MULTIVALVULAR INFECTIVE ENDOCARDITIS CLINICAL FEATURES, ECHOCARDIOGRAPHIC DATA AND OUTCOMES

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Summary

Little information is available concerning patients with multivalvular endocarditis (MVE) that simultaneously affects at least two cardiac valves. Current understanding of MVE is primarily based on sporadic case reports 6-9 and rarely on systematic retrospective investigation.
Our aim was to investigate clinical and echocardiographic characteristics, microbiological profile, management and outcomes of multivalvular endocarditis in a Tunisian tertiary-care centre.
This retrospective study included 225 patients admitted between 2001 and 2005 for the management of infective endocarditis as determined by the Duke criteria. Subsequently, they were divided into two groups: Group 1: multivalvular endocarditis patients (29 patients), Group 2: monovalvular endocarditis patients (196 patients).
Group 1 patients were younger. Male sex was predominant in the two groups. Most of the patients of the two groups had underlying heart disease, essentially rheumatic heart disease. In group 1, there was more mitral insufficiency, more aortic insufficiency (p=0.002), but less aortic stenosis. Groups 2 patients had more mechanical valve prostheses (p=0,004) .The majority of the patients of the two groups have fever. The dental procedures are the most frequent infectious side entry in the two groups. The most frequently involved germ was the staphylococcus in the case of multivalvular disease (46.7% vs 37.3%) and streptococcus in the case of monovalvular disease (26.7% vs 38.2%), but without a significant difference. The localization of vegetations in multi valvular IE were: mitro aortic in 25 cases, Based on the TTE and the TEE, there were more vegetations in group 1 (p=0,048). Vegetations sized between 10 and 15 mm were more frequent in the group 1 (p=0,019). Valvular perforations (p=0,070), valvular abscess formation (p=0,414), and acute pericardial effusion (p=0,051) were more frequent in group 1. During their hospital period, urgent surgical indication was more frequent in group 1(62, 1% vs. 51, 3%; p=0,279), with more frequent hemodynamic indication (acute left heart failure) (72, 2% vs. 47%; p=0,049). Hospital mortality was higher in the group 1 (21, 4% vs. 17, 2%; p=0,586), but without a statistical significance.
Our data suggest that complications of multi-valvular endocarditis, and those of uni-valvular endocarditis are similar except for heart failure. Heart failure is statistically more common in multi-valvular endocarditis but without great influence on mortality.

Keywords : Multivalvular endocarditis, Univalvular endocarditis, Surgery, Staphylococcus

INTRODUCTION

Infective endocarditis (IE) involving multiple cardiac valves is uncommon. The majority of echocardiographically demonstrated endocarditis occurs in a single valve; the involvement of two valves occurs much less frequently, and triple- or quadruple- valve involvement is extremely rare [1–2]. Demonstration of multi-valvular involvement in patients with suspected IE is important. Mortality rate is more likely to be higher in patients with infection of two or more valves than a single valve and these patients might require early operations for the management of complications [3]. However, despite its clinical importance, it has not been studied as a separate clinical entity. In the absence of guidelines based on prospective randomised studies, the optimal therapeutic strategy is still being widely discussed. Thus, whereas some authors still believe in an exclusively medical approach to, a majority agrees to consider a combined medical and surgical approach to be the best attitude.

The aim of our study was to describe clinical, echocardiographic and microbiological characteristics of patients with multivalvular endocarditis and their short-term and long-term outcomes compared with single valve endocarditis.

METHODS

2.1. Patient population

The medical records of all adult patients with documented native valve IE were reviewed. The diagnosis of endocarditis was qualified as definite or possible according to the DUKE criteria [8]. Patients were admitted to the Hédi-Chaker University Hospital between January 2001 and December 2005. Of 225 patients who met the Duke criteria for IE, 29 patients had multi-valvular endocarditis. Subsequently, our population was divided into two groups: Group 1: multivalvular endocarditis patients (29 patients), Group 2: monovalvular endocarditis patients (196 patients)

Of 29 cases of multi-valvular endocarditis reviewed, various parameters were collected for each patient, including the predisposing heart condition, initial clinical presentation, biological data, results of microbiological tests (we typically performed three to six sets of aerobic and anaerobic blood cultures. When blood cultures remained negative, specific analyses were performed including additional sets for blood cultures on enriched media and serological tests for Coxiella burnetti, Brucella, Mycoplasma pneumoniae, Chlamydiae spp, fungi, Aspergillus and Bartonella), echocardiographic features, duration of antibiotic treatment, treatment strategies, time and type of surgery, as well as the short- and long-term evolution. These data were analyzed and compared with 196 uni-valvular endocarditis.

