Interactive CardioVascular and Thoracic Surgery 26 (2018) 783–789
doi:10.1093/icvts/ivx423 Advance Access publication 10 January 2018

ORIGINAL ARTICLE

Cite this article as: Tomšič A, Hiemstra YL, van der Pas SL, Putter H, Versteegh MIM, van Brakel TJ *et al*. Early and long-term outcomes of mitral valve repair for Barlow's disease: a single-centre 16-year experience. Interact CardioVasc Thorac Surg 2018;26:783–9.

Early and long-term outcomes of mitral valve repair for Barlow's disease: a single-centre 16-year experience†

Anton Tomšič[a,*], Yasmine L. Hiemstra[b], Stephanie L. van der Pas[c], Hein Putter[c], Michel I.M. Versteegh[a], Thomas J. van Brakel[a], Nina Ajmone Marsan[b], Robert J.M. Klautz[a] and Meindert Palmen[a]

[a] Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, Netherlands
[b] Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands
[c] Department of Medical Biostatistcs, Leiden University Medical Center, Leiden, Netherlands

* Corresponding author. Department of Cardiothoracic Surgery, Leiden University Medical Centre, K6-S, PO Box 9600, 2300 Leiden, Netherlands. Tel: +31-71-5263445; fax: +31-71-5266899; e-mail: a.tomsic@lumc.nl (A. Tomšič).

Received 10 September 2017; received in revised form 22 November 2017; accepted 7 December 2017

ADULT CARDIAC

Abstract

OBJECTIVES: Following mitral valve repair for Barlow's disease, recurrent mitral regurgitation (MR) is believed to occur frequently and is mainly attributed to disease progression.

METHODS: Between January 2000 and December 2015, 180 patients (40% women, mean age 58.7 ± 13.5 years) with Barlow's disease underwent mitral valve repair. To provide a longitudinal assessment of mitral valve repair durability, a multistate model for interval-censored observations (4 states: 1, Grade 0/1+ MR; 2, Grade 2+ MR; 3, Grade 3+/4+ MR; 4, reintervention/death) was developed. The mechanism of recurrent MR was assessed echocardiographically.

RESULTS: Early mortality was 1.7%. After hospital discharge, 6 late reinterventions were performed. With death as a competing risk, the 10-year overall reintervention-free survival and reintervention rates were 79.8% (95% confidence interval 72.7–87.6%) and 4.5% (95% confidence interval 2.0–10.2%), respectively. Echocardiographic follow-up was available for 165 (93%) of hospital survivors with a total of 480 examinations. The incidence of both recurrent Grade 2+ and Grade 3+/4+ MR was relatively low up to 10 years after surgery. Grade 2+ MR did not always progress to higher regurgitation grade during the follow-up period. Grade 3+/4+ regurgitation was highly associated with valve-related morbidity and mortality. Recurrent MR (≥Grade 2+) was predominantly related to the technical aspects of valve repair.

CONCLUSIONS: Despite the complex valve abnormalities observed in patients with Barlow's disease, mitral valve repair can be performed with good early and late outcomes and low rates of recurrence of MR up to 10 years after surgery. Early and late valve repair durability is good and remains stable over time, suggesting that underlying disease progression has limited clinical significance.

Keywords: Mitral valve • Mitral valve repair • Barlow's disease

INTRODUCTION

Barlow's disease presents the most severe form of degenerative mitral valve disease and is characterized by severe annular, leaflet and subvalvular abnormalities. Improved understanding of valve dysfunction and growing surgical expertise nowadays allows for restoration of mitral valve competency in the majority of these patients [1, 2]. However, recurrent mitral regurgitation (MR) remains a concern even in the hands of experienced surgeons [3, 4].

Surgical valve repair strategy in Barlow's disease differs from the repair strategy in other forms of degenerative disease as it needs to take into account the profound annular abnormalities seen in these patients [5–8]. Even when corrected for known surgical risk factors for recurrent MR, Flameng *et al.* [3] have previously demonstrated that recurrent MR occurs at a linearized rate of 2.9% per year for patients with Barlow's disease. The authors proposed that Barlow's disease carries an inherent tendency to disease progression even after a successful valve repair. Other authors have later reached similar conclusions [2]. On the contrary, it has previously been proposed that valve degeneration occurs as a consequence of abnormal mechanical stress that will, in genetically predisposed individuals, result in the activation of valve interstitial cells and extracellular matrix remodelling [9]. Mitral valve repair should therefore also aim to eliminate any excessive stress to the mitral valve apparatus. Disease progression after an initially successful valve repair is thus possibly inherent to the technique of valve repair rather than the disease itself. To provide further insight into the repaired valve performance, the application of longitudinal data analysis rather than time-to-event methods has been advised [10]. This could provide

†Presented at the 31st Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 7–11 October 2017.

further understanding of the course of the disease following successful valve repair.

