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ORIGINAL ARTICLE

AORTIC VALVE REPLACEMENT FOR PATIENTS WITH SEVERE AORTIC STENOSIS AND SEVERE LEFT VENTRICULAR DYSFUNCTION - MORTALITY RISK FACTORS

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ABSTRACT

Severe left ventricular dysfunction increases the surgical risk of aortic valve replacement on aortic valvular stenosis. Several risk factors of hospital mortality have been reported in heterogeneous series.
The aim of this study was to identify mortality risk factors of aortic valve replacement in patients with severe aortic stenosis and severe left ventricular dysfunction. To avoid biases of associated diseases, our study has been focused on isolated aortic stenosis.
46 patients, with AS and severe left ventricular dysfunction who underwent AVR were enrolled in this retrospective study. The mean age was 59 ± 12.70 years. 69.6% of patients were in class III or IV NYHA. The mean left ventricular ejection fraction (LVEF) was 32.3 ± 5.3%, and the mean EuroSCORE was 12.20 ± 8.70. The hospital mortality was 15.20%. The morbidity was marked mainly by low output syndrome in 30.4% of cases. A logistic regression in univariate analysis reveals functional class, renal failure, congestive heart failure and LVEF as factors related to the risk of hospital mortality. Multivariate logistic regression analysis found renal failure (OR = 11.94, CI [2.65 -72.22], p = 0.03) and congestive heart failure (OR = 25.33, CI [3 43 -194.74], p = 0.009) as independents risk of hospital mortality. The mean follow-up was 59.6 ± 21 months. Late mortality was 5%.
Congestive heart failure and preoperative renal failure are the main independents hospital mortality's risk factors of aortic valve replacement in patients with severe aortic stenosis and severe left ventricular dysfunction. Late mortality might be inversely related to the LV recovery.

KEY WORDS: Severe Aortic Stenosis, Aortic Valve Replacement, Left Ventricular Dysfunction, Risk Factors.

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INTRODUCTION

Currently, surgery is the gold standard in the treatment of severe aortic stenosis [1]. The Left ventricular dysfunction increases a surgical risk but should not contraindicate the aortic valve replacement with whom the earnings are documented. [2-5] The literature reports several risk factors associated with postoperative mortality but most published series are heterogeneous including patients with other associated disease. The main objective of this study was to identify the mortality risk factors of aortic valve replacement in patients with severe aortic stenosis and severe left ventricular dysfunction.

MATERIALS AND METHODS

Patients

A retrospective study covering a period from January 2000 to January 2016 was conducted in Cardiovascular Surgery Departments of the Avicenna University Hospital in Rabat (Morocco). It concerned 46 patients who underwent isolated aortic valve replacement (AVR) for severe isolated aortic stenosis (AS) associated with severe left ventricle (LV) dysfunction
Criteria inclusion:

• Severe aortic stenosis (aortic area <1cm2 or indexed aortic surface area <0.6 cm2/m2)
• Left ventricle ejection fraction (LVEF) < 40%
• Patients who were followed in our department or followed by their family doctor.
Exclusion criteria:
• Aortic insufficiency > grade I
• Associated valve disease requiring surgical correction
• Coronary artery disease or history of myocardial infarction
• Patients lost to follow-up.

Methods

Clinical, paraclinical and operatives data were collected from patient's medical records. Postoperative follow up was carried out either by the cardiologists of our unity who then called the patients or by referring cardiologists who provided the needed data. All patients in our series underwent transthoracic echocardiography (TEE) by an experienced cardiologist. All measurements were made in accordance with the relevant recommendations of the European Society of Echocardiography [6], and those of the American Society of Echocardiography [7].

The LV dimensions were obtained by the TM and the two-dimensional (BD) modes; the aortic surface was calculated with the continuity equation and the transvalvular pressure gradient was measured by the modified Bernouilli equation. The LV ejection fraction was evaluated by Simpon's method.

Congestive heart failure was defined as cardiac insufficiency with repetitive pulmonary edema episode despite continuous digitalo-diuretic support.

All patients underwent coronary angiography except one patient operated in extreme emergency.