2.2. Definitions

Endocarditis was considered to be active if the patient had positive blood cultures, operative findings of acute inflammation, or positive cultures or Gram stain of excised tissue. Endocarditis was considered to be healed if the operation occurred more than 6 weeks after the initial diagnosis, a course of antibiotics was completed, blood cultures were negative at the time of the operation, and cultures and Gram stains of intraoperatively excised tissue were negative. Culture-negative endocarditis was defined by the absence of positive culture in patients presenting with clinical signs of endocarditis. The diagnosis was confirmed at operation by the presence of surgical findings of endocarditis (presence of vegetations, leaflet perforation, valvular or perivalvular tissue destruction…). All resected surgical specimens were cultured.

2.3. Treatment

For all patients in the medically treated group, antibiotic treatment was initiated at admission and continued intravenously for at least four weeks. The initial choice of antibiotics was directed by the clinical context and suspected causative organisms. All operated patients were initially treated with antibiotics. Indications for surgery included refractory heart failure related to valvular dysfunction, persistent bacteriemia or fungal infection despite intensive medical therapy, myocardial or perivalvular abscess, peripheral systemic emboli, large vegetations seen on echocardiography and perivalvular leak for PVE.

2.4. Statistical analysis

The statistical analysis was performed using the SPSS 15.0 statistical package. Continuous variables were presented as means ± standard deviations (SD) and categorical variables as percentages. Continuous variables were compared with Student's t tests, and categorical variables

with the student's square test or Fisher's exact test, where expected values were <5. A two-sided p value of 0.05 was established as the level of statistical significance for all tests.

RESULTS

- *Clinical characteristics*

Of 225 IE patients reviewed, 29 patients (13%) had multiple-valve involvement. The patients' age range was 1–73 years (mean age was 31.27 years). The sex ratio was 1.41. 25 cases of multi-valvular endocarditis involved mitro- aortic valves (Table I). Predisposing factors, which were found in various combinations in 24 out of 29 patients (82,7%), were rheumatic heart disease in 14 patients (50%), degenerative heart disease in one patient and congenital heart disease in 3 patients (10,7%). There was not a significant differentiation between the two groups regarding the underlying cardiopathy. Patients in Group I had more frequently native valves disease. The predisposing valvular diseases were aortic stenosis (2 patients; 7.4%), mitral regurgitation (8 patients; 27.6%), aortic insufficiency (10 patients; 35.7%), mechanical prosthesis (1 patient). Recent dental procedure was found in five patients (17.2%). None was addicted to intravenous drugs. A large proportion of the patients was in New York Heart Association functional classes III (18 patients (62%)).
Clinically, a new or changing murmur was detected in seven of the 14 patients (50%). Most patients (82.8%) had fever at admission. Systolic murmur was present in 22 patients (75.9%). Osler's nodes (3.4%), Janeway lesions (3.4%), or petechiae (3.4%) were not detected in the majority of our patients. Erythrocyte sedimentation rate (ESR) was elevated in all patients (100%) with a range of 22–140 mm/h.

Table I: Comparison of clinical characteristics in the two groups.

	Group 1 (n=29)	Group 2 (n= 196)	P
Mean Age (years)	31.27±17.64	42.17±17.69	0.002
Male sex n (%)	17 (58.6%)	112 (57.1%)	0.006
Rheumatic heart disease n (%)	14 (50%)	76 (38.8%)	0.187
Congenital heart disease n (%)	3 (10.3%)	27 (13.7%)	0.643
Degenerative valve disease	1 (3.4%)	19 (9.6%)	0.289
NYHA functional class			
II	4 (13.7%)	19(9.6%)	0.634
III	18 (62%)	78 (39%)	0,04
Aortic regurgitation n (%)	10 (35.7%)	26 (13.5%)	0.003
Aortic stenosis n (%)	9 (4.8%)	2 (7.4%)	0.525
Mitral regurgitation n (%)	8 (28.6%)	34 (17.3%)	0.126
Prosthetic valve n (%)	1 (3.6%)	54 (27.7%)	0.004

- *Microbiology*

While staphylococcus was the most common microorganism which occurred in 46.7% of multivalvular endocarditis patients versus 37.3% in case of single endocarditis, Streptococcus was more frequent in monovalvular disease (26.7% vs 38.2%), but without a significant difference. We had no methicillin-resistant strains among patients infected with Staphylococcus aureus.
The infective agents found in these 29 patients were Staphylococcus aureus in seven patients

followed by streptococci viridians (e.g. Streptococcus mutans, Streptococcus sanguis, and Streptococcus mitis) in five patients; acinetobacter baumanii in one patient and brucella in one case. Culture-negative endocarditis occurred in 15 patients (51.7%). In cases of prosthetic endocarditis, the frequent bacterial agent identified in the monovalvular group was staphylococcus aureus (10 patients; 40%). In the multivalvular group, Brucella endocarditis was the only case diagnosed.

