Outcomes following aortic valve replacement for isolated aortic stenosis with left ventricular dysfunction

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ABSTRACT

Background: Severe aortic stenosis (AS) is associated with a poor prognosis in patients with left ventricular dysfunction (LVD). Survival is estimated at less than 2 years without aortic valve replacement (AVR). Limited data are available on the effects and outcomes of AVR in such patients, especially in the absence of concomitant coronary artery disease (CAD).

Methods: This was a retrospective study which identified 33 patients over an approximate 10 year period who underwent surgical AVR for severe isolated AS and LVD (LVEF ≤50%). Patients were excluded if they had a prior valve replacement, mixed valve disease, <18 years old or the presence of CAD. Overall survival was analysed using the Kaplan-Meier curve and Cox proportional hazards model. The changes in postoperative LVEF and NYHA functional class, following AVR, was assessed using the Friedman test and ANOVA.

Results: Operative mortality was 15% with 5 deaths. Female sex and hyperlipidaemia were identified as predictors of early mortality by univariate analysis. LVEF improved in survivors from a mean of 39 ± 10% - 49.8 ± 8.7% at a 1 year follow-up (p=0.04). Younger age was identified as an independent predictor of LVEF recovery (p=0.04). There was no difference in outcomes in patients with low baseline transvalvular gradients compared to those with higher gradients. There was significant symptomatic improvement noted in all survivors following AVR (p<0.01).

Conclusion: Left ventricular function has a slower rate of recovery, compared to an earlier improvement of NYHA functional class after AVR for severe isolated AS and pre-operative LVD. In this high-risk group the findings support AVR in patients with LVD.

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INTRODUCTION

Severe aortic stenosis (AS) is associated with a poor prognosis in patients with left ventricular dysfunction (LVD). Survival is estimated at less than 2 years in patients without aortic valve replacement (AVR).[1,2] A reduced ejection fraction may be related to the severity of the AS and chronic pressure overload of the left ventricle, rather than depressed myocardial contractility (afterload mismatch). Relief of the valvular obstruction, by valve replacement, should allow recovery of left ventricular size and function.[3,4] However, there is a greater surgical risk and morbidity in patients with AS and LVD, which need to be considered.[5,6]

Most studies that have described the effects of AVR on ventricular function included patients with coronary artery disease (CAD), which may contribute independently to LVD. Since the presence of CAD is associated with a reduced survival rate following AVR,[2] we aimed to eliminate this variable and evaluate the isolated effect of AVR in those without concomitant CAD. There is no known published data available on survival, changes in ventricular function and long-term follow up from any South African institute to date. The purpose of this study was to determine the effects of AVR on left ventricular function and to describe the clinical outcomes in patients with isolated severe AS and LVD. The hypothesis was that AVR in patients with isolated AS and LVD improves LV function.

MATERIALS AND METHODS

Study population

Between 2004 and 2013, 1 573 chart records were analysed from the medical database of Inkosi Albert Luthuli Central Hospital, utilising the ICD-9 coding of AVR and AS. These

records were used to identify patients who underwent surgical AVR for isolated AS in the presence of severe LVD defined as left ventricular ejection fraction (LVEF) ≤50%. Patients were excluded if they had undergone a prior valve replacement, mixed valve disease, <18 years old or the presence of CAD, as determined by cardiac catheterisation and coronary angiography.

Thirty-three patients were eligible for entrance into the study and all medical records were reviewed retrospectively, including clinical and demographic characteristics pre-operatively together with 2D Doppler echocardiographic results, operative and follow-up data. A EuroScore II model was calculated for each patient undergoing AVR to estimate the operative risk of mortality. The study was approved by the biomedical research committee of the University of KwaZulu-Natal.

Echocardiography

All patients underwent comprehensive 2D Doppler echocardiographic examination performed by an experienced echocardiographer and all reports were assessed by a cardiologist. The left ventricular diameters, ejection fraction, mean and peak aortic gradients, as well as the native valve orifice area were measured. LVEF was estimated by Teichholz M-mode method. No patients in the study group were noted to have undertaken stress echocardiography with dobutamine in the presence of low transvalvular gradients.