Surgical techniques

The Aortic valve replacement was performed under cardiopulmonary bypass (CPB) conducted in moderate hypothermia through a median sternotomy. Until 2002, the myocardial protection was provided by intermittent cold crystalloid cardioplegia (St. Thomas). After 2002, a cold blood cardioplegia was used.

Follow-up

Early postoperative stage was defined as 6 months after surgery and the late operative stage was defined as the period beyond 1 year after AVR.

Hospital mortality was defined as death at any time before discharge from hospital.

During follow-up, patients were contacted directly and were individually requested to make an appointment with the primary surgeon and referring cardiologist. They were investigated by a visit, including physical examination, chest X radiogram , ECG and echocardiogram.

Occasionally, the follow-up data was obtained by telephone contact with their cardiologist.

Statistical Analysis

Statistical analysis was done with the software "Statistical Package for the Social Sciences" (SPSS version 11.5, Chicago, Illinois, USA). The distribution of quantitative variables was tested by the Kolmogorov-Smirnov test. Continuous variables were expressed as means (M) with standard deviation (SD) or medians (MD) with interquartile range (IQR). Student's t-test was used in order to compare and study the relationships between the continuous variables whenever the data was normally distributed, and Non-parametric Mann-Whitney test was used in the others cases. Categorical variables were described as numbers and percentages (%) and analyzed using the $\chi 2$ test or Fisher's exact test, as appropriate. One-way analysis of variance with the post hoc Bonferroni test (for normal distribution with equal variance between groups) was applied for quantitative variables between paired groups of data.

Mortality risk factors were studied with logistic regression analysis and presented as adjusted odds ratio (OR) with a confidence interval (CI) of 95%.

Survival curves for time-to-event variables were constructed on the basis of all the available follow-up data using Kaplan-Meier estimates and were compared with the log rank test. A two-sided α level of 0.05 was used for all superiority testing.

A p-value < 0.05 was considered to be significant.

RESULTS

Baseline Clinical Characteristics

We collected data of 46 patients with severe AS and severe dysfunction of the left ventricle (LV) who underwent AVR during period extended over a 16-year.The mean age was 59 ± 12.70 years with male predominance. All patients were symptomatic and 69.6% of them were in class III or IV NYHA. The mean LVEF was 32.3 ± 5.3% and the mean EuroSCORE was 12.20 ± 8.70. Only 3 patients underwent the test of contractile reserve by echocardiography with low-dose of dobutamine. This test was positive in the 3 cases. The general characteristics of our patients are shown in Table 1.

Variables	n = 46
Age[1] (years)	59 ± 12.7
Sex[3] Male/Female	37/9 (80.4 %)
BSA[2]	1.7 [1.67 ; 1.85]
NYHA[3]	
-II	14 (30.4%)
-III	20 (43.5%)
-IV	12 (26.1%)
Angina pectoris[3]	18 (39%)
Syncope[3]	4 (8.7%)
Congestive heart failure[3]	6 (13%)
Etiologies[3]	
-Degenerative	32 (69.6%)
-Rhuematic	12 (21.1%)
-Congenital	2 (4.3%)
Comorbidities [3]	
-Hypertension	17 (37%)
-Diabetes	5 (11%)
-Renal failure	8 (17.4%)
-AIS	1 (2.2%)
CT index[2]	0.6 [0.59 ; 0.65]
Aortic valve area (mm)[1]	0.6 ± 0.2
Preoperative LVEDD (mm)[1]	62 ± 7.4
Preoperative LVESD (mm)[1]	49 ± 8
Preoperative LVEF [1] (%)	32 ± 8
Mean transvalvular gradient [1] (mmHg)	51,6 ± 19
SPAP [1] (mmHg)	48.7 ± 23.5
Logistic regression Euroscore [1]	12.2 ± 8.7

1: expressed as means standard deviation (SD); 2: expressed as medians with interquartile range (IQR); 3: described as numbers and percentages (%).BSA: body surface area; AIS: Acute ischemic stroke; CT: cardio-thoracic; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary arterial pressure.

Table 1: Preoperative patients characteristics.

