

Enlargement of the Left Atrium Strongly Predicts Postoperative Mortality Following Heart Valve Surgery

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Background: Enlargement of the left atrium has been thoroughly studied in many clinical situations, especially its association with mortality and morbidity.

Patients and Methods: The study cohort included patients with rheumatic valve pathology such as stenosis and regurgitation. All patients underwent valvular surgical procedures including mitral valve replacement (MVR), aortic valve replacement (AVR), AVR with coronary artery bypass grafting (CABG), MVR with CABG, or AVR and MVR with or without CABG. This study included patients who underwent surgery between 2002 and 2017.

Results: Three hundred and forty-six patients were included in this study. The mean patient age was 51.6±16.1 years; 37% of the patients underwent AVR, 28% underwent MVR, and 13% underwent a combination of MVR with AVR, AVR with CABG in 6%, and MVR with CABG in 10%. The operative mortality rate was 5.8% (n=20). Univariate analysis revealed that the predictors of mortality included age ($P < 0.001$), body mass index (BMI) ($P = 0.003$), type of surgery performed ($P = 0.007$), hypertension ($P = 0.005$), emergent surgeries ($P = 0.018$), left atrial diameter ($P = 0.003$), cross-clamp time greater than 90 minutes ($P = 0.007$), postoperative acute kidney injury (AKI) ($P = 0.044$), postoperative stroke ($P = 0.049$), and surgical site infection ($P = 0.047$). Multivariate analysis revealed that predictors of mortality included age ($P = 0.028$, AOR=10.6), BMI ($P = 0.003$, AOR=3.12), re-exploration ($P = 0.006$, AOR=8.38), length of intensive care unit stay ($P \leq 0.002$, AOR=4.55), and left atrial diameter ($P = 0.003$, AOR=10.64).

Conclusion: Enlargement of the left atrium has been studied extensively as a predictor of mortality and morbidity in different clinical situations, to the extent that some authors suggest adding it to risk stratification models. In this study, left atrial size >4 cm was found to strongly predict mortality after rheumatic heart valve surgery.

Keywords: valve surgery, mortality, mitral, aortic, left atrial size

Introduction

Although its incidence is declining, rheumatic heart valve disease is still an endemic disease in developing countries and has begun to rise in developed countries due to migration of refugees. In its two pathologic presentations; stenosis and regurgitation, it causes a wide range of symptoms, like shortness of breath, fatigue, chest pain, syncope, and even sudden death. The procedure of choice is still surgical replacement, either by the open technique, trans-aortic valve implantation, or surgical valve repair. In Jordan, similar to other countries in the developing world, rheumatic valve disease is still the main pathology, rather than degenerative pathology, which is the leading cause of valve pathology in the developed world.¹

Clinical factors that predict mortality after valve replacement surgery have been thoroughly investigated in several studies.²⁻⁴ Older age, coronary artery disease, high creatinine level, and congestive heart failure (HF) have been frequently found as predictors of mortality after rheumatic heart valve surgery in patients undergoing aortic or mitral valve surgery.³ In the northern part of Jordan, we previously identified clinical factors that predict mortality and morbidity following heart valve surgery, including age, use of a biological valve, emergency valve surgery, Ejection Fraction (EF) less than 35%, pump run

time, cross-clamp time, use of beta-blockers for less than one month before surgery, and type of surgical procedure performed.^{5–7}

In this study, we investigated the association between an enlarged left atrium and mortality following different types of valve replacement surgery in Jordanian patients.

Patients and Methods

Patients

The cohort of patients studied included 346 patients who were admitted to our institute for valve surgery between July 2002 and December 2017. Among these, 29% underwent isolated mitral valve replacement surgery (MVR), 37% underwent replacement of the aortic valve (AVR), 6% underwent AVR combined with coronary artery bypass grafting surgery (CABG), 10% underwent MVR combined with CABG, and 14% underwent combined surgery of AVR and MVR with or without CABG. Rheumatic heart disease was diagnosed by a supervising consultant cardiologist, based on the patient's history, clinical findings, echocardiographic examination, and postoperative histopathological examination. Exclusion criteria were repeat cardiac surgery and aortic dissection requiring aortic root replacement.