The aim of this study was to explore the early and late patient- and valve-related outcomes of mitral valve repair in patients with Barlow's disease. Moreover, we aim to gain in-depth information on mitral valve repair performance by analysing echocardiographic follow-up data in a longitudinal data analysis model for repeated echocardiographic measurements.

METHODS

Study population

Between January 2000 and December 2015, 684 consecutive adult patients underwent surgical intervention for MR due to degenerative mitral valve disease at our institution. Patients with accompanying active mitral valve infective endocarditis were excluded. Of the total patients, 185 (27%) patients showed both echocardiographic and surgical characteristics of Barlow's disease. These included excessive leaflet tissue, bileaflet myxomatous degeneration and mitral annular disjunction [6, 11]. Mitral valve repair was attempted in all cases and successfully performed in 181 (98%) patients. Excluding 1 patient who underwent valve repair with the edge-to-edge technique, 180 patients who underwent valve repair present the final study cohort.

Study methods

Pre-, intra-, and postoperative data were collected from our computerized patient registry. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through patient questionnaires. Our Institutional Medical Ethics Committee approved this study, and written informed consent was obtained. Patient follow-up was closed in February 2017. Details on patient follow-up are provided in Supplementary Material A.

Surgical procedure

During the study period, a repair-all strategy was applied and eventual valve replacement was only performed in case of an unsatisfactory intraoperative result of valve repair. Median sternotomy ($n = 157$), partial sternotomy ($n = 13$) or lateral mini-thoracotomy was performed ($n = 10$). Standard cannulation techniques with central or peripheral cannulation (according to the surgical approach utilized) and intermittent warm blood cardioplegia for cardioprotection were used in all cases.

We have previously reported our surgical repair strategy in patients with Barlow's disease [7]. This includes discrimination between true and functional leaflet prolapse that occurs in patients with Barlow's disease as a consequence of profound annular motion abnormalities. In such cases, echocardiographic evidence of anterior mitral valve leaflet (AMVL) prolapse in a combination with annular displacement and abnormal annular motion suggests that AMVL prolapse can be resolved by annular stabilization alone. The final discrimination between true and functional leaflet prolapse is made during surgical valve analysis.

Commissural prolapse was treated predominately by papillary muscle head repositioning. To treat posterior mitral valve leaflet (PMVL) prolapse and excessive tissue, quadrangular resection with annular plication (earlier in our series) or leaflet sliding techniques (later in our series) was used when excessive tissue in height and width was present. Alternatively, a triangular resection combined with shortening polytetrafluoroethylene neochords were used to correct for excessive leaflet in width and height, respectively. True AMVL prolapse was treated predominantly with polytetrafluoroethylene neochords. Full, semi-rigid ring annuloplasty was performed in all except 1 patient who underwent a full, flexible ring implantation. Ring sizing was based on the surface area of the AMVL.

Intraoperative and predischarge echocardiography were performed by experienced echocardiographists to confirm the success of valve repair. Oral anticoagulation with a target international normalized ratio of 2.0–3.0 was continued for 3 months after surgery. In the presence of other indications, oral anticoagulation was continued as indicated.

