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Journal of Cardiology 84 (2024) 86–92

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Mitral regurgitation in atrial fibrillation: Is a simple repair enough to tackle a complex problem?

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ARTICLE INFO

Article history:
Received 10 August 2023
Received in revised form 24 November 2023
Accepted 4 December 2023
Available online 14 December 2023

Keywords:
Atrial fibrillation
Mitral valve repair
Recurrent mitral regurgitation

ABSTRACT

Background: Clinical and echocardiographic results of valve repair for mitral regurgitation in the setting of atrial fibrillation are poorly studied.
Methods: Between January 2008 and December 2020, 89 patients underwent valve repair for mitral regurgitation in the setting of atrial fibrillation. Clinical and echocardiographic follow-up data were collected and studied. The primary composite endpoint consisted of all-cause mortality or hospitalization for heart failure.
Results: Valve repair with true-sized annuloplasty was performed in 83 (93 %) and restrictive annuloplasty in 6 (7 %) patients. Early mortality occurred in 3 (3 %) and residual mitral regurgitation in 1 (1 %) patient. During a median follow-up of 5.4 years (interquartile range 3.4–9.5), 25 patients died, 6 due to end-stage heart failure. Ten patients were hospitalized for heart failure. The estimated event-free survival rate at 10 years was 48.2 % (95 % CI 33.5 %–62.9 %). Recurrent mitral regurgitation was observed in 14 patients and most often caused by leaflet tethering. When analyzed as a time-dependent variable, recurrent regurgitation was related to the occurrence of the primary endpoint (hazard ratio 3.192, 95 % CI 1.219–8.359, $p = 0.018$). On exploratory sub-analyses, no recurrent regurgitation was observed after restrictive annuloplasty or in patients with paroxysmal atrial fibrillation. Moreover, recurrent regurgitation was observed more often when signs of left ventricular impairment were present preoperatively.
Conclusions: Despite good initial results, recurrent regurgitation was a frequent observation after valve repair for mitral regurgitation in atrial fibrillation and had an effect on heart failure related morbidity and mortality. Refinements in the timing of surgery and surgical technique might help improve outcomes.

Introduction

According to Carpentier's classification of mitral valve disease, type I mitral valve dysfunction will combine annular dilation with normal leaflet motion and result in regurgitation due to loss of leaflet coaptation [1]. Surgical repair aims to restore coaptation by annular remodeling using true-sized ring annuloplasty. Atrial fibrillation is a common underlying cause of type I dysfunction. It is the most frequent atrial rhythm disorder with a growing prevalence seen in Western countries and characterized by atrial structural, architectural, contractile, and/or electrophysiological changes and might, among others, manifest itself as mitral regurgitation in the absence of other valve lesions [2].

Late clinical and echocardiographic results of valve repair for mitral regurgitation in the setting of atrial fibrillation are to date poorly explored. Recent studies suggest that recurrent regurgitation might, surprisingly, not be uncommon after an initially successful repair [3–6]. This might be related to the fact that mitral regurgitation in atrial fibrillation is not caused solely by annular dilation but might mechanistically also be related to impaired mitral annular dynamics, insufficient leaflet adaptation, and impaired left ventricular dynamics [7–10]. Moreover, as atrial fibrillation has a central role in the pathogenesis of valve dysfunction, adequate control or prevention of recurrent episodes might have a beneficial effect on outcomes [3].

The aim of this study is to explore the clinical outcomes and durability of surgical mitral valve repair for type I dysfunction in the setting of

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https://doi.org/10.1016/j.jjcc.2023.12.001

atrial fibrillation and explore risk factors related to recurrent regurgitation after an initial successful repair.

Methods

Study population

Adult patients undergoing mitral valve surgery between January 2008 and December 2020 at Leiden University Medical Centre, Netherlands, were eligible for inclusion. Included were patient with mitral regurgitation in the setting of atrial fibrillation and no other etiologies. The indication for surgery was based on the severity of mitral and tricuspid valve regurgitation, hereto related geometrical and functional changes of cardiac chambers, and the presence of heart failure and atrial fibrillation-related symptoms. Patients with other types of mitral valve disease, including degenerative or rheumatic valve disease, active or healed infective endocarditis or ventricular functional mitral valve disease (mitral regurgitation in the presence of ischemic or non-ischemic cardiomyopathy) or with a history of previous cardiac surgery (excluding thoracoscopic MAZE procedure) were excluded. Patient history, preoperative echocardiograms, and operative reports were reviewed to correctly identify the underlying disease. Based on disease severity, patients were subdivided into three groups:

- **Stage 1 disease**: mitral regurgitation without left ventricular dilation and normal systolic ventricular function (ejection fraction ≥50 %),
- **Stage 2 disease**: mitral regurgitation with left ventricular dilation and normal systolic ventricular function (ejection fraction ≥50 %),
- **Stage 3 disease**: mitral regurgitation with impaired systolic left ventricular function (ejection fraction <50 %),

In all patient with Stage 2 or 3 disease, no evidence of ischemic or other type of primary ventricular cardiomyopathy (e.g. non-ischemic dilative cardiomyopathy or myocarditis) was present and changes to the left ventricle were considered secondary to atrial fibrillation and hereto related mitral regurgitation (e.g. atrial fibrillation induced tachycardiomyopathy and long-lasting volume overload).

Data collection

Preoperative, intraoperative and postoperative data were collected from our computerized patient database. Survival data for all patients were obtained from municipal civil registries. Clinical follow-up data were obtained during routine postoperative visits and through telephonic interviews. Regular echocardiographic follow-up was performed, as recommended [11]. Echocardiography was performed at 3 and 12 months after index surgery and biennially thereafter. For patients in whom postoperative follow-up was not performed in our institution, all available echocardiographic reports were obtained and reviewed to assess the recurrence and mechanism of mitral regurgitation.

Ethics statement

The local institutional Ethics Committee of Leiden University Medical Centre provided formal approval for the current study (number P16.003, date of approval 14-06-2021) and written patient consent was obtained from all participants.

Surgical technique

Mitral valve repair was performed by implanting a true-sized full semi-rigid annuloplasty ring. The choice of ring type was at the discretion of the operating surgeon. Ring sizing was determined after measurement of the surface area of the anterior mitral valve leaflet. In 6/89 (7 %) patients, restrictive mitral annuloplasty was performed as some evidence of leaflet restriction was seen on intraoperative echocardiography. In these cases, the implanted ring was downsized with one or two ring sizes. Tricuspid valve repair was performed in the presence of ≥grade 2+ tricuspid regurgitation and/or significant annular dilation (annular diameter ≥ 40 mm or ≥21 mm/m^2 body surface area). In selected patients with a prolonged history of atrial fibrillation, right ventricular dysfunction and/or pulmonary hypertension, tricuspid valve repair was considered even in the presence of less severe annular dilation (annular diameter > 35 mm) [12].

The indication for and the type of concomitant ablation were based on patient history, duration of atrial fibrillation, and the extent of left atrial dilation. As a general rule of thumb, no concomitant ablation was performed in cases of a very prolonged history of permanent atrial fibrillation (typically >5 years of accepted atrial fibrillation) or severely dilated atria (left atrial volume index ≥70 ml/m^2).

Echocardiographic analysis

Transthoracic 2-dimensional echocardiography was performed in all patients before surgery, before discharge, and during follow-up. Left ventricular and left atrial dimensions were assessed in the parasternal long-axis view. Apical 2- and 4-chamber views were used to measure left atrial volume, left ventricular end-diastolic and end-systolic volumes. The Simpson's biplane method was used to calculate left ventricular ejection fraction [13]. Mitral regurgitation severity was graded according to current recommendations using a multi-parametric approach, and was classified as mild (1+), mild–moderate (2+), moderate–severe (3+), and severe (4+) [14].

Study endpoints

The primary study endpoint was a composite endpoint of all-cause mortality and hospitalization for heart failure. Secondary endpoints included all-cause mortality, mitral valve reintervention, and freedom from recurrent mitral valve regurgitation. Early mortality was defined as mortality occurring within 30 days after the operation or during index hospitalization. Residual and recurrent regurgitation were defined as ≥grade 2+. Data are reported according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions [15].

Statistical analysis

Continuous data are presented as means ±standard deviation for normally distributed and medians with interquartile range (IQR) for skewed data. Categorical data are presented as counts and percentages. Freedom from time-related events was estimated using the Kaplan–Meier method and differences between groups were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to analyze variables associated with the primary endpoint or all-cause mortality (variables included in the model: demographic and comorbidities presented in Table 1, echocardiographic characteristics, including left ventricular end-systolic diameter, left ventricular ejection fraction, and mitral regurgitation recurrence) and mitral regurgitation recurrence (including variables, known or presumed to have an effect on the recurrence of regurgitation; this included age, gender, mitral regurgitation jet orientation, left ventricular end-systolic diameter, left ventricular ejection fraction, indexed left atrial volume, concomitant ablation and grade 1+ residual regurgitation on predischarge echocardiogram). To assess the effect of mitral regurgitation recurrence on the primary endpoint and all-cause mortality, the former was analyzed as a time-dependent covariable. For each model, a univariable analysis was initially performed. Variables demonstrating a p-value <0.20 were included in the multivariable model with a backward selection method. A level of p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Table 1
Preoperative patient and echocardiographic characteristics.