The electronic medical records of eligible patients were used to retrieve clinical, echocardiographic, and surgical data, which were reviewed and analyzed later. Patients' previous medication use was documented, and the duration of use was adopted to stratify them (one month or less or more than a month before surgery). An ALT (HD1) 6000 ht (2–4 MHz probe, Philips Medical Systems Inc., Bothell, WA, USA) was used to perform preoperative two-dimensional transthoracic echocardiography imaging studies. These studies were used to evaluate the left ventricular ejection fraction, degree of regurgitation in the mitral/aortic/tricuspid valves, and dimensions of the left atrium (diameters) as part of the preoperative evaluation of the patients. To measure the left atrial diameter, the long-axis view was calculated by measuring the antero-posterior dimension in M-mode. The normal diameters range from 2.5 to 4 cm. Coronary catheterization was performed for all patients aged 35 years, while in patients aged less than 35 years, it was performed only if there was an indication. The primary endpoint was mortality within 30 days of surgery. The Institutional Review Board (IRB) at KAUH and Jordan University of Science and Technology (JUST) approved the study. The study was performed in accordance with the principles of the Declaration of Helsinki, 1975. Informed consent was waived by the IRB committee due to the retrospective nature of the study, as the research could not be carried out practically without the waiver. In addition, the research involves no more than minimal risk to the patients, and it will not adversely affect the rights or privacy of the participants given the importance of the knowledge to be gained. Patient data were anonymized and confidentiality was maintained.

Operative Procedure

Median sternotomy was the standard approach for all the patients. All the patients underwent surgery using a cardiopulmonary bypass machine. Arterial cannulation was performed centrally on the distal ascending aorta, while venous cannulation was performed through two-stage cannulation in AVR patients, and bicaval cannulation was used in patients undergoing MVR. In patients who underwent combined valve replacement and CABG, all distal anastomoses using vein grafts were performed first, starting with the right coronary artery, followed by the circumflex artery, and then the diagonals were performed. Continuous anastomoses were performed using 7/0 polypropylene sutures. Valve replacement was performed next, and left internal thoracic artery-to-left anterior descending anastomoses (LIMA-LAD) were performed subsequently. A transverse incision in the proximal part of the ascending aorta, approximately 1.5 cm from the origin of the right coronary artery, was made to approach the aortic valve, while MVR was performed through an incision in the interatrial groove. In cases of valve replacement, complete excision of the valve leaflets, and proper decalcification of the annulus, interrupted pledged polyester [2/0] sutures were used in both the aortic and mitral positions. Proper sizing was performed and the valve was downloaded using the parachuting technique. Mechanical valves were offered for all patients younger than 65 years, except if patients chose the biologic valve, whereas biological valves were offered for those 65 years or older.

Statistical Analysis

SPSS version 22 was used for data analysis. Frequencies and percentages were used to summarize categorical variables, while mean \pm standard deviation was used for continuous variables. Left atrial diameter was dichotomized into >4 cm or ≤ 4 cm.

Independent sample *t*-tests or χ^2 tests were used to analyze independent variables for 30-day mortality, as appropriate. P-values are reported for bivariate analyses. All independent variables that were significantly associated with mortality ($P < 0.05$) were included in a backward conditional logistic regression model (entry at $P = 0.05$, removal at $P = 0.2$). Adjusted odds ratios (AOR) and P-values are reported. The alpha level for all analyses was set at 0.05.

A logistic regression model was used to include variables that were significantly associated with 30-day mortality at the bivariate level. These included age, body mass index (BMI), surgery performed on emergency bases, type of surgery performed, hypertension, aortic cross-clamp time >90 minutes, use of B-blockers for $>$ a month before surgery, use of biological valves, re-exploration for bleeding, postoperative acute kidney injury (AKI), intensive care unit (ICU) stay of >3 nights, postoperative stroke, sternal wound infection, and left atrial diameter >4 cm.

Results

Three hundred and forty-six patients met the inclusion criteria were included in this study. The mean patient age was 51.6 ± 16.1 years. Male sex constituted 51% of patients ($n=178$); 21% of the patients were diabetic, while 44.6% had hypertension (Tables 1 and 2). Approximately 32% of patients had CAD and 23% had HF.

The thirty-day mortality rate was 5.8% ($n=20$); 6 patients died as a result of sepsis, 8 as a result of multi-organ failure, and 3 due to stroke. In 3 patients, the cause of death was not documented in their files. The medications used were as follows: aspirin (33%), clopidogrel (16%), statins (25%), ACEi (28%), β -blockers (35%), and loop diuretics (49%). Clopidogrel was the only medication that was stopped 5–7 days before surgery.

Predictors of Mortality

The univariate predictors of mortality after surgery are presented in (Tables 1 and 2). These variables included age ($P < 0.001$), BMI ($P = 0.003$), operation type ($P = 0.007$), hypertension ($P = 0.005$), emergency surgery ($P = 0.018$), left atrial diameter ($P = 0.003$), use of B-blockers (none or less than a month) before surgery ($P = 0.01$), use of biological valve in the mitral position ($P = 0.016$), length of stay in the ICU after surgery ($P = 0.022$), re-exploration for bleeding ($P = 0.019$), cross-clamp time greater than 90 minutes ($P = 0.007$), postoperative AKI ($P = 0.044$), postoperative stroke ($P = 0.049$), and surgical site infection ($P = 0.047$).