Study end-points

Postoperative mortality and morbidity end-points were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery and European Association for Cardio-Thoracic Surgery Guidelines [10]. Early mortality was defined as mortality within 30 days after the operation or during the index hospitalization. The severity of MR was evaluated using a multiparametric integrative approach, including qualitative and quantitative assessments as currently recommended [12]. The severity of MR was graded on a 4-grade scale: 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe) and 4+ (severe). To explore the mechanism of mitral valve repair failure, echocardiograms were re-evaluated by a cardiologist experienced in cardiac echocardiography (N.A.M.). Pseudoprolapse was defined as a condition in which the free edge of one mitral valve leaflet was displaced above the free edge of the opposing leaflet in systole without over-riding the plane of the annulus. Early recurrent MR was arbitrarily defined as ≥Grade 2+ MR observed within the first 2 years after the initial operation. Late recurrent MR was defined as ≥Grade 2+ MR observed later than 2 years after the initial operation.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or median and interquartile range (IQR) when non-normally distributed. Categorical data are presented as counts and percentages. The cumulative incidences of reintervention and death were estimated using the Aalen–Johansen estimator [13]. For the remaining analyses, a multistate model for interval-censored observations was developed [14]. The follow-up for the multistate model was set at 3 months after the operation. The following 4 states were defined: 'Grade 0 or 1+ MR', 'Grade 2+ MR', 'Grade 3+ or 4+ MR' and the terminal state 'reintervention/death' (Fig. 1). This type of multistate model is designed for situations where patients can move back and forth between states (i.e. echo grades) and where the times at which a patient changes state (e.g. moves from Grade 2+ to Grade 3+) are not exactly observed. The hazards of transitioning between the states were taken to be constant, after tests for a change in hazard at 1.5 or 2 years were not significant. In the unadjusted analyses, none of the 7 hazards were assumed to be equal to each other. For the adjusted analyses, 3 hazards were allowed: deterioration (moving to a higher state), improvement (moving to a

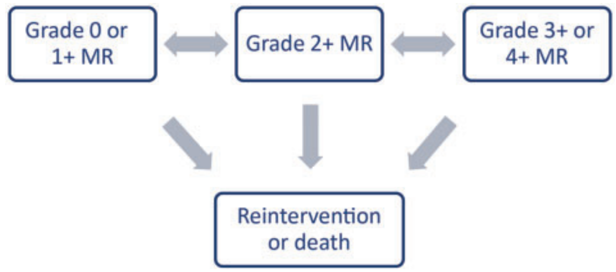


Figure 1: Multistate model design. State 'reintervention/death' presents a terminal state while transitions between other states are freely allowed. MR: mitral regurgitation.

Table 1: Baseline characteristics

	n = 180
Age, years	58.7 ± 13.5
Female gender	72 (40.0)
NYHA class	
I	69 (38.3)
II	87 (48.3)
III–IV	24 (13.4)
Preoperative atrial fibrillation	66 (36.7)
Hypertension	58 (32.2)
Renal impairment	
Moderate (CC 85–50 ml/min)	80 (44.4)
Severe (CC <50 ml/min)	5 (2.8)
Extracardiac arteriopathy	1 (0.6)
History of TIA or CVA	4 (2.2)
Chronic lung disease	11 (6.1)
Diabetes mellitus	2 (1.1)
Non-elective surgery setting	3 (1.7)
Critical preoperative state	1 (0.6)
Left ventricular ejection fraction	
>60%	127 (70.6)
30–60%	53 (29.4)
Left ventricular end-systolic diameter >45 mm	12 (6.7)
Pulmonary hypertension (sPAP >50 mmHg)	7 (3.9)
Leaflet prolapse	
None	4 (2.2)
Isolated anterior	5 (2.8)
Isolated posterior	24 (13.3)
Bileaflet	147 (81.7)
Mitral annular calcification	32 (17.8)

Data are presented as *n* (%).
CC: creatinine clearance; CVA: cerebrovascular accident; NYHA: New York Heart Association; SD: standard deviation; sPAP: systolic pulmonary artery pressure; TIA: transient ischaemic attack.

lower state) or reintervention/death (moving to the terminal state). First, univariate analyses at the 15% level were performed. Then, a multivariate model was made, in which covariates were constrained to only have an effect on those hazards on which they had a significant effect in the univariate analyses. The multistate models were estimated using the MSM package in R [15].

RESULTS

Baseline characteristics

The baseline characteristics of the whole study cohort are presented in Table 1. On admission, the majority of patients were symptomatic and a history of atrial fibrillation was present in more than one-third of patients. Left ventricular functional impairment and left ventricular dilatation were present less often. The majority of patients showed echocardiographic evidence of bileaflet prolapse, and in a relatively high proportion of patients, mitral annular calcification was seen. The majority of patients underwent elective surgery.

