P*
Endocarditis, n	36	18	
Cutaneous manifestations	7 (19%)	0 (0%)	.08
Abscess	3 (11%)	6 (33%)	.07
Periannular complications	9 (25%)	10 (56%)	.43
Heart failure	12 (33%)	12 (67%)	.04

* *S viridans* indicates *Streptococcus viridans*.

TABLE 4. **Univariate Analysis for In-Hospital Mortality as an Event in Left-Sided Endocarditis Caused by *S viridans****

Variables	No Event	Event	*P*
Endocarditis, n	44	10	
Nosocomial	4 (9%)	3 (33%)	.09
Multivalve	9 (21%)	5 (50%)	.09
Mitral valve	21 (48%)	1 (10%)	.04
Periannular complications	12 (27%)	7 (70%)	.43
Heart failure	17 (39%)	7 (70%)	.09

* *S. viridans* indicates *Streptococcus viridans*.

TABLE 5. **Factors Independently Associated With Death or Need for Urgent Surgery in Patients With Left-Sided Endocarditis Caused by *S viridans****

	OR	95% CI
In-hospital mortality and urgent surgery		
Periannular complications	5.1	1.4-19.6
Heart failure	4.1	1.1-15.4
In-hospital mortality		
Periannular complications	6.2	1.4-28.1

* CI indicates confidence interval; OR, odds ratio; *S viridans*, *Streptococcus viridans*.

DISCUSSION

In the preantibiotic and earliest antibiotic era, streptococci were the most frequent cause of IE, responsible for 80% of the cases.[25,26] Their relative importance has diminished over the years due to the regression of rheumatic heart disease, better oral and dental care, simpler chemoprophylaxis and decreased incidence of streptococcal bacteremia.[20] The largest group in percent term is viridans streptococci, among which *S sanguis* I and II, *S mutans, S mitior, S salivarius,* and *S milleri* are the most important species causing endocarditis (in order of frequency). The capacity of these microorganisms to cause endocarditis has been related to their ability to produce an exopolysaccharide similar to dextran. Although in the past they were highly sensitive to the bactericidal action of penicillin, bacte-

ria with decreased (MIC between 0.1 mg/L and 1 mg/L) or resistant (MIC>2 mg/L) sensitivity to penicillin are common.[13]

The few published series on *S viridans* endocarditis are outdated and do not report on recent microbiological changes.[27-29] In addition they have several limitations (not present in our series) that prevent application of the conclusions: *a)* they include a low number of patients and do not differentiate between right-sided and left-sided endocarditis; *b)* only a few variables are analyzed; and *c)* they do not systematically perform transesophageal echocardiography, an essential tool for determining the diagnosis and prognosis of patients with endocarditis.

Fewer cases of *S viridans* endocarditis were observed in our series, as compared to earlier studies.[27-29] The microbiological spectrum of endocarditis seems to be changing and the frequency of *S viridans* endocarditis is lower than in the earlier series because of the lower current incidence of streptococcal bacteremia. However, these episodes were reported in tertiary hospitals, and the cases referred by other centers have a poorer course and a predominance of more aggressive microorganisms. Previous reports have pointed out that the varying etiology of endocarditis described in the literature depends more on hospital characteristics, population treated, and the incoming transfers, than on actual epidemiological differences of a geographic nature.[30]

S viridans species have been identified as the most frequent cause of endocarditis in native left valves,[12,25,26,31-33] although several studies report a higher incidence of *S aureus* endocarditis.[8,9,13,34,35] Nevertheless, early-onset prosthetic valve endocarditis caused by *S viridans* is infrequent.[13,34] Among the 116 episodes of prosthetic valve endocarditis in our series, a high percentage were early-onset (46%), which explains the low incidence of prosthetic valve endocarditis due to *S viridans*.

Our study showed a high percentage of cases with no previous triggering factors for the disease. Most patients in whom the microorganism was identified had recently undergone a periodontal procedure before the onset of symptoms. The microorganisms implicated are present in the normal flora of the oral cavity, and dental procedures that involve soft tissue bleeding, periodontal surgery and professional dental cleaning may lead to bacteriemia that can cause endocarditis in patients with predisposing cardiac lesions.[13]

Although the microorganism is not very aggressive, the valve damage caused by *S viridans* species in our series was similar to that of the remaining endocarditis cases, and this explains why the percentage of patients who developed heart failure was similar and the need for urgent surgery was, in almost all cases, heart failure. This may result from the fact that the disease onset is more insidious, delaying the diagnosis and favoring significant damage in the perivalvular region.

As expected, we found fewer clinical complications among patients with *S viridans* endocarditis. *S aureus* is a paradigm of an endocarditis-causing microorganism, producing acute disease and frequent complications due to its aggressiveness, and responding poorly to antibiotic therapy.[2,17-20] *S viridans* species exhibit a better response to medical treatment, decreasing the onset of the severe systemic manifestations of endocarditis, such as septic shock, renal failure and cerebrovascular accidents. In this regard, only 4% of patients with *S viridans* endocarditis required urgent surgery due to infection that could not be controlled with antibiotic therapy, versus 12% for other endocarditis (P=.07).

The overall mortality of the patients with left-sided *S viridans* endocarditis was lower than that of the other patients with left-sided endocarditis, and even lower than that of *S aureus* endocarditis. This may be because the systemic infectious syndrome occurring in endocarditis is better controlled in patients with *S viridans* endocarditis, as suggested by milder kidney involvement, fewer patients with septic shock and lower leukocyte counts.

Our study is the first to analyze the factors determining the prognosis in patients with left-sided endocarditis due to *S viridans*. We considered in-hospital mortality (regardless of cause) and the need for urgent surgery to be events, as we assumed that the patient would have died without surgery. On this basis we found that heart failure and periannular complications were the prognostic determinants of this condition. When in-hospital mortality alone was considered as an event, only periannular complications retained prognostic power, possibly because such complications imply more complex surgery with poorer results.

CONCLUSIONS

Although *S viridans* is a relatively non-aggressive microorganism, in the case of left-sided endocarditis it leads to valve damage similar to other types of endocarditis, although with a more favorable prognosis due to an easier control of the resulting general infectious syndrome. The predictive factors that determine the prognosis of left-sided *S viridans* endocarditis are heart failure and periannular complications.

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