Table 3 shows the logistic regression analysis performed to identify the independent predictors of mortality after adjusting for other variables and potential confounders. Age ($P = 0.028$, AOR=10.6), BMI ($P = 0.003$, AOR=3.12), re-exploration ($P = 0.006$, AOR=8.38), length of ICU stay ($P \leq 0.002$, AOR=4.55), and LA diameter >4 cm ($P = 0.003$, AOR=10.64) were independent predictors of postoperative mortality.

Discussion

Following CABG, valve surgery is second in terms of frequency of performance as open-heart surgery in Jordan. Our studies results regarding mortality and morbidity after valve operations have been published previously (5–7). According to these studies, age, emergency valve surgery, EF $<35\%$, use of beta-blockers for more than a month before surgery, use of a tissue valve, type of surgery performed, pump run time, and cross-clamp time were all found to be independent predictors of mortality after valve heart surgery.^{5–7}

In practice, one can be considered a preoperative predictor of mortality. Left atrium enlargement has been shown in many clinical situations to be a predictor of morbidity and mortality^{8,9} Ferreira et al⁸ showed that, in terms of echocardiographic criteria, the increase in left atrium volume was the only determinant associated with a need for mechanical ventricular assist device, heart transplantation and death in patients with dilated cardiomyopathy. Incident HF,¹⁰ atrial fibrillation,¹¹ stroke,¹² and even death^{12,13} have been reported to be associated with left atrial enlargement. In patients with type II diabetes mellitus, enlargement of the left atrium has also been reported as an independent predictor of cardiovascular morbidity and mortality.⁹

Table I Distribution of Participants by Pre-Operative Mortality and Background Characteristics

		Not Dead		Dead		Total	P-value
		n	%	n	%		
Overall		326	94.2%	20	5.8%	346	
Age in Years (Mean)		50.70		65.60		51.56	0.000
BMI (mean)		26.34		29.03		26.50	0.003
Gender	Female	159	94.6%	9	5.4%	168	0.743
	Male	167	93.8%	11	6.2%	178	
	Total	326	94.2%	20	5.8%	346	
Operation Type	AVR	119	96.0%	5	4.0%	124	0.007
	MVR	95	96.0%	4	4.0%	99	
	AVR + MVR	42	100.0%	0	0.0%	42	
	AVR + CABG	15	78.9%	4	21.1%	19	
	MVR + CABG	28	87.5%	4	12.5%	32	
	AVR+MVR+CABG	3	100%	0	00.0%	3	
	Others	24	88.9%	3	11.1%	27	
	Total	326	94.2%	20	5.8%	346	
Syncope	NO	280	94.9%	15	5.1%	295	0.150
	YES	39	100.0%	0	0.0%	39	
	Total	319	95.5%	15	4.5%	334	
Hypertension	NO	182	98.4%	3	1.6%	185	0.005
	YES	137	91.9%	12	8.1%	149	
	Total	319	95.5%	15	4.5%	334	
Diabetes	NO	248	95.8%	11	4.2%	259	0.822
	OHG	51	94.4%	3	5.6%	54	
	Insulin	13	92.9%	1	7.1%	14	
	Total	312	95.4%	15	4.6%	327	
Smoking (never/ever)	Never smoked	222	94.9%	12	5.1%	234	0.448
	Ever smoked	91	96.8%	3	3.2%	94	
	Total	313	95.4%	15	4.6%	328	
History of HF	NO	244	94.9%	13	5.1%	257	0.435
	YES	68	97.1%	2	2.9%	70	
	Total	312	95.4%	15	4.6%	327	
Pre-operative Renal Impairment	NO	292	95.4%	14	4.6%	306	0.488
	YES	10	90.9%	1	9.1%	11	
	Total	302	95.3%	15	4.7%	317	
EF	Normal	162	95.3%	8	4.7%	170	0.941
	Mild	57	96.6%	2	3.4%	59	
	Moderate	33	94.3%	2	5.7%	35	
	Severe	15	93.8%	1	6.3%	16	
	Total	267	95.4%	13	4.6%	280	
Emergency / Urgent	Elective	295	95.2%	15	4.8%	310	0.018
	Urgent	13	81.3%	3	18.8%	16	
	Total	308	94.5%	18	5.5%	326	

(Continued)

Table 1 (Continued).