Table 2: Intraoperative details

	n = 180
Mitral valve annulus	
Annular plication	61 (33.9)
Decalcification	26 (14.4)
Annuloplasty ring size	36 (IQR 32–38)
Anterior mitral valve leaflet	
Resection	3 (1.7)
Neochords	83 (46.1)
Chordal transfer	1 (0.6)
Chordal shortening	1 (0.6)
Posterior mitral valve leaflet	
Resection	150 (83.3)
Sliding plasty	132 (73.3)
Neochords	55 (30.6)
Chordal transfer	2 (1.1)
Chordal shortening	1 (0.6)
Papillary muscle head repositioning	2 (1.1)
Identation closure	35 (19.4)
Commissures	
Anterior commissure	26 (14.4)
Papillary muscle head repositioning	19 (10.6)
Commissuroplasty	6 (3.3)
Neochords	1 (0.6)
Posterior commissure	65 (36.1)
Papillary muscle head repositioning	57 (31.7)
Commissuroplasty	7 (3.9)
Neochords	1 (0.6)
Aortic cross-clamp time (min)	153 (IQR 137–200)
Cardiopulmonary bypass time (min)	203 (IQR 174–250)
Second pump run	14 (7.8)
Concomitant procedures	
Tricuspid valve repair	95 (52.8)
Radiofrequency ablation	56 (31.1)
Coronary artery bypass grafting	16 (8.9)
Aortic valve intervention	5 (2.8)
Thoracic aorta replacement	2 (1.1)

Data are presented as *n* (%).

Early results

The intraoperative details on mitral valve repair and concomitant procedures performed are provided in Table 2. Early mortality was 1.7% (3 patients, Table 3). The cause of death was multiorgan failure in 2 patients and perioperative myocardial infarction in 1 patient. All of the deceased patients were symptomatic and had a history of atrial fibrillation. No major postoperative complications occurred in most (81.7%) patients.

Postoperative resting mitral valve gradient was 3.26 ± 1.42 mmHg and was significantly lower in patients in whom no annular plication was used (2.92 ± 1.22 and 3.93 ± 1.56, $P < 0.001$). No significant systolic anterior motion was present in any of the patients. In 2 (1.1%) patients, significant residual MR (≥Grade 2+) was observed on predischarge echocardiography (Supplementary

ADULT CARDIAC

Table 3: Postoperative complications

	n = 180
Early mortality	3 (1.7)
Sternal wound infection	0 (0)
Prolonged intubation (>24 h)	20 (11.1)
Renal failure	5 (2.8)
Permanent stroke	2 (1.1)
Early reoperation	19 (10.5)
Re-exploration for bleeding and/or cardiac tamponade	17 (9.4)
Early valve reoperation	2 (1.1)

Data are presented as n (%).

Material, Fig. S1) and both underwent early reoperation. One patient showed residual AMVL prolapse and underwent reoperation on postoperative day 8. Valve replacement was performed as a durable repair was considered unlikely because of a severely degenerated and malformed AMVL. The second patient showed residual PMVL prolapse and underwent mitral valve re-repair on postoperative day 8.

Late clinical outcome

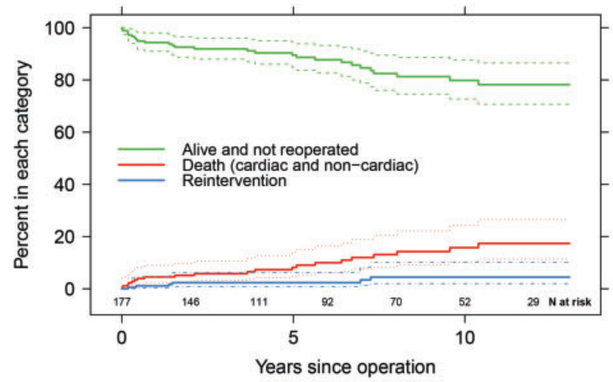
There were 22 late deaths. The cause of death was valve related in 10 (intracranial bleeding in 2; death following mitral valve reoperation in 1; end-stage heart failure with recurrent MR in 1; sudden, unexplained death in 6) and cardiac related but not valve related in 3 (myocardial infarction in 1; type A aortic dissection several years after the initial procedure in 1; end-stage heart failure in 1) patients. The cause of death was not cardiac related in 9 patients.

Following hospital discharge, 6 late reinterventions were performed. The cause of reintervention was prosthetic valve endocarditis in 1 patient, suture line defect of the PMVL in 1 patient, recurrent MR in 3 patients and secondary MR in 1 patient. Taking all-cause death and mitral valve reintervention as competing risks, the 5- and 10-year cumulative incidence of reintervention-free survival were 89.5% [95% confidence interval (CI) 84.8–94.4%] and 79.8% (95% CI 72.7–87.6%), respectively (Fig. 2).