Statistical analysis

Statistical analysis was performed using SPSS version 23 for Windows and Microsoft Excel. Continuous variables were expressed as mean ± standard deviation and as numbers with percentages for categorical variables. Continuous variables were compared with the 2 sample t test or Wilcoxon rank sum test when available, and categorical variables with the x^2 test or Fisher exact test when available. For multivariate analysis, the factors associated with mortality on univariate analysis were entered into a model for logistic regression. Predictors of mortality with proven evidence demonstrated in the literature were also included into the model. Overall survival was analysed using the Kaplan-Meier and Cox proportional hazards model. The changes in the post-operative ejection fraction and New York Heart Association (NYHA) functional class following AVR was assessed using the Friedman test. A multivariate model of the analysis of variance (ANOVA) test and linear regression models was performed to assess the independent association between change in LVEF and patient variables. For all statistical tests, a p value of ≤0.05 was considered significant.

RESULTS

The pre-operative and demographic data are presented in Table I. The average age of patients was 65 ± 13.2 years (range 44 - 89) with calcific AS being the common aetiology in the

TABLE 1: Baseline characteristics of patients.
Data are expressed as mean ± standard deviation (range) for continuous variables and n (%) for categorical variables. NYHA indicates New York Heart Association, ACE indicates angiotensin converting enzyme, LVEF indicates left ventricular ejection fraction.

Characteristic	Findings (n=33)
Age, years	65 ±13
Gender (Male/Female)	18/15 (55/45)
Racial group	
African	10 (30)
Indian	13 (40)
White	9 (27)
Coloured	1 (3)
Aetiology (n) %	
Calcific	29 (88)
Congenital/bicuspid	3 (9)
Rheumatic	1 (3)
Co-morbidities	
Hypertension	12 (36)
Diabetes Mellitus	5 (15)
Hyperlipidemai	3 (9)
Nil	13 (39)
Syncope	10 (30)
NYHA Class	
Grade I	3 (9)
Grade II	5 (15)
Grade III	21 (64)
Grade IV	4 (12)
Admission for heart failure	10 (30)
Rhythm	
Sinus	29 (88)
Atrial fibrillation	4 (12)
Medical therapy	
Diuretics	27 (82)
ACE inhibitor	11 (33)
Calcium channel blocker	3 (9)
Smoker	7 (21)
Haemodynamic status	
Systolic arterial blood pressure, mmHg	122 ± 17
Heart rate, beats per minute	98 ±17
LVEF, %	39 ± 10
Severity of LV dysfunction (LVEF %)	
Moderate (36 - 50%)	76 (25)
Severe (21 - 35%)	15 (5)
Very severe (<20%)	9 (3)
Aortic valve area, cm^2	0.61 ± 0.26
Mean transvalvular gradient, mmHg	45.7 ± 18.6
Peak transvalvular gradient, mmHg	78.5 ± 29.1

majority of patients (87.9%). Twenty-five patients (75.7%) were severely symptomatic (NYHA Class 3 and above) with 10 patients (30.3%) requiring admission for heart failure. The average pre-operative ejection fraction was 39 ± 10% and mean valve area 0.61 ± 0.26cm^2.

Clinical outcome

Mortality

The 30 day hospital mortality was 15.1% (5 of 33 patients), in comparison to the EuroScore II predicted mortality risk of 2.73% (Table II). Three of the deaths occurred intra-operatively due to cardiac arrest and the other 2 as a result of complete heart block and intractable heart failure. The mean time to death, following admission, was 11 days ± 8. Female sex (p=0.01) and hyperlipidaemia (p=0.05) were identified as significant risk factors for death by univariate analysis (Table III). Other predictors which may be of clinical relevance included: older age (p=0.1), higher baseline heart rate (p=0.09), history of syncope (p=0.14) and prior admission for heart failure (p=0.14).

These factors, together with other familiar predictors of peri-operative mortality found in the literature, were included in the multivariate logistic regression model. Older age (95% CI 0.02 - 0.19, p=0.015), female sex (95% CI 0.03 - 0.65, p=0.029) and hyperlipidaemia (95% CI 0.14 - 1.09, p=0.013) were found to be independent predictors of peri-operative mortality.