	N = 89
Demographics	
Gender (female)	52 (58)
Age (years)	74 (IQR 67–79)
Comorbidities	
Hypertension	53 (60)
History of stroke	14 (16)
Diabetes mellitus	8 (9)
Chronic obstructive pulmonary disease	9 (10)
Peripheral vascular disease	6 (7)
NYHA class	
II	44 (49)
III/IV	39 (44)
Hospitalization for heart failure	18 (20)
History of atrial tachycardias	
Atrial fibrillation	90 (100)
Paroxysmal	13 (15)
Persistent	24 (27)
Long-standing persistent or permanent	52 (58)
Duration of atrial fibrillation (years)	3.8 (IQR 1.5–7.9)
Atrial flutter	9 (10)
Permanent pacemaker implantation	11 (12)
His bundle ablation	3 (3)
Electric cardioversion	31 (35)
Catheter ablation	4 (5)
Thoracoscopic MAZE procedure	1 (1)
Echocardiographic characteristics	
Left ventricular ejection function (%)	53 ± 9
Left ventricular ejection fraction ≤50 %	28 (31)
Left ventricular end diastolic diameter (mm)	49 (IQR 44–54)
Left ventricular end systolic diameter (mm)	30 (IQR 26–36)
Indexed left atrial volume (ml/m^2)	50 (IQR 42–69)
Impaired right ventricular function	33 (37)
Mitral regurgitation grade	
2+	17 (19)
3+	39 (44)
4+	33 (37)
Posterior direction of mitral regurgitant jet	20 (23)
Tricuspid regurgitation grade	
2+	28 (32)
3+	8 (9)
4+	16 (18)
Pulmonary artery pressure (mmHg)	31 (IQR 27–39)
Disease severity	
Stage 1	49 (55)
Stage 2	11 (12)
Stage 3	29 (33)

Data are presented as N (%), means ± standard deviation or medians with interquartile ranges. NYHA, New York Heart Association.

Table 2
Intraoperative data.

	N = 89
Mitral valve repair	89 (100)
Restrictive mitral annuloplasty	6 (7)
Ring size	
26	6 (7)
28	19 (21)
30	32 (36)
32	16 (18)
34	13 (15)
36	2 (2)
38	1 (1)
Ring type	
Physio[a]	22 (25)
Physio II[a]	59 (66)
Other	8 (9)
Tricuspid valve repair	75 (84)
Ring size	
24	1 (1)
26	2 (2)
28	17 (19)
30	19 (21)
32	31 (35)
34	6 (7)
Ring type	
MC3[a]	21 (24)
Physio Tricuspid[a]	46 (52)
Contour 3D[b]	8 (9)
Tricuspid valve replacement	1 (1)
Concomitant ablation	55 (62)
Pulmonary vein isolation	12 (14)
Box lesion	4 (5)
Modified left sided MAZE	36 (40)
Bi-atrial MAZE	3 (3)
Left atrial exclusion or amputation	66 (74)
Concomitant procedures	
Coronary artery bypass surgery	12 (14)
Aortic valve or root replacement	10 (11)

Data are presented as N (%).
[a] Edwards Lifesciences, Irvine, CA, USA.
[b] Medtronic, Minneapolis, MN, USA.

Results

Preoperative characteristics and intraoperative details

A total of 89 patients met the inclusion criteria for the current study cohort. The majority of patients (52 patients, 58 %) were female (Table 1) and 11 patients (12 %) had previously undergone permanent pacemaker implantation. Advanced symptoms of heart failure (New York Heart Association class III or IV) were often seen and a considerable proportion of patients (18 patients, 20 %) had a clinical history of hospitalization for heart failure.

Successful mitral valve repair was performed in all patients while concomitant tricuspid valve repair or replacement was performed in 76 (85 %) patients (Table 2). Concomitant ablation was performed in almost two-thirds of patients with 66 (74 %) of patients undergoing left atrial exclusion or amputation.

Postoperative course

Early mortality occurred in 3 (3 %) patients, related to right ventricular failure in 1 patient and multi-organ failure in the remaining 2 patients. In 1 of the latter patients, residual mitral regurgitation occurred early after the index operation. The patient underwent a reoperation during the same hospitalization but sadly died thereafter.