Eleven patients experienced a thromboembolic event. Five of these were cerebrovascular accidents and 6 were cerebral transient ischaemic attacks. No events were fatal. Six patients experienced serious haemorrhagic complications resulting in death in 2 (intracranial bleeding in both cases) patients. There was one episode of infective endocarditis (occurring 1 month after the initial intervention), resulting in a reoperation.

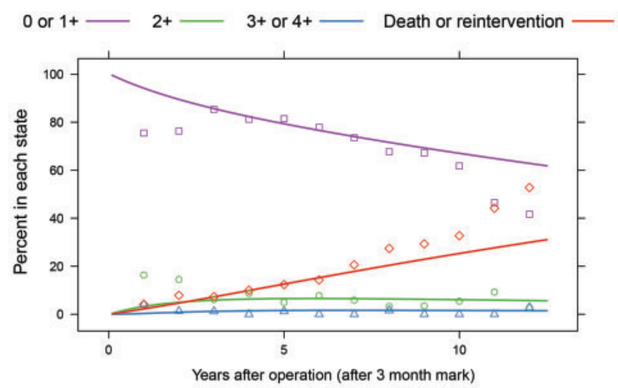
Late echocardiographic outcome

Figure 3 shows the time-related changes in the percentage of patients in various states over time. As expected, patients alive and free from reintervention showed good repair durability up to 10 years after the initial operation. Interestingly, Grade 2+ MR did not always progress with time but remained stable or even regressed with time (upon any of the following echocardiographic measurements; Supplementary Material, Fig. S2). When stratifying patients based on the observed severity of MR, the reintervention-free survival probability was best for patients without any



	5-year cumulative incidence		10-year cumulative incidence	
		95% confidence interval		95% confidence interval
Reintervention	2.3%	0.9%-6.1%	4.5%	2.0%-10.2%
Cardiac death	4.9%	2.5%-9.6%	10.0%	5.8%-17.2%
Non-cardiac death	3.3%	1.4%-8.0%	5.8%	2.7%-12.5%
Alive without reintervention	89.5%	84.8%-94.4%	79.8%	72.7%-87.6%

Figure 2: Competing risk of outcomes. Time-related parametric estimates with 95% confidence intervals (dashed lines) are presented for the following mutually exclusive categories: death (red), reintervention (blue) and patients alive without reintervention (green).



	5-year cumulative incidence		10-year cumulative incidence	
		95% confidence interval		95% confidence interval
Grade 0/1+ MR	79%	63% - 85%	67%	39% - 75%
Grade 2+ MR	7%	0% - 10%	6%	0% - 10%
Grade 3+/4+ MR	2%	0% - 3%	2%	0% - 3%
Death or reintervention	13%	8% - 37%	25%	18% - 61%

Figure 3: Multistate model demonstrating the time from the initial operation-dependent percentage of patients in each of the predefined states. MR: mitral regurgitation.

significant MR (Supplementary Material, Fig. S2). All transitions from state 1 to state 4 were deaths. All transitions from state 3 to state 4 were valve-related events: 5 were reinterventions and 1 was valve-related death (end-stage heart failure with recurrent MR).

Multivariate analysis showed only male gender as a statistically significant protective factor (hazard ratio 0.32, 85% CI 0.11–0.91) against repaired valve functional deterioration (Supplementary Material, Table S1). In particular, posterior mitral valve leaflet resection (no leaflet resection was performed in a relatively small number of patients in whom only excessive tissue in height was present and treated by implanting shortening neochords) or the presence of annular calcification did not affect repaired valve performance. Multivariate analysis demonstrated only advanced patient age (>60 years; HR 3.21, 85% CI 1.16–8.85) as a significant risk factor for transition to state 4.

Mechanism of recurrent mitral regurgitation

Echocardiographic assessment revealed that recurrent MR was most commonly related to the technical aspects of valve repair (Table 4). Early recurrent MR (within the first 2 years after surgery) was seen in 11 patients. This was caused by residual prolapse/billowing and suture line defect in 5 patients and 1 patient, respectively. Leaflet restriction—usually combined with pseudoprolapse of the opposite mitral valve leaflet—was the cause in 4 patients, while the cause of recurrent MR was not clear in 1 patient.

Late recurrent MR was seen in 9 patients. A combination of leaflet restriction with or without pseudoprolapse of the opposite leaflet presented the most common cause of repair failure. In 1 patient, valve analysis upon reoperation revealed that leaflet restriction was likely caused by the repositioned papillary muscle head. Recurrent prolapse (evidence of chordae rupture was also seen on echocardiography) as the sole cause of repair failure was seen in only 1 patient. Of notice, leaflet thickening as the cause of recurrent MR was seen in 1 patient only.