- *Echocardiographic data*

All patients underwent transthoracic echocardiography (TTE), with addition of transesophageal echocardiography (TEE) in 22 patients (45,8%).

Definite vegetations were found in 19 patients (65.5%), and vegetations were found in 10 patients (34.5%). Vegetations are more frequently described in patients with multivalvular disease. They have greater dimensions, and they are more mobile. They are frequently associated with valvular mutilation and acute pericardial effusion.

The comparison of clinical, microbiological and echocardiographical characteristics between the two groups is summarized respectively in table I, table II and table III.

The in hospital complications (table IV) were more frequent in patients with multi-valvular IE compared with uni-valvular endocarditis but without a statistical difference. In hospital complications included acute renal failure, septic embolism, cerebral vascular accident, and congestive heart failure. No prosthesis desinsertion was diagnosed in our series. Among the complications, only congestive heart failure was statistically more common in the multivalvular versus the univalvular group (P=0.01). The early valve replacement surgery and mortality were not significantly different in both groups. Early surgery in patients with multivalvular IE, does not significantly decrease mortality (11, 8% vs. 36, 4%; p=0,164) (11, 8% vs. 22, 4%; p=0,275) (table V). Thirty percent of the patients (9 patients) were discharged after successful medical management alone and 55% (16 patients) underwent valve replacement. Mean follow-up was 29.52 months (range 3 to 147 months). Recurrences occurred in 10 among the 94 survivors, with a mean delay of 21, 7 months. Late surgery was needed in 22 patients (24% of the survivors), none of them in an urgent setting for recurrent endocarditis (table VI).

The reasons for late surgery were severe aortic stenosis in six cases, mitral regurgitation in eight cases and aortic regurgitation in seven cases.

Table II: Comparison of microbiological characteristics in the two groups.

	Group 1 (n=29)	**Group 2 (n= 196)**	**P**
Staphylococcus Aureus n (%)	7 (46.7%)	38 (37.3%)	0.484
Streptococcus n (%)	4 (26.7%)	39 (38.2%)	0.386
Other germs n (%)	3 (10.3%)	27 (13.7%)	0.702
Culture negative endocarditis n (%)	15 (51.72%)	92 (48.4%)	0,611

Table III : Comparison of echocardiographical characteristics in the two groups.
TTE: Transthoracic echocardiography,
TEE: Transesophageal echocardiography

	Group 1 (29)	Group 2 (196)	P
Vegetations TTE n (%)	24 (82.7%)	127(75.1%)	0.048
Vegetations TEE n (%)	26 (89.6%)	128 (75.57%)	0.084
Vegetation size: 10-15 mm n (%)	13 (52%)	46 (28.6%)	0.019
Mobile vegetations n (%)	8(44.4%)	25 (25%)	0.091
Valvular perforation n (%)	4 (16%)	8 (5.3%)	0.07
Annular abscess n (%)	4 (22.2%)	15 (15%)	0.443
Pericarditis n (%)	1 (3, 6%)	3 (1, 8%)	0.465

Table IV: Complications of univalvular and multivalvular endocarditis.

	Group 1 (n=29)	Group 2 (n= 196)	p
In hospital death n (%)	6 (20, 6%)	32 (16, 3%)	0.567
Cardiogenic shock	7 (24, 1%)	27 (14, 5%)	0.049
Congestive heart failure n (%)	21 (72%)	79 (40%)	0,01
Acute renal failure	10 (31%)	54 (29%)	0,51
Septic embolism n (%)	1 (5.6%)	7 (7%)	1
Neurological complications	33 (17, 7%)	7 (24, 1%)	0.442
Early surgery n (%)	18 (62.1%)	49 (51.3%)	0.279

Table V: Correlation between early surgery and mortality in the two groups.

	Group 1 (n=29)	Group 2 (n=196)	p
Mortality after early surgery n (%)	2 (11, 8%)	2(22, 4%)	0,275
Mortality after only medical therapy n (%)	4 (36, 4%)	30(15.3%)	0,04
In hospital death n (%)	6 (20, 6%)	32 (16,3%)	0.567

Table VI: Late surgery and endocarditis recurrence in the two groups.