High grade atrioventricular conduction disorders were common and in 22 (28 %) patients a de novo 3rd degree atrioventricular block occurred. In most patients, conduction recovered, but 3 (4 %) patients needed postoperative permanent pacemaker implantation. Predischarge transthoracic echocardiography demonstrated no significant residual regurgitation [no mitral regurgitation in 67/86 (78 %) and grade 1+ in 19/86 (22 %) patients] in any patient discharged from hospital.

Late clinical outcomes

Survival status was available for all patients with a median follow-up duration of 5.4 (IQR 3.4–9.5) years. During follow-up, 10 patients were hospitalized for worsening heart failure and 25 patients died. Cause of death was end-stage heart failure in 6 patients, cerebrovascular accident in 3 patients, bleeding complications in 2 patients, and infective endocarditis in 1 patient. In 5 patients, the cause of death was unknown while in the remaining 8 patients, the cause of death was not cardiac related.

The estimated 5- and 10-year event-free survival rates were 79.5 % [95 % confidence interval (CI) 70.1 %–88.9 %] and 48.2 % (95 % CI 33.5 %–62.9 %), respectively (Fig. 1). The estimated 5- and 10-year overall survival rates were 80.7 % (95 % CI 71.5 %–89.9 %) and 59.1 % (95 % CI 45.2 %–73.0 %), respectively. Mitral valve reintervention was performed in 1 patient, 3.8 years after the index operation. Ring dehiscence was the cause of recurrent regurgitation and a re-repair was performed.