DISCUSSION

Our study showed that a systematic valve repair strategy in Barlow's disease, utilizing a combination of leaflet resection techniques, subvalvular apparatus manipulation, neochords implantation and annular stabilization, is highly reproducible and will allow valve repair to be performed in nearly all patients. Recurrent MR—occurring early or late—was most commonly related to the technical aspects of valve repair and not disease progression. Furthermore, once occurring, Grade 2+ MR did not always progress with time during the follow-up period.

We adhere to an early surgery approach in all patients with degenerative mitral valve disease and advise surgery to asymptomatic patients with severe MR, regardless of the expected repair complexity. This is in line with the recommendations of the American Heart Association/American College of Cardiology on the management of valvular heart disease [16]. On the other hand, the recently updated guidelines from the European Society

Table 4: The mechanism of recurrent MR in patients in whom ≥Grade 2+ MR was seen at any point during the follow-up period

Case	Year of surgery	AMVL	PMVL	Time to first observation		Last observation		Reintervention	Time to reintervention (years)
				MR grade	Years	MR grade	Years		
1	2001	Prolapse		2+	0.5	4+	1.1	Yes (MVR)	1.5
2	2002	Restriction (left ventricular dilatation)	Restriction (left ventricular dilatation)	3+	1.8	2+	7.3	Yes (aortic root replacement + restrictive mitral annuloplasty)	7.3
3	2002		Suture line defect	4+	0.1	4+	0.1	Yes (re-repair)	0.6
4	2004	Not clear	Not clear	2+	2.0	2+	11.0	No	
5	2004	Residual billowing (insufficient leaflet coaptation)		2+	1.8	2+	10.7	No	
6	2005	Restriction	Pseudoprolapse	4+	1.0	4+	1.0	Yes (MVR)	1.4
7	2009		Restriction	3+	1.2	3+	1.2	No	
8	2010		Restriction	2+	1.6	2+	1.6	No	
9	2012	Pseudoprolapse (possibly neochord too long)		2+	1.5	2+	2.5	No	
10	2013	Pseudoprolapse (possibly neochord too long)		3+	1.0	3+	2.8	No	
11	2014	Prolapse		2+	1.1	2+	2.5	No	
12	2003	Thickened leaflet	Restriction+thickened leaflet	2+	8.5	2+	12.5	No	
13	2004	Unknown	Unknown	2+	7.3	2+	8.8	No	
14	2004	Restriction	Relatively short but mobile (loss of coaptation)	2+	8.9	3+	12.6	No	
15	2006	Pseudoprolapse	Restriction (possibly due to the repositioned papillary muscle)	2+	3.5	4+	7.0	Yes (MVR)	7.0
16	2006		Pseudoprolapse	2+	5.8	2+	5.8	No	
17	2007	Restriction	Decreased mobility	2+	6.1	2+	8.7	No	
18	2008		Prolapse	3+	4.7	4+	5.7	No	
19	2008	Restriction	Pseudoprolapse	3+	8.1	3+	8.8	No	
20	2012	Pseudoprolapse	Restriction	2+	3.1	2+	3.1	No	

AMVL: anterior mitral valve leaflet; MR: mitral regurgitation; MVR: mitral valve replacement; PMVL: posterior mitral valve leaflet.

of Cardiology/European Association of Cardio-Thoracic Surgery advise considering surgery in asymptomatic patients only when favourable anatomy (flail leaflet) or significant left atrial dilatation is present [17]. The high proportion of patients in whom successful valve repair with a documented good result was feasible is believed to support an early surgical approach even in patients with complex valve pathology. It is, however, imperative that such patients are referred to centres with sufficient experience in reconstructive valve surgery.

The majority of patients underwent valve repair through standard full sternotomy with—especially later in our series—limited midline skin incision (approximately 10–15 cm in length). Previous studies have demonstrated favourable results of the minithoracotomy approach to valve repair in patients with Barlow's disease [18, 19]. However, this includes significant modifications of the mitral valve repair technique when compared with our technique. We remain reluctant to utilize the edge-to-edge repair technique in patients with degenerative mitral valve disease because this technique has been demonstrated to have a profound effect on diastolic transvalvular mitral valve gradients [20]. We have to acknowledge, however, that patients with Barlow's disease usually present with large valve orifice areas and large annuloplasty rings-making functional mitral valve stenosis unlikely to occur regardless of the repair technique utilized- are utilized to complement valve repair. In our opinion, the decision on the type of approach should be based on the decision of the informed patient and projected repair complexity. Surgical approach should not determine the strategy of mitral valve repair.