Surgical Results

Thirty-nine mechanical and seven biological prosthesis were implanted. The average diameter was 21.8 ± 1.6 mm. The median duration of CPB was 91.5 min (IQ [80.7; 129.5]), whereas the mean aortic cross-clamp time was 70.5 ± 21.7 min. Inotropic support was used during weaning from cardiopulmonary bypass in 91.3% cases.

The median mechanical ventilation time was 8.5 hours. The mean length of stay in the intensive care unit was 48 hours.

Operative mortality and post-operative outcomes

The hospital mortality rate was 15.20% mainly due to low cardiac output syndrome. Postoperative morbidities included low cardiac output in 30.4% of cases, multiple organ failure and cardiogenic shock in 4.3% of cases. Operative and early postoperative data are reported in Table 2.

A logistic regression in univariate analysis allowed to reveal the functional class, renal failure, congestive heart failure and LVEF as factors related to the risk of hospital mortality. Indeed, the risk of postoperative mortality was 8.20 times higher when NYHA class increases. The presence of congestive heart failure or kidney failure increased the operative risk, respectively by 24.66 and 11.66 times, while the increase in LVEF by one unit reduce this risk by 1.16 times (OR = 0.86, CI [0.77- 0.96], p = 0.01). However, in multivariate analysis, kidney failure (OR = 11.94, CI [2.65 -72.22], p = 0.03) and congestive heart failure (OR = 25.33, CI [3 43 -194.74], p = 0.009) were the only independent predictors of early mortality (Table 3).

Thirty-nine surviving were followed. The average duration of follow-up was 59.6 ± 21 months. Late mortality was 5% (one patient died after an hemorrhagic stroke and a second one in the aftermath of a non Hodgkin's lymphoma). Figure 1 illustrates the Kaplan-Meier survival for the entire cohort. Functional status was significantly improved (81% of the patient was in NYHA class I).Only 35% of patients required long term digitalo-diuretic support (Table 4).

Variables	n = 46
X clamp time[1] (mn)	70.5 ± 21.7
CPB time[2] (mn)	91.5 [80.7 ; 129.5]
Prosthesis size[1] (mm)	21.8 ± 1.6
Use of positive inotropic agents[3]	42 (91.3%)
Mechanical ventilation time[2] (h)	8.5 [7 ; 10]
ICU stay[1](h)	48 [48 ; 72]
Early postoperative LVEDD[1] (mm)	60.3 ± 8
Early postoperative LVESD [1](mm)	46.4 ± 8.4
Early postoperative LVEF[3] (%)	37.8 ± 10
Mean transprosthesis gradient[1] (mmHg)	12.4 ± 3.7
Complications	
-Bleeding[1] (ml)	453.5 ± 265
-Low output syndrome[3]	14 (30.4%)
- Cardiogenic shock [3]	2 (4.3%)
-Acute renal failure[3]	2 (4.3%)
-Third-degree AV block[3]	1 (2.2%)
-Wound infection[3]	1 (2.2%)
Hospital mortality[3]	7(15.2%)

1: expressed as means standard deviation (SD); 2: expressed as medians with interquartile range (IQR); 3: described as numbers and percentages (%). X clamp: cross clamping; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; ICU: intensive care unit; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; AV: atrioventicular.

Table 2: Operative and early postoperative data.

Variable	Univariate Analysis			Multivariate Analysis		
	0R	95% IC	P Value	Ajusted 0R	95% IC	P Value
Age	1.02	[0.95 - 1.10]	0.51			
Sex	0.65	[0.68 - 6.16]	0.70			
Renal failure	**11.66**	**[1.90 - 72]**	**0.008***	**11.94**	**[2.65 - 72.22]**	**0.03***
CHF	**24.66**	**[3.13 - 194.53]**	**<0.001***	**25.33**	**[3.43 - 194.74]**	**0.009***
NYHA	**8.20**	**[1.60 - 42.30]**	**0.01***	10.60	[0.20 - 577]	0.25
CT index	16875	[0.001 - 2 10^{11}]	0.24			
Etiologies	1.42	[0.30 - 7.22]	0.67			
Preoperative LVEF	**0.86**	**[0.77 - 0.96]**	**0.01***	1.00	[0.80 - 1.23]	0.99
Preoperative LVEDD	1.00	[0.90 - 1.12]	0.93			
Preoperative LVESD	1.05	[0.95 - 1.16]	0.30			
Mean transvalvular gradient	1.00	[0.96 - 1.04]	1			
Aortic valve area	0.45	[0.005 - 39.30]	0.72			
SPAP	1.00	[0.98 - 1.05]	0.46			
X clamp time	1.00	[0.96 - 1.04]	0.94			
CPB time	**1.02**	**[1.00 - 1.04]**	**0.02***	1.02	[0.99 - 1.05]	0.16
Bleeding	1.00	[0.99 - 1.00]	0.41			