All patients who died were in NYHA Class 3 pre-operatively but this was not significantly different to survivors. Those with low transvalvular gradients were not found to have an increased risk of mortality (Table IV).

Post-operative outcomes

The mean duration of stay in survivors was 17 days (±13). Twenty-one patients (75%) had no post-operative complications. Tachyarrhythmias, complete heart block requiring permanent pacing, deep vein thrombosis, worsening heart failure and acute kidney injury requiring renal replacement therapy were identified as the major causes of morbidity.

Long-term survival and follow up

Figure 1 shows the Kaplan-Meir survival curve of the study population. Overall 1 year survival was predicted at 78.8% (95% CI: 0.61 - 0.89). Two patients were lost to follow-up and were not included in the survival analysis. No patients died during the follow-up period. The remaining survivors were followed up for a mean of 337 days ±150. There was a significant symptomatic improvement noted in all survivors following AVR (p<0.01). Seventy-five percent of patients were in NYHA Class 3 or 4 pre-operatively and none in the post-operative follow-up period (Table V). Three patients required readmission

TABLE II: Observed and Predicted Operative Mortality Stratified by EuroSCORE II Risk Model.

Level of risk	Number of patients	Observed mortality % (actual number)	Predicted mortality %
Low (0 - 2)	14	14.23 (2)	1.24
Moderate (2 - 5)	16	6.25 (1)	2.64
High (>5)	3	66.67 (2)	5.72
Overall	33	15.15 (5)	2.73

TABLE III: Univariate analysis of peri-operative mortality. Data are expressed as mean ± standard deviation (range) for continuous variables and n (%) for categorical variables.

Characteristic	Survived (n=28)	Demised (n=5)	P value
Age, years	63 ± 12	74 ± 12	0.10
Gender (male/female) n (%)	18/10 (64/36)	0/5 (0/100)	0.01
Calcific AS	24 (86)	5 (100)	1.00
Hypertension	10 (36)	2 (40)	1.00
Diabetes Mellitus	3 (11)	2 (40)	0.15
Hyperlipidaemia	1 (4)	2 (40)	0.05
No known co-morbidities	13 (46)	0 (0)	0.13
Syncope	7 (25)	3 (60)	0.15
NYHA Class III - IV	20 (71)	5 (100)	0.34
Prior admission for heart failure	7 (25)	3 (60)	0.14
Atrial fibrillation	4 (14)	0 (0)	1.00
Smoker	5 (18)	2 (40)	0.30
Systolic blood pressure (mmHg)	123 ± 18	116 ± 7	0.44
Heart rate (beats/minute)	86 ± 18	98 ± 16	0.09
Type of prosthesis Mechanical Bioprosthesis Unknown due to intra-operative death	 13 (46.4) 15 (53.6) 0 (0)	 0 (0) 2 (40) 3 (60)	0.49
Prosthesis size (mm)	20.78 ± 2.51	21 ± 0	0.91
Baseline LVEF (%)	38.6 ± 11.2	42.8 ± 4.4	0.60
Aortic valve area (cm^2)	0.61 ± 0.26	0.55 ± 0.24	0.71
Mean aortic valve gradient (mmHg)	43.9 ± 17.6	55.6 ± 22.4	0.29
Peak aortic valve gradient (mmHg)	75.9 ± 27.6	93 ± 36	0.37
Left atrial size (mm)	49.2 ± 10.8	47.8 ± 11.8	0.71
Post-operative complications	7 (25)	2 (40)	0.60

following AVR due to warfarin toxicity and heart failure. Cox proportional hazards model did not determine any significant factors that led to improved overall survival.