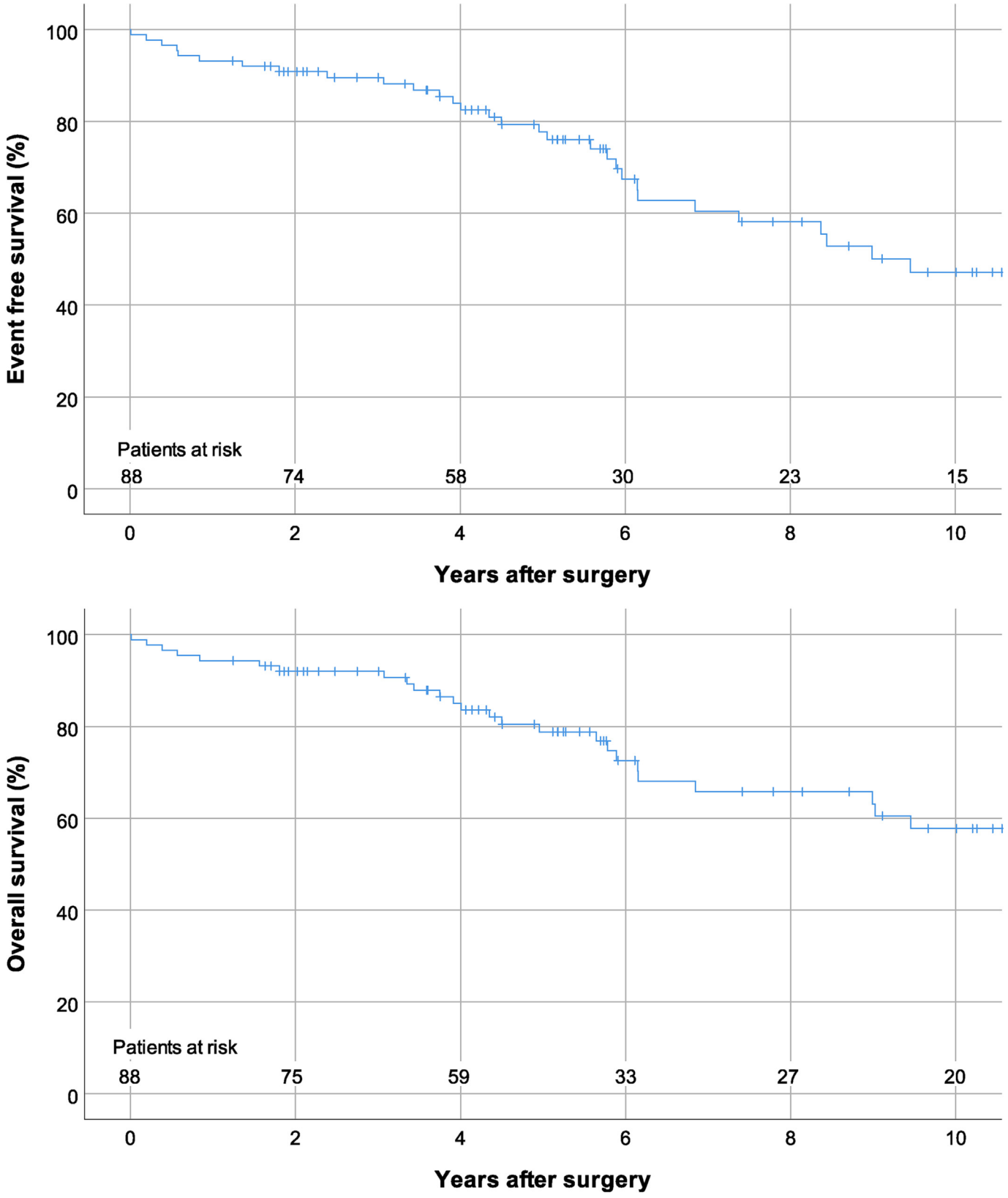

Fig. 1. Kaplan-Meier survival demonstrating event-free survival (above) and overall survival rate (below) for the whole patient cohort.

Recurrence of mitral regurgitation

Echocardiographic follow-up was available for 80/86 (93 %) hospital survivors with a median follow-up time of 4.0 (IQR 2.0–7.8) years. After surgery, 14 patients developed recurrent regurgitation, at a median time of 4.0 (IQR 1.9–7.6) years. The estimated freedom from recurrent regurgitation rates at 5 and 10 years after surgery were 82.5 % (95 % CI 71.5 %–93.5 %) and 57.0 % (95 % CI 36.2 %–77.8 %), respectively (Fig. 2).

Of the 14 patients who developed recurrent regurgitation, echocardiographic studies were available to analyze the mechanism of

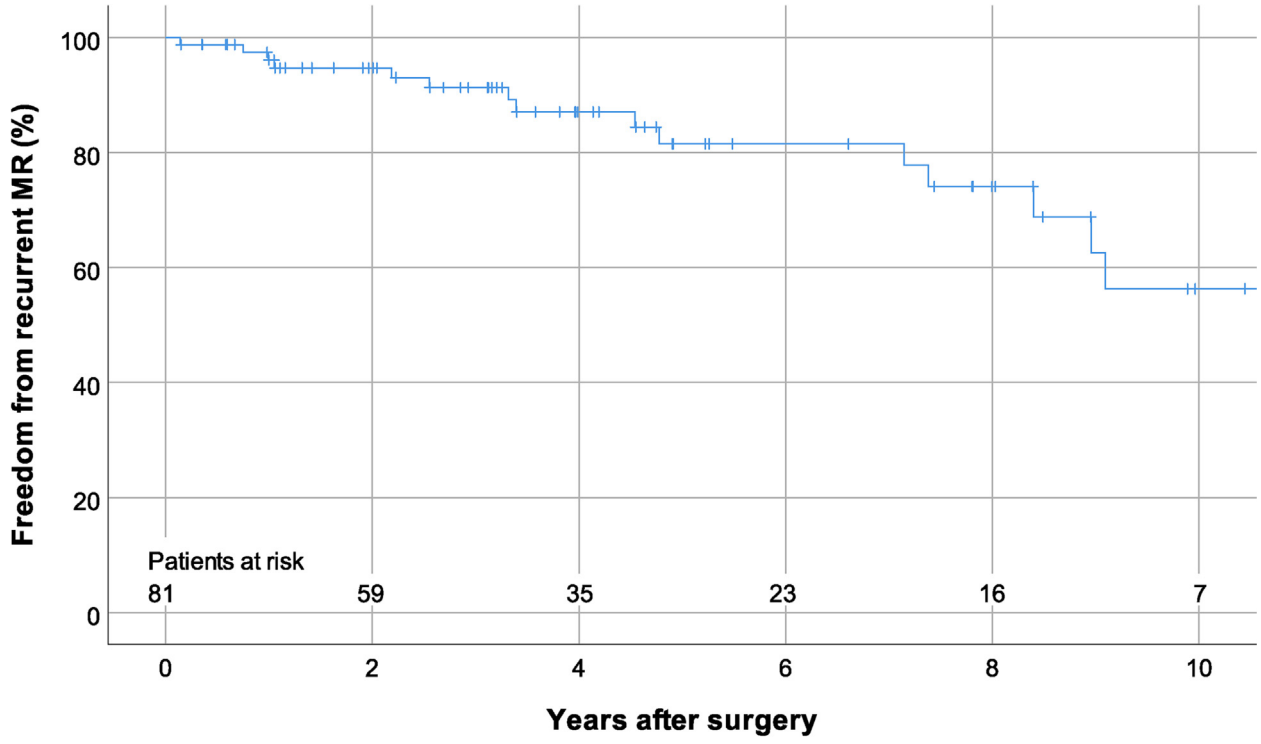

Fig. 2. Kaplan-Meier survival curve, demonstrating freedom from recurrent mitral regurgitation (MR) rate for the whole patient cohort.