Interestingly, female gender had a negative effect on valve repair durability. Our study is not the first to report such findings and further studies are needed to explore the underlying causes of such observations [21]. Our results further suggest that even Grade 2+ MR after mitral valve repair might remain stable for years. In line with this observation, the time-related probability of death or reintervention appeared only moderately higher once Grade 2+ MR was observed. There are several possible explanations for these findings. Such observations can be partially explained by the fact that grading of the severity of MR is based on arbitrarily defined grades while the amount of regurgitant flow presents a continuous biological parameter. The severity of MR is dependent on various factors that can present an extrinsic and reversible cause of repaired valve function deterioration [10]. On the other hand, it should be acknowledged that the follow-up time in our patients was limited. In these patients, the severity of MR might progress in the future and necessitate reoperation. Taking this into consideration, close follow-up should be advised in all patients, while further research is needed to assess the clinical significance of our findings. On the other hand, the occurrence of ≥Grade 3+ MR was clearly related to valve-related morbidity and mortality. Importantly, the underlying mechanism needs to be taken into account when assessing the expected clinical significance and prognosis of 'recurrent MR'. Our observations should therefore be interpreted with caution.

In a previous study on 348 patients (including 83 patients with Barlow's disease) who underwent successful valve repair for degenerative mitral valve disease, Flameng *et al.* [3] have shown that recurrent MR (>2/4 MR) occurs most commonly because of recurrent leaflet prolapse or leaflet thickening. They hypothesized that even after a sound surgical repair, disease progression presents an inherent characteristic of Barlow's disease. We argue that valve repair that successfully resolves any excessive stress on the mitral valve leaflets and subvalvular apparatus should provide good repair durability even in cases of Barlow's disease. To assure a stable, durable valve repair, a large surface area of leaflet coaptation without any residual malaposition of the mitral valve leaflets—that would result in undesirable tension to the leaflets and chordae tendineae—needs to be achieved. Annular stabilization is of utmost importance in these patients as annular abnormalities (diminished annular saddle shape and abnormal motion) increase the strain exerted to the mitral valve leaflets. Ring annuloplasty with a suitable annuloplasty device that mimics the normal systolic annular saddle shape can resolve these issues. This is supported by the fact that leaflet thickening was an uncommon observation in our experience, despite the fact that this has been reported to present the most common mechanism of repair failure in patients with degenerative disease [22]. The very low rate of disease progression as a cause of failure underlines that these operations stabilize the disease and could therefore be advised even to asymptomatic patients.

In our experience, the most common mechanism of recurrent MR was leaflet restriction, usually combined with pseudoprolapse of the opposite leaflet. Hypothetically, this could present a consequence of leaflet resection. Contrary to this speculation, leaflet resection did not predict worsening of repaired valve function on multivariate analysis. We speculate that resection will not *per se* induce clinically significant leaflet restriction. However, 'excessive' leaflet resection might well induce leaflet restriction and eventually result in pseudoprolapse of the opposite leaflet. Loss of sufficient leaflet coaptation height will induce excessive residual strain on the mitral valve leaflet(s), indicating instability of valve repair in the long term. This would explain the similarity in the mechanism of early and late recurrent MR seen in our experience. It also suggests that even late recurrent MR can be directly related to the technical aspects of valve repair. Furthermore, insufficient height of leaflet coaptation might result from other technical aspects of valve repair (inadequate ring sizing) and might in patients with Barlow's disease result from the inability to prevent abnormal annular motion. In our opinion, this provides a possible argument for the utilization of semi-rigid instead of flexible annuloplasty devices in these patients. However, the effect of various annuloplasty devices on annular motion in patients with Barlow's disease needs to be studied further.

Limitations

Our study is retrospective in nature and therefore subject to the inherent weaknesses of a retrospective analysis. The valve repair technique has somehow evolved throughout the study period (i.e. abandonment of the annular plication technique) and might have affected the results. We reason that this could have only a limited effect on repair durability. Furthermore, our results in terms of repaired valve performance are based on our experience only and the observations might not be applicable to other techniques of valve repair. Finally, MR severity was—based on the accepted recommendations—scored on a graded scale. Such simplification inevitably results in a loss of possibly relevant information regarding repaired valve durability. However, analysing MR severity on a continuous scale would be statistically very complex to conduct and interpret.