Echocardiographic changes

An analysis of variance (ANOVA) test concluded that a lower pre-operative LVEF was associated with prior admission for heart failure (p=0.01) and a smaller critical aortic valve area (p=0.03). An improvement of LVEF was noted in survivors from a mean of 39 ± 10% to 49.8 ± 8.7% at a mean 1 year follow-up period (p=0.04) (Figure 2). Further echocardiographic analysis was analysed at a mean of 610 days ±123 days post aortic valve replacement, which further confirmed an improved LVEF of +9% in comparison to the pre-operative EF (p=0.02). Younger age (p=0.04) was the only identifiable significant independent predictor of LVEF recovery. By multivariate analysis, pre-operative to post-operative change in LVEF correlated with a sustained decline in the peak aortic valve gradient from a mean of 78.51 ± 29.11mmHg to 31.87 ± 17.44 (p<0.01) at 1 year following AVR. Mean aortic valve gradients were not consistently recorded post-operatively and were therefore not analysed.

Patients with low mean transvalvular gradients (≤40mmHg) and those with high transvalvular gradients (>40mmHg) both demonstrated a similar improvement of LVEF recovery from baseline at 1 year following AVR (Table IV).

TABLE IV: Comparison of echocardiographic data and observed mortality of patients with high vs. low transvalvular gradients.
Echocardiographic data are expressed as mean ± standard deviation and mortality as n (%).

	Transvalvular gradient ≤40mmHg (n=14)	Transvalvular gradient >40mmHg (n=19)	P value
LVEF (%)	36.6 ± 12.3	41.2 ± 8.8	0.32
Aortic valve area (cm^2)	0.65 ± 0.25	0.58 ± 0.27	0.42
Mean transvalvular aortic gradient (mmHg)	31.5 ± 11.0	56.1 ± 16.0	0.04
Peak transvalvular aortic gradient (mmHg)	56.5 ± 15.6	94.6 ± 26.1	<0.01
LVEF following AVR 1 week 6 months 1 year	 34.2 ± 10.7 36.1 ± 12.3 48.2 ± 9.1	 36.5 ± 9.6 43.1 ± 13.7 51.4 ± 8.5	 0.56 0.22 0.39
Peak gradient following AVR at 1 year	40.8 ± 17.7	23.6 ± 13.0	0.01
Mortality	1 (7%)	4 (21%)	0.27

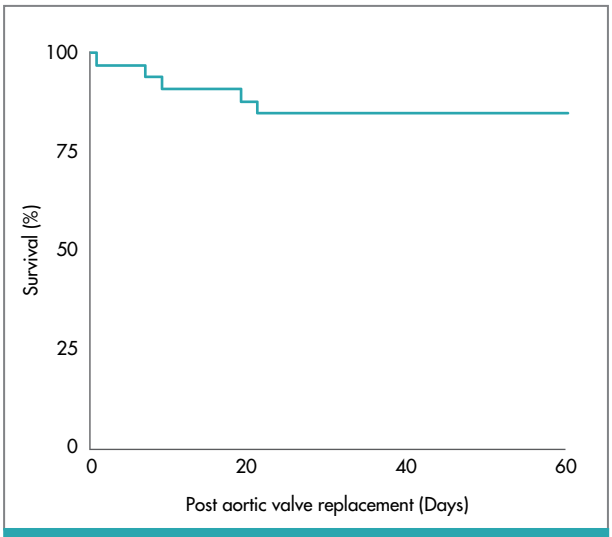

FIGURE 1: Kaplan-Meier curve of the study population.

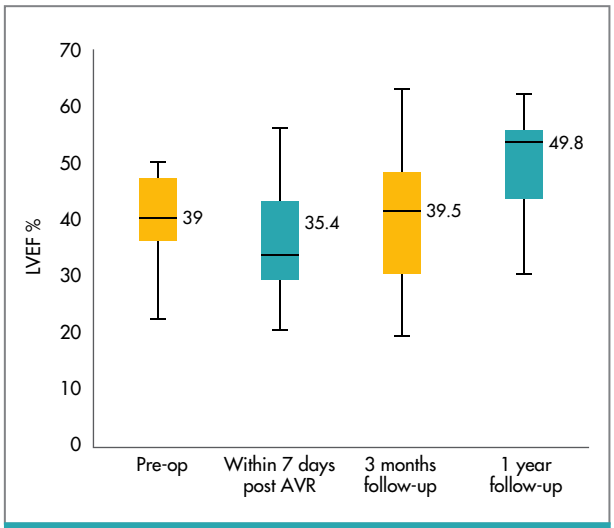

FIGURE 2: Left ventricular ejection fractions (LVEF) depicted pre-operatively (pre-op) and during the follow-up period. Solid horizontal lines indicates mean EF; the rectangular box represents the upper and lower quartiles, and vertical line, the highest and lowest mean values.