OR: odds ratio; CI: confidence interval; CHF: congestive heart failure; CT: cardio-thoracic; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary arterial pressure. X clamp: cross clamping; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump.

*p-value < 0.05 was considered to be significant.

Table 3: Univariate and multivariate analysis of risk factors of hospital mortality

Variables	n = 46
Controlled patients	39
Follow up period[2](months)	59.6± 21
NYHA[3]	
-I	30 (81%)
-II	20 (19%)
Use of digitalo-diuretic treatment[3]	13 (35%)
Late complications	
-Cerebrovascular accident	2 (4.3%)
-Congestive heart failure	1 (2.2%)
Late postoperative LVEF [1](%)	50.3 ± 10
Late death[3]	2 (5 %)

1: expressed as means standard deviation (SD); 2: expressed as medians with interquartile range (IQR);3: described as numbers and percentages (%).
LVEF: left ventricular ejection fraction.

Table 4: Long-term outcomes

DISCUSSION

AS with LV dysfunction represents 5-15% of the overall AS [2,8,9]. It carries a dismal prognosis with an expected survival of < 2 years when treated medically [10].

Currently; the only effective therapy is the removal of the mechanical obstruction by aortic valve replacement (AVR) or by percutaneous aortic valve replacement (PAVR) as a therapeutic option [11]

Despite the benefit of AVR in AS with left ventricular dysfunction which was, at first , demonstrated in 1978 by Smith et al in a series of 19 patients and then confirmed in a larger series of 154 patients with high transvalvular gradient [12,13], the operative risk remains significantly higher.

However, the postoperative prognosis of these patients remains better, compared to those treated medically [2,14]. In our study, the hospital mortality was 15.20% mainly due to low cardiac output. This rate reached the margin of 8-21% reported in the literature [2,7].

There are many variables that can contribute to assess the postoperative prognosis; however, none of them alone should contraindicate the surgical procedure. Several factors are considered as associated with unacceptable risk of operative mortality. They include: age, female gender, class III-IV of NYHA, renal failure, congestive heart failure, LVESD> 54mm, severe pulmonary hypertension, absence of contractile reserve (CR) and low trans-aortic valvular gradient [4,7,8,15,16]. However most of those series are heterogeneous, including patients with other associated lesions, especially, coronary or valvular disease other than aortic stenosis.

The pejorative nature of the association of coronary disease and severe aortic stenosis has been well demonstrated by Powell et al who reported an operative mortality rate of 45% in patients with a history of myocardial infarction [17]. Similarly the presence of valvular lesions, including moderate mitral insufficiency was also reported as associated with high postoperative risk [15,18].

In addition, concomitant systemic hypertension leads to a significant increase in LV afterload which impairs myocardial function and increased perioperative complications and mortality [19-22].

In order to avoid a biase of the association with other disease lesions, our study has been focused on isolated AS with severe left ventricular dysfunction. It displayed renal failure and congestive heart failure as independents factors statistically associated with a risk of hospital mortality.

In a multicenter study, Clavel et al reported that patients with low transaortic gradient were a high-risk population with an operative mortality rate of 18%. The risk was even higher when transvalvular gradient was ≤ 20 mmHg [9.23]. Our study did not reveal any increased rate of hospital mortality with low transaortic gradient. This finding concords with the report of Borowski et al. They showed a similar postoperative mortality rate in a low gradient group and a high gradient one [24].