	Group 1 (n=23)	Group 2 (n=137)	p
Late surgery n (%)	18 (78.2%)	9 (6.5%)	< 0.001
Endocarditis recurrence n (%)	9 (39.1%)	3 (2.1%)	< 0.001

DISCUSSION

The occurrence of multi-valvular endocarditis is uncommon. The majority of IE cases involve a single valve, and demonstration of double-, triple-, or even quadruple-valve involvement by echocardiography is less frequent [1–3]. We reviewed the medical records of patients who were admitted to our hospital over a 4-year period with documented IE to determine the incidence and presentation of multi-valvular endocarditis using the Duke criteria. In this study we report here that among 225 patients with documented IE reviewed, there were 29 patients (13%) who had multi-valvular endocarditis and 196 with uni-valvular endocarditis. The incidence of multivalvular endocarditis was 18% in the series reported by Kim and colleagues [4] and 31% in that of David and colleagues [5]. Twenty five patients had mitro aortic valves IE had been demonstrated, and one case of right heart valve IE. Three patients had three valve involvements in our series. There was no quadruple-valve IE. All patients had two- valve IE in the experience of Kim and colleagues [4]. The most common etiologic micro-organism in patients with multi-valvular endocarditis was staphylococcus (46.7%), Staphylococci, are able to infect previously normal heart valves and usually cause an acute illness [6] [4]. All the strains of S. aureus were methicillin sensitive. Streptococcus viridans was the most frequent cause of native multivalvular endocarditis in the population of Yao *et al* [7], which was consistent with the report by Mihaljevic and colleagues [8] but was different from the report by Kim and colleagues [4]. Since the 1960s, the percentage of cases caused by viridans streptococci has decreased to about 35% [9]. Two patients (14%) in our series had enterococci as the etiologic agent. Enterococci normally inhabit the gastrointestinal and genitourinary tracts and are the causes in 5–10% of patients with IE [11]. 3 cases of congenital heart disease were noted. IE was used to diagnose the disease. As many people live in rural areas where poverty and lack of health care is prevalent, it is not until endocarditis develops that CHD is diagnosed. Biventricular involvement of multiple valves in these patients can be attributed to left-to-right ventricular communication. The infection on one side of the heart could easily spread through the left-to-right shunt. In the series of Yao [7], MVE was diagnosed preoperatively by TTE in only 50.0% of patients and by preoperative TEE in 77.3%. Fortunately, MVE was confirmed through surgical exploration in all patients. The same author found that two basic principles are important for the successful demonstration of MVE. First, the use of TEE is extremely helpful for demonstration of multivalvular involvement before surgery when the TTE images are not optimal. The use of TEE increases sensitivity and specificity to about 90% [10]. Second, careful intraoperative exploration plays a significant role in confirming the diagnosis of MVE, especially in patients with risk factors such as severe aortic root abscess, predisposing CHD with shunt, intravenous drug use, and so on. Although there are reports that suggest that patients with either infection of the aortic valve or infection of two or more valves are more likely to die or require early operation for management of complications [3], the mortality rate in our series was 21.4%, which is similar to that of single-valve IE (17.2%). This hospital mortality of 12.4% compares favorably with that in Kim's series [4], Mihaljevic's series [8], and Yao's series [7] which reported operative mortalities of 21%, 16% and 12, 5%, respectively (table 7). Mitral and aortic valve replacement was the only technique used in our series. Feringa and coworkers thought that when feasible, mitral valve repair is preferred for the surgical treatment of infective endocarditis affecting the mitral valve [11], [7]. For aortic valve endocarditis, Aranki and coworkers [12] reported

excellent results using standard prosthesis replacement.

Among the complications, only congestive heart failure was statistically more common in the multi-valvular versus the uni-valvular group in our series. Embolic events were rare probably due to the frequency of early surgery in our series. Recurrent endocarditis was 39% in our series, which was not similar to those reported for single valve endocarditis and for Yao's population [7]. This high rate can be avoided by the radical resection of all infected tissues in patients with MVE, the necessity of additional intraoperative interventions depending on the operative pathologic status [7].Thus, we can produce satisfactory in-hospital and long-term results, similar to those in patients with a single infected heart valve.

Table VII: Review of the different series in the literature dealing with multivalvular endocarditis.

	Muller (1999)	Mihaljevic (2001)	Letranchant (2002)	Yao (2009)	Our series
N (patients)	35	63	42	48	29
Age (years)	47	49	58	42	31.27
Male Sex (%)	72	62	74	83	58.6
Predisposing cardiopathy (%)	72	-	45	85	75
Prosthesis (%)	11	37	9	0	3.7
Heart failure (%)	44	49	57	100	24.1
Embolic events (%)	12	-	43	16	24.1
Streptococcus (%)	70	28	69	29	26.7
Staphylococcus (%)	16	31	14	18,7	46.7
Vegetations (%)	-	61	71	-	92.9
Valvular surgery (%)	100	100	71	100	62.1
Inhospital mortality (%)	4	16	26	12,5	21.4

CONCLUSION

The incidence of multi-valvular endocarditis occurred in 13% of our series of IE, with involvement of mitral and aortic valves being most common. Staphylococci are the most common etiologic microorganisms identified in patients with multivalvular IE. Only congestive heart failure was found to be statistically more common in multivalvular than uni-valvular endocarditis.

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