recurrence in 12 patients. Leaflet tethering was the cause of recurrent regurgitation in 7/12 patients (Fig. 3), insufficient height of leaflet coaptation with anterior leaflet malapposition in 1/12 patients and ring dehiscence in 1/12 patients. The cause of recurrent regurgitation was unclear in the last 3 patients.

Adjusted risk factors analysis

Analyzed as a time-dependent variable, recurrent mitral regurgitation emerged as a risk factor for the occurrence of the primary endpoint [hazard ratio (HR) 3.192, 95 % CI 1.219–8.359, $p = 0.018$] and all-cause mortality (HR 3.648, 95 % CI 1.301–10.227, $p = 0.014$) (**Online material A** and **Online material B**).

On multivariable Cox proportional hazards regression analysis, mitral regurgitation grade 1+ on predischarge echocardiography emerged as a risk factor for mitral regurgitation recurrence (HR 3.562, 95 % CI 1.162–10.916, $p = 0.026$) (**Online material C**).

Explorative subgroup analyses

No recurrence of regurgitation was seen in patients who underwent restrictive mitral annuloplasty (**Online material D**). Moreover, no recurrent regurgitation was observed in patients with a history of paroxysmal atrial fibrillation (**Online material E**). When patients were divided into subgroups based on disease severity, Stage 1 disease patients demonstrated a trend towards better freedom from recurrent regurgitation (**Online material F**). Multivariable Cox regression analysis demonstrated that Stage 3 (HR 3.930, 95 % CI 1.087–14.204, $p = 0.037$) but not Stage 2 (HR 2.888, 95 % CI 0.478–17.443, $p = 0.25$) disease was related to worse echocardiographic outcomes.

Discussion

The results of our study show that surgical repair for mitral regurgitation in the setting of atrial fibrillation can be performed safely with low perioperative mortality and morbidity. Patients usually present with heart failure symptoms and preserved left ventricular ejection fraction. In a significant proportion of patients, the underlying disease, atrial fibrillation, has already progressed to involve the left ventricle. Early echocardiographic results of valve repair are good but, albeit initial successful repair, recurrent regurgitation occurs quite frequently during follow-up. As expected, recurrence of regurgitation is related to impaired clinical outcomes and might be prevented by combining an early surgical approach with optimalization of surgical repair strategy.

The good safety profile of intervention seen in our study is comparable to other reports, supporting the safety of surgical procedure in this patient cohort [3,4,16–18]. Moreover, mitral valve repair was feasible in all patients and significant (≥grade 2+) residual regurgitation was seen in only one patient. A large proportion of patients underwent concomitant tricuspid valve intervention. As atrial fibrillation is related to bi-atrial dilation, a high rate of concomitant tricuspid valve intervention was expected. While it is important to acknowledge the proportion of patients who encountered high-grade conduction disorders, possibly related to tricuspid valve surgery, it is noteworthy that the majority of these cases resolved without the need for permanent pacemaker implantation. In the light of the results of the Left Atrial Appendage Occlusion during Cardiac Surgery (LAAOS III) trial, left atrial occlusion should be considered in all of these patients [19].

Compared to conservative treatment, Balogh et al. have recently shown that surgical repair significantly decreases the risk of mortality and hospitalization for heart failure in patients suffering from atrial functional mitral regurgitation [18]. However, surgical repair did not eliminate the risk of heart failure-related morbidity and mortality. We observed similar results and recurrent regurgitation was the only risk factor related to event-free and overall survival in risk-adjusted analyses.