LV contractile reserve, accessed by Dobutamine stress echocardiography, can be useful to assess anatomic severity and prognosis. Thus, Tribouilloy found an operative mortality rate of 32% in patients who did not have CR vs 5% in those with CR [16,25,26].

Similarly, Monin and colleagues demonstrated that patients with a CR had a better prognosis than those without CR, both groups of patients had a longer life expectancy compared to patients treated medically though. [27]

Although the lack of CR is correlated with high postoperative mortality, it should not be considered by itself a surgical contraindication because the potential of myocardial recovery after surgery are not excluded [28].

Since 2012, we began to study the contractile reserve (CR) of LV by echocardiography with low-dose of dobutamine. Only three of our patients underwent this test. All of them had a contractile reserve.

After a median follow-up of 59.6± 21 months late mortality occurred in 2 (5%) patients. Beyond 5 years, survival rate was 78%.We could not determine factors that might relate to the risk of late mortality since our 2 late deaths were classified as non-cardiac origin.

At long term course, Morris et al reported that 72% of surviving have improved their LVEF and have had a better survival curve [29].

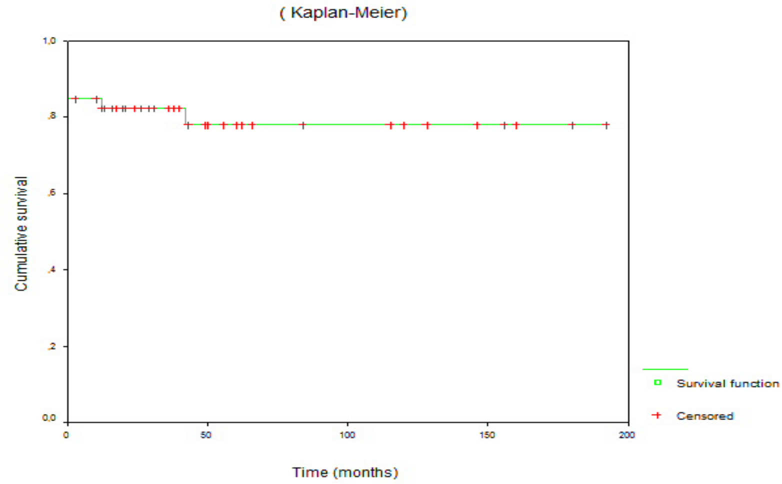

Figure 1: Survival estimate function

Many risk factors of late death have been reported, specially: advanced age, male gender, diabetes mellitus, Severe pulmonary hypertension, preoperative class III and IV NYHA, preoperative use of high doses of diuretic, preoperative circulatory assistance by intra-aortic balloon pump and prosthesis–patient mismatch [30,31,32].

Finally, our study demonstrated that LVEFF increased, by 5.5 units in the early postoperative stage and was associated with improved survival rate. Similarly, Vaquette et al concluded that patients who improve their LVEF more than 10 units had a better long-term survival than patients who did not [33].

Variable	Preoperative (G1)	Early postoperative period (G2)	Late postoperative period (G3)	P Value
LVEF	32 ± 8	37,8 ± 10	50,3 ± 10	G2 Vs G1 p < 0,0001* G3 Vs G2 p < 0,0001* G3 Vs G1 p < 0,0001*

LVEF: left ventricular ejection fraction. G: group *p-value < 0.05 was considered to be significant.

Table 5: Evolution of LVEF in preoperative, early postoperative and late postoperative period

CONCLUSION

Despite severe left ventricular dysfunction, aortic valve replacement in aortic stenosis can be tenable with excellent results. Congestive heart failure and preoperative renal failure are the main independents risks factors of hospital mortality. Late mortality might be inversely related to the LV recovery.

STUDY LIMITATION

Our study is prone to the biases of its retrospective nature. The small sample size might decrease the weight of the statistical results. The young age of our patients and their heterogeneous etiologies could influence the results. Additionally, contractile reserve evaluation during dobutamine infusion was not performed in enough patients to allow risk stratification in this series. All ours conclusion should be considered carefully.

CONFLICTS OF INTEREST

The authors declare having no conflicts of interest related to this article.

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