		Not Dead		Dead		Total	P-value
		n	%	n	%		
Overall		326	94.2%	20	5.8%	346	
ACE-I use	No or less than 1 month	243	94.6%	14	5.4%	257	0.140
	More than 1 month	72	98.6%	1	1.4%	73	
	Total	315	95.5%	15	4.5%	330	
B-blockers use	No or less than 1 month	107	91.5%	10	8.5%	117	0.010
	More than one month	207	97.6%	5	2.4%	212	
	Total	314	95.4%	15	4.6%	329	

Table 2 Distribution of Participants by Intra and Post-Operative Mortality Characteristics

		Not Dead		Dead		Total	P-value
		n	%	n	%		
Overall		326	94.2%	20	5.8%	346	
Type of valve used (aortic)	Biological	33	18.4%	2	6.0%	35	0.399
	Mechanical	146	81.6%	11	7.5%	232	
	Total	179	100%	13	7.3%	346	
Type of Valve (mitral)	Biological	28	16.7%	5	17.9%	32	0.016
	Mechanical	140	83.3%	4	2.9%	144	
	Total	168	100%	9	5.4%	346	
Pump Time	<120	196	95.6%	9	4.4%	205	0.214
	>120	67	91.8%	6	8.2%	73	
	Total	263	94.6%	15	5.4%	278	
Aorta cross Clamp time	< 90 MIN	203	97.1%	6	2.9%	209	0.007
	> 90 MIN	56	88.9%	7	11.1%	63	
	Total	259	95.2%	13	4.8%	272	
Intra Operative blood transfusion	No	246	95.3%	12	4.7%	258	0.687
	Yes	56	96.6%	2	3.4%	58	
	Total	302	95.6%	14	4.4%	316	
Re-exploration	No	299	95.8%	13	4.2%	312	0.019
	Yes	8	80.0%	2	20.0%	10	
	Total	307	95.3%	15	4.7%	322	
Prolonged Intropes Support (> 48 Hours)	NO	256	96.2%	10	3.8%	266	0.206
	Yes	48	92.3%	4	7.7%	52	
	Total	304	95.6%	14	4.4%	318	
Post-Operative Renal Failure	NO	298	95.8%	13	4.2%	311	0.044
	YES	10	83.3%	2	16.7%	12	
	Total	308	95.4%	15	4.6%	323	
Pneumonia/Sepsis	NO	303	95.9%	13	4.1%	316	0.531
	Pneumonia	12	92.3%	1	7.7%	13	
	Total	315	95.7%	14	4.3%	329	

(Continued)

Table 2 (Continued).

		Not Dead		Dead		Total	P-value
		n	%	n	%		
Overall		326	94.2%	20	5.8%	346	
ICU Stay	Less than one week	228	95.8%	10	4.2%	238	0.022
	More than one week	42	87.5%	6	12.5%	48	
	Total	270	94.4%	16	5.6%	286	
Post-Operative Stroke/TIA	NO	310	95.7%	14	4.3%	324	0.049
	YES	3	75.0%	1	25.0%	4	
	Total	313	95.4%	15	4.6%	328	
Sternal Infection	NO	314	95.7%	14	4.3%	328	0.047
	YES	3	75.0%	1	25.0%	4	
	Total	317	95.5%	15	4.5%	332	
LA Diameter before surgery	More than 4	182	91.0%	18	9.0%	200	0.003
	Less than or equal 4	144	98.6%	2	1.4%	146	
	Total	326	94.2%	20	5.8%	346	

In patients with aortic valve stenosis (AS), regardless of the mode of treatment, whether medical or surgical, left atrial enlargement was found to be a strong predictor of mortality, in addition to known predictors of outcome,¹⁴ and the authors suggested that it can be assessed in clinical practice for preoperative risk stratification. This conclusion was replicated in this study. Even in patients with asymptomatic aortic valve stenosis, left atrial enlargement as a measure of left ventricular diastolic dysfunction has been shown to be a predictor of mortality.¹⁵

From a pathophysiologic point of view, as the left atrial contraction at the end-diastole “left atrial kick” is considered to contribute significantly to cardiac output and as this “kick” is reduced when the left atrium is enlarged, left atrial enlargement consequently has adverse hemodynamic consequences due to impairment of left ventricular filling during the diastolic phase in these patients. Conversely, increased left ventricular stiffness as a consequence of progressive left ventricular dysfunction can lead to progressive mitral regurgitation, and thus, increased LA size.¹⁶ In a vicious cycle, enlargement of the left atrium can further impair left ventricular filling due to increased filling pressure or atrial fibrillation. Systolic dysfunction and left atrial enlargement can also be a consequence of mitral regurgitation,¹⁷ so the “history” of mitral regurgitation in terms of severity and duration can be reflected at the size of the left atrium. As left ventricular myocardial ischemic remodeling can result in mitral regurgitation, which in turn can lead to left atrial enlargement, mitral regurgitation can be considered a strong indicator of mortality. Moreover, ischemia and dilatation both enhance endothelin-1 (ET-1) synthesis. We have previously demonstrated that atrial ET-1 levels are strongly and independently correlated with LA enlargement of the left atrium as well as the severity of mitral regurgitation in atrial fibrillation patients.¹⁶