TABLE V: Mean change in New York Heart Association (NYHA) Class between genders prior to and following aortic valve replacement.
Data are expressed as mean ± standard deviation.

Gender	NYHA Class Pre-op	NYHA Class at 3 months	NYHA Class at 1 year
Male	2.55 ± 0.98	1.29 ± 0.59	1.25 ± 0.44
Female	3.06 ± 0.26	2.0 ± 0.87	1.62 ± 0.52
Total	**2.78 ± 0.78**	**1.53 ± 0.76**	**1.36 ± 0.49**

DISCUSSION

In various studies and databases mortality rates in symptomatic and asymptomatic individuals undergoing AVR range from as low as 1 - 3% in patients younger than 70 years to as high as 8% in older adults.[6]

In patients undergoing AVR for severe AS, LVD is a major prognostic indicator, with mortality rates of between 10 - 25% reported.[7,8] Despite increased mortality, AVR has been demonstrated to improve symptoms in survivors and improve survival compared to conservative management.[1,9] AVR is often not offered to these patients due to increased operative risk. Iung B, et al. found that 33% of patients in this group were declined AVR due to depressed LVEF (<50%) and advanced age.[10]

LVD may be due to concomitant coronary artery disease (CAD), a major cause of LVD,[11] and the mortality and outcomes of these patients may be influenced by dual pathology.

More recently, transcatheter aortic valve replacement (TAVR) has become a therapeutic recommendation in patients who have a high surgical risk.[12] However, when comparing TAVR to surgical AVR in patients with severe AS and LVD, no significant differences in mortality was found.[13,14] Currently, surgical AVR remains the gold standard in patients who are deemed fit for surgery. No patient in this study group underwent TAVR due to unavailability of the procedure at the study centre.

The overall early mortality of 15% found in this study is similar to ranges previously reported.[15] All patients that demised were female with no evidence of a higher incidence of comorbidities. These findings are consistent with other sex-based outcome studies following surgical AVR.[16,17] This, however, contrasted to the findings of a large New York study population of over 6 300 patients which found lower body surface area, which may or may not be linked to female sex, as a risk factor for medium term mortality following AVR.[18] Factors such as body fat composition, which may delay healing, as well as the postmenopausal state, which may confer an increased risk to death following surgery, have been postulated.[19]

Although hyperlipidemia was identified as a statistically significant risk factor for mortality (p=0.05), this should be a cautious interpretation considering the small sample size represented only 3 patients overall who had accompanying hyperlipidemia. Nevertheless, several studies have emerged that suggest AS is an active cellular process similar to atherosclerosis.[20,21] An elevated serum low density lipoprotein level has been proposed as a marker that increases the rate of disease progression in AS.[22,23]

Three of the 5 patients that demised had a history of syncope as well as a history of admission for heart failure. Although these characteristics did not approach statistical significance (p=0.14) it is certainly clinically relevant in this scenario. The average survival following the onset of syncope is estimated to be 2 - 3 years and in the presence of congestive cardiac failure at 1.5 years.[24] Therefore, prior to the development of symptoms and in the presence of concomitant LVD (LVEF <50%), AVR has been recommended as a Class I indication by the American College of Cardiology/American Heart Association guidelines and European Society of Cardiology guidelines.[6,12]

The cause of impaired left ventricular systolic function in patients with severe AS is multifactorial. Patients with impaired left ventricular systolic function not due to other causes, e.g. coronary artery disease, cardiomyopathy etc. have 2 basic causes namely afterload mismatch and contractile dysfunction. Afterload mismatch is characterised by the inability of myocardial fibers to shorten due to severe obstruction at aortic valve level.[25] Wall stress is elevated in comparison to contractile dysfunction, but the measurement of wall stress is difficult and gradients across the aortic valve are used as a surrogate. Thus, patients with reduced ejection fraction with gradients in the severe range will have an improvement in ejection fraction when the obstruction is relieved.[3]