CONCLUSION

Despite the complex valve abnormalities observed in patients with Barlow's disease, mitral valve repair can be safely performed with good early and late outcomes. Early surgical intervention seems to be justified, despite the complexity of valvular abnormalities normally observed. Early repair failure is largely related to the technical aspects of valve repair. Late deterioration of repaired valve function occurs infrequently and also appears inherent to the surgical technique, suggesting that underlying disease progression has limited clinical significance.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Adams DH, Anyanwu AC, Rahmanian PB, Abascal V, Salzberg SP, Filsoufi F. Large annuloplasty rings facilitate mitral valve repair in Barlow's disease. Ann Thorac Surg 2006;82:2096–100; discussion 101.

[2] Jouan J, Berrebi A, Chauvaud S, Menasche P, Carpentier A, Fabiani JN. Mitral valve reconstruction in Barlow disease: long-term echographic results and implications for surgical management. J Thorac Cardiovasc Surg 2012;143:S17–20.

[3] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135:274–82.

[4] Newcomb AE, David TE, Lad VS, Bobiarski J, Armstrong S, Maganti M. Mitral valve repair for advanced myxomatous degeneration with posterior displacement of the mitral annulus. J Thorac Cardiovasc Surg 2008; 136:1503–9.

[5] Clavel MA, Mantovani F, Malouf J, Michelena HI, Vatury O, Jain MS *et al.* Dynamic phenotypes of degenerative myxomatous mitral valve disease: quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8:e002989.

[6] Eriksson MJ, Bitkover CY, Omran AS, David TE, Ivanov J, Ali MJ *et al.* Mitral annular disjunction in advanced myxomatous mitral valve disease: echocardiographic detection and surgical correction. J Am Soc Echocardiogr 2005;18:1014–22.

[7] Klautz RJ, Tomsic A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg 2016; doi: 10.1510/mmcts.2016.001.

[8] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse: potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14:32.

[9] Rabkin E, Aikawa M, Stone JR, Fukumoto Y, Libby P, Schoen FJ. Activated interstitial myofibroblasts express catabolic enzymes and mediate matrix remodeling in myxomatous heart valves. Circulation 2001;104:2525–32.

[10] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL *et al.* Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135: 732–8.

[11] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958–66.

[12] Zoghbi WA, Enriquez SM, Foster E, Grayburn PA, Kraft CD, Levine RA *et al.* Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

[13] Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Stat 1978;5:141–50.

[14] Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–430.

[15] Jackson CH. Multi-state models for panel data: the msm package for R. J Stat Softw 2011; 38:1–28.

[16] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA *et al.* 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2017;135:e1159–95.

[17] Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al.* 2017 ESC/EACTS guidelines for the management of valvular heart disease. J Cardiothorac Surg 2017;52:616–64.

[18] da Rocha E Silva JG, Spampinato R, Misfeld M, Seeburger J, Pfanmuller B, Eifert S *et al.* Barlow's mitral valve disease: a comparison of neochordal (loop) and edge-to-edge (Alfieri) minimally invasive repair techniques. Ann Thorac Surg 2015;100:2127–33; discussion 33–5.

[19] De Bonis M, Lapenna E, Del Forno B, Di Sanzo S, Giacomini A, Schiavi D *et al.* Minimally invasive or conventional edge-to-edge repair for severe mitral regurgitation due to bileaflet prolapse in Barlow's disease: does the surgical approach have an impact on the long-term results? Eur J Cardiothorac Surg 2017;52:131–6.

[20] Jahren SE, Hurni S, Heinisch PP, Winkler B, Obrist D, Carrel T *et al.* Transvalvular pressure gradients for different methods of mitral valve repair: only neochordoplasty achieves native valve gradients. Interact CardioVasc Thorac Surg 2018;26:248–56.

[21] Chan V, Chen L, Elmistekawy E, Ruel M, Mesana TG. Determinants of late outcomes in women undergoing mitral repair of myxomatous degeneration. Interact CardioVasc Thorac Surg 2016;23:779–83.

[22] Chan V, Elmistekawy E, Ruel M, Hynes M, Mesana TG. How does mitral valve repair fail in patients with prolapse? Insights from longitudinal echocardiographic follow-up. Ann Thorac Surg 2016;102:1459–65.