In accordance with Carpentier's principles and contemporary practice of reconstructive mitral valve surgery, annular remodeling and stabilization with a true-sized annuloplasty ring has represented our repair technique of choice. Despite the absence of significant residual regurgitation on pre-discharge echocardiography, recurrent regurgitation occurred more often than expected. Reports on repair durability in

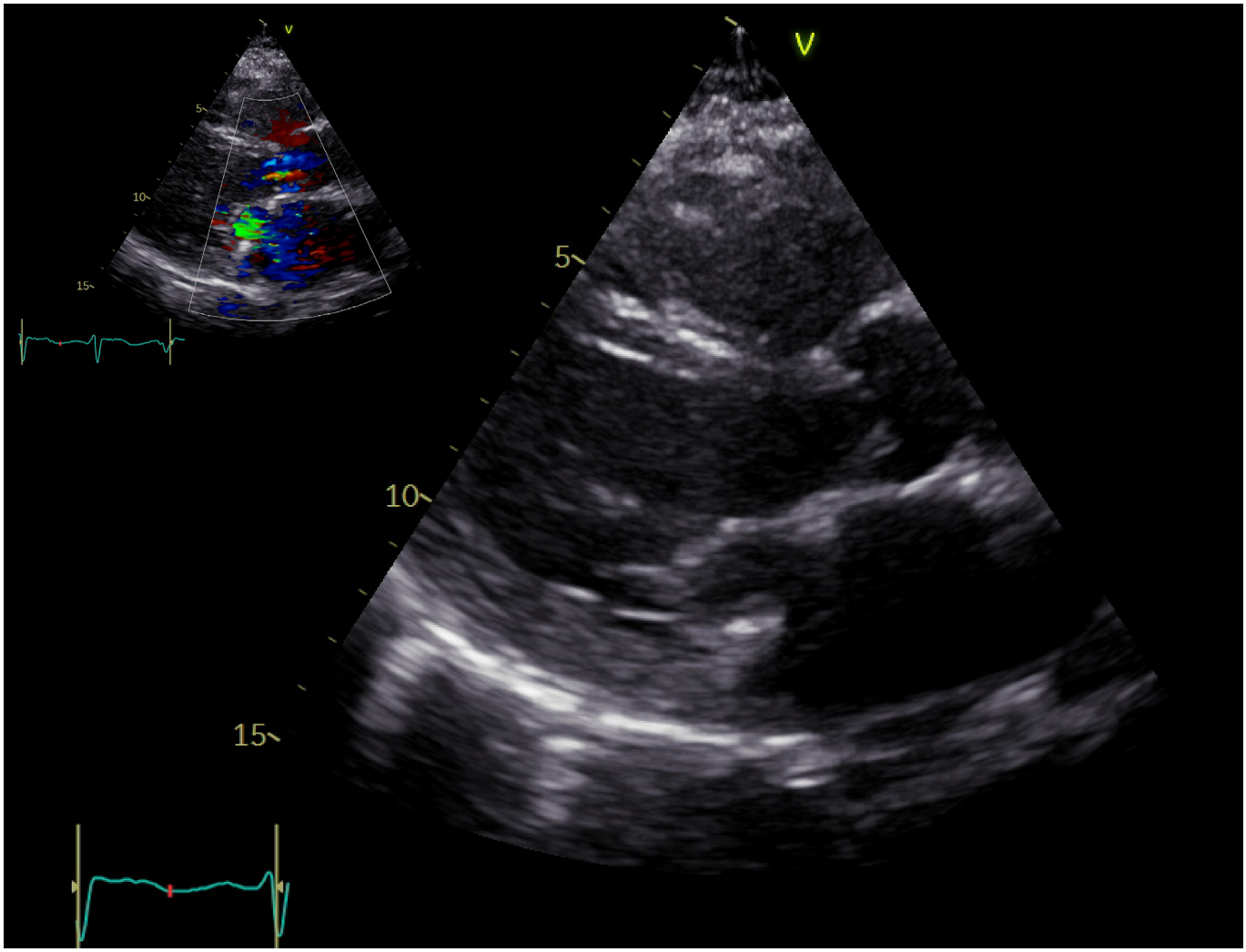

Fig. 3. During follow-up, recurrent mitral regurgitation was most often caused by leaflet tethering.

comparable patients are scarce and limited by small cohorts and short follow-up duration. In similar patient cohorts, freedom from recurrent regurgitation rates of 65 % at 3 years and 90 % and 5 years have recently been reported [3,4]. The mechanism of recurrent regurgitation in these patients remains to date not understood.