In this study, no significant improvement was noted on LVEF on average at 1 week and 3 months post-operatively following AVR. This contrasted with findings of an earlier and sustained improvement in NYHA functional class at 3 months (p<0.01). At an approximate 1 year follow-up, however, a significant improvement in LVEF was evident (p=0.04). This data is similar to that reported by Robiolio et al. who examined 24 patients with severe AS (AVA <0.8cm). Fourteen of these patients had pre-operative LVD (LVEF <50%). It was noted that LVEF did not improve 1 week post-operatively, however, after 6 months LVEF had significantly improved from a mean of 38% to 57%.[26] Our study can therefore also conclude that left ventricular ejection fraction improves late after AVR in patients with AS and reduced ejection fraction. Considering the favourable response to surgery, it is also likely that afterload mismatch was the cause of the left ventricular dysfunction. The reason for a late recovery in LVEF may be inversely related to pre-operative LVD and the aortic valve area, as has been previously reported.[27] The most likely reason however, in the setting of this study, is probably related to the surgical intervention. Cardiac surgery results in several factors leading to myocardial stress that affect the post-operative course of patients. Triggers such as ischaemia, ischaemia-reperfusion, operative trauma and oxidative stress can lead to myocardial inflammation and apoptosis. This may eventually result in persistent myocardial dysfunction and prolonged depression of cardiac contractility.[28] Although aortic cross-clamp times were

unavailable for reporting in this study, it has been identified as an independent predictor of post-operative LVD and severe cardiovascular morbidity, with an escalated risk of 1.4% per 1 minute increase.[29]

Other factors associated with left ventricular recovery, following surgery, include the absence of a prior history of hypertension, heart failure and myocardial infarctions. Mild to moderate mismatch between patient body surface area and the prosthesis, including low post-operative aortic valve gradient, has also been shown to contribute to post-operative left ventricular dysfunction.[30]

LIMITATIONS

Due to the retrospective nature of the study, it was subject to selection bias and several limitations. This was a single centre study seeking to identify appropriate patients over a 10 year period. Given the rare association between isolated AS and LVD, which represents <5% of individuals with AS,[2] the relatively small sample size was expected. This limited the quality of results that could be produced and the ability to infer any significant conclusions from the risk factors associated with death. However, only a few larger series, with a maximum cohort of 46 such patients[15] were found in the literature, of which the outcomes were similar. Furthermore, Connolly, et al.[4] and Pereira, et al.[1] included patients with severe LVD and CAD below <35% , whereas in our study the baseline left ventricular function was only moderately impaired with an average of 39%. Post-operative mean aortic valve gradients were not documented in all patients and could thus not be analysed. This is due to the retrospective nature of the study and the lack of conformity between individual echo cardiographer reporting. Ejection fraction was calculated from the Teicholtz method. This formula calculates LVEF from left ventricular linear dimensions, however, its reliability depends upon the geometric assumptions of the left ventricular shape. The accuracy of echocardiographic data could not be compared to the values obtained from complete cardiac catheterisation, as this invasive procedure was not performed in all patients. Regardless, Doppler echocardiography is considered reliable and is the preferred investigation to assess disease severity in AS.[6,31] Considering once again that all patients with co-morbid CAD and/or myocardial infarctions were excluded from our study it is unlikely that other variables, besides afterload mismatch, may have had an influence on the LVEF which strengthens the validity of the results obtained. All our patients underwent surgical AVR; no patients were considered for transcatheter AVR due to the unavailability of the procedure.

CONCLUSION

Left ventricular function has a slow rate of recovery, which improves late following AVR in patients with severe isolated AS and pre-operative LVD. Functional class improves early following valve replacement with a longstanding favourable clinical response. Unless a specific contraindication to surgery exists, the findings of this study support early AVR in patients with LVD, which is in line with previously published reports for this high risk group.

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Conflict of interest: none declared.

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