Postoperative atrial fibrillation is a predictor of mortality and morbidity,¹³ as left atrial enlargement is associated with postoperative atrial fibrillation,¹⁸ suggesting a common mechanism by which left atrial enlargement can contribute to postoperative morbidity and mortality. In a previous study on the same cohort, we showed that LA enlargement was associated with postoperative atrial fibrillation.⁷

It has been suggested that rheumatic heart disease has been eradicated in developed countries due to improved lifestyles and use of antibiotics.¹⁹ However, migration in many developed countries and refugee crises have led to an increase in rheumatic heart disease, a pathology that has not been treated in these areas for a long time.²⁰ Our findings emphasize that rheumatic valve surgery should be performed earlier to achieve better clinical outcomes.

Limitations of the Study

This study was limited by its retrospective nature and missing data. Elevated red cell distribution width, which reflects variability in the size of red blood cells (anisocytosis) due to erythrocyte dysfunction or inflammation, has been found to

Table 3 Adjusted Effect of Selected Variables on Perioperative Mortality

Variables		Not Dead		Dead		Total	Logistic Reression Results	
		n	%	n	%		AOR	P-value
Overall		326	94.2%	20	5.8%	346		
Age in Years (Mean)		50.70		65.60		51.56	1.083	0.032
BMI		26.34		29.03		26.50	1.213	0.003
ACE-i	No or less than 1 month	243	94.6%	14	5.4%	257	Ref.	0.173
	More than 1 month	72	98.6%	1	1.4%	73	0.071	
	Total	315	95.5%	15	4.5%	330		
Type of Valve (mitral)	Biological	28	84.4%	5	15.6%	32	Ref.	0.066
	Mechanical	140	97.2%	4	2.8%	144	0.040	
	NO	159	93.5%	11	6.5%	170	0.108	
	Total	326	94.2%	20	5.8%	346		
Re-exploration	No	299	95.8%	13	4.2%	312	Ref.	0.006
	Yes	8	80.0%	2	20.0%	10	78.038	
	Total	307	95.3%	15	4.7%	322		
Aorta Cross Clamp time	< 90 MIN	203	97.1%	6	2.9%	209	Ref.	0.160
	> 90 MIN	56	88.9%	7	11.1%	63	3.589	
	Total	259	95.2%	13	4.8%	272		
ICU Stay	Less than one week	288	95.8%	10	4.2%	238	Ref.	0.002
	More than one week	42	87.5%	6	12.5%	48	44.555	
	Total	330	94.4%	16	5.6%	346		
LA Diameter before surgery	Less than or equal 4	144	98.6%	2	1.4%	146	Ref.	0.030
	More than 4	182	91.0%	18	9.0%	200	10.638	
	Total	326	94.2%	20	5.8%	346		

be a predictor of mortality after valvular surgery.^{21,22} Future prospective studies are recommended to include complete data on red blood cell count and anisocytosis. The European System for Cardiac Operative Risk Evaluation (EUROScore II) is a helpful risk classification model that has been widely used to predict in-hospital mortality in patients undergoing heart surgery. Future studies that consider EuroScore are recommended.

Conclusion

Enlargement of the left atrium has been studied extensively as a predictor of mortality and morbidity in different clinical situations, to the extent that some authors suggest adding it to risk stratification models. In this study, left atrial size >4 cm was considered a strong predictor of mortality after rheumatic heart valve surgery.

Abbreviations

AVR, aortic valve replacement; MVR, mitral valve replacement; CABG, coronary artery bypass grafting; AKI, acute kidney injury; BMI, body mass index; LA, left atrium; AOR, adjusted odds ratio; TAVI, trans-aortic valve implantation; HF, heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction; LIMA, left internal mammary artery;

LAD, left anterior descending; ICU, intensive care unit; CAD, coronary artery disease; ACE-i, angiotensin converting enzyme-inhibitor; ET-1, endothelin 1; IRB, Institutional Research Board.

Ethics Approval

Approved by the IRB.

Informed Consent/Consent to Publish

Waived by IRB.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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