On adjusted analyses, mild regurgitation on predischarge echocardiography emerged as a risk factor for recurrent regurgitation. The presence of any residual regurgitation is surprising as the repair technique is, at least in theory, straightforward. Mild residual regurgitation can be theoretically explained by either a disproportionally small posterior leaflet, that is not taken into account when annuloplasty sizing is based on the surface area of the anterior leaflet, or a to date underappreciated accompanying mechanism of valve dysfunction. Studies on the pathogenesis of mitral regurgitation in the setting of atrial fibrillation suggest a contribution of diminished annular contraction and saddle shape, insufficient mitral valve leaflet remodeling, and atriogenic leaflet tethering and restricted leaflet motion, in addition to annular dilation [7,8,20,21]. Moreover, adverse effects of atrial fibrillation on the structure and function of the left ventricular myocardium are increasingly being recognized [22]. In our experience, detailed echocardiographic analysis demonstrated that leaflet tethering was the most common mechanism of recurrent regurgitation. Our results therefore suggest that changes in the function and geometry of the left ventricle in atrial fibrillation-related cardiomyopathy might progress even after an initially sound surgical correction. This is supported by a recent study by Ye et al., demonstrating that in patients comparable to those included in our study, the left ventricular end-systolic diameter exhibits a gradual increase over several years following surgery [23]. This phenomenon is likely the contributing factor leading to repair failure, as indeed observed on detailed analysis of follow-up echocardiograms in our study.

In a recent study from our group, we have demonstrated that in atrial functional mitral regurgitation, global longitudinal strain, a sensitive marker of left ventricular systolic dysfunction, is impaired in almost half of patients, even when left ventricular ejection fraction is normal (≥50 %) [24]. In the current study we have therefore decided to study all patients with mitral regurgitation in the setting of atrial fibrillation and divided our patient population based on the degree of left ventricular involvement. A prognostic effect of disease stage on echocardiographic outcomes was observed.

In our practice, concomitant ablation was performed in almost two-thirds of patients and the decision to perform ablation was based on the assumed efficacy and benefit of ablation in these patients. We were reluctant to perform concomitant ablation in severely dilated atria and in patients with a prolonged history of atrial fibrillation. However, surgical ablation demonstrated a protective trend against recurrent regurgitation. In line with this observation, Chen et al. have reported that restoration of sinus rhythm is related to improved valve repair durability in atrial functional mitral regurgitation [3]. This might reflect a positive effect of sinus rhythm restoration on valve function and disease progression or reflect the fact that restoration of sinus rhythm is more likely

successful in patients with less severe disease. In patients undergoing transcatheter ablation for atrial fibrillation, restoration of sinus rhythm is related to a decrease in the severity of mitral regurgitation [10].

The results of our study add to the growing body of evidence that demonstrate that mitral regurgitation in the setting of atrial fibrillation is a complex and progressive disease. Given the recurrent regurgitation rates observed in our study, valve repair could be combined with anterior leaflet augmentation or valve replacement might be considered, as recently studied by Morisaki et al. [25]. Nevertheless, it is essential to acknowledge that both techniques primarily target the mitral valve, and come with specific limitations, particularly an increased risk of valve-related events in the case of valve replacement. In these patients, the disease originates from the left atrium and disease progression, as implied by our results, is significantly affected by left ventricular involvement. Interestingly, we observed no recurrent regurgitation after restrictive annuloplasty. The latter is an established technique for valve repair in ventricular functional mitral regurgitation with documented good repair durability [26]. Combining restrictive mitral valve annuloplasty with ablation for atrial fibrillation and a low threshold for tricuspid annuloplasty in all patients suffering from mitral regurgitation in the setting of atrial fibrillation might be a better suited operation strategy, aimed at treating the underlying disease lesion and its most important complication.

Limitations

This is a retrospective study with limitations inherent to the study design. After the discharge echocardiogram, follow-up was performed either at our institution or affiliated clinics. We have compensated for the lack of centralized follow-up by importing and reassessing all available echocardiographic studies performed at affiliated clinics into our system. When this was not possible, all available echocardiographic reports were collected and reviewed. The decision to perform concomitant ablation was based on the presumed efficacy and benefit of the procedure. This needs to be taken into account when the demonstrated effect of concomitant ablation on recurrence of mitral regurgitation is interpreted. Finally, we have performed a comprehensive review of patients' history, preoperative echocardiography and intraoperative reports to include only patients in whom mitral valve and, as seen in some patients, ventricular dysfunction were caused solely by atrial fibrillation. Nevertheless, the possibility of primarily ventricular involvement cannot be excluded with absolute certainly in all patients.

Conclusions

Surgical repair for mitral regurgitation in the setting of atrial fibrillation can be performed safely with good early results. However, heart failure symptoms and mortality are often seen even after an initial good repair. Recurrence of mitral regurgitation is more frequent than expected and is related to impaired clinical outcomes. Refinements in surgical technique might help improve valve repair durability and improve patient prognosis.

Funding

No funding.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2023.12.001.

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