Surgical therapy of organic mitral valve disease: Strategy and outcomes

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Risk factors and clinical significance of elevated mitral valve gradient following valve repair for degenerative disease

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ABSTRACT

Background. The risk factors and clinical effect of elevated mitral valve gradients after valve repair for degenerative valve disease remain insufficiently understood.

Methods. Between January 2004 and December 2015, 484 patients underwent valve repair for degenerative disease. A true-sized full annuloplasty ring was implanted in all cases. We analysed the effect of preoperative and intraoperative factors on the post-repair gradient. Additionally, we explored the effect of post-repair gradient on long-term outcomes.

Results. On linear regression analysis, post-repair mitral valve gradients were associated with patient age (coefficient=-0.110, standard error=0.005, P=0.034), body surface area (coefficient=0.905, standard error=0.340, P=0.008), implanted annuloplasty ring size (coefficient=-0.181, standard error=0.018, P<0.001), and the use of Physio I ring (coefficient=0.414, standard error=0.122, P=0.001). On multivariable analysis, post-repair mitral valve gradient was not associated with overall survival [hazard ratio (HR) 1.034, 95% confidence interval (CI) 0.889-1.203, P=0.66] or freedom from atrial fibrillation (HR 0.849, 95% CI 0.682-1.057, P=0.14), but did emerge as a risk factor for mitral valve reintervention (HR 1.378, 95% CI 1.033-1.838, P=0.029). Two out of 11 reinterventions were performed due to mitral valve stenosis and in both patients, high post-repair gradients were seen readily on predischarge echocardiography.

Conclusion. Following valve repair for degenerative mitral valve disease, elevated gradients occur even when true-sized annuloplasty is performed. The late clinical results of valve repair with elevated post-repair gradient are impaired and further studies are needed to explore preventive measures aimed at resolving the issue.

INTRODUCTION

Surgical mitral valve (MV) repair is the treatment of choice for mitral regurgitation (MR) due to degenerative disease with high valve reparability, repair durability and freedom from reoperation rates readily established [1, 2]. When the results of MV repair are examined in further detail, the problem of elevated post-repair gradients, following an otherwise successful repair without residual regurgitation, has emerged as a subject of debate [3-5].

The problem of elevated post-repair MV gradients was initially described in patients after restrictive mitral annuloplasty for ischemic MR [4] but may also be of clinical importance in patients with degenerative MR [3, 5]. To justify the growing enthusiasm for early surgery of yet asymptomatic patients with degenerative MR, optimal patient- and valve-related results are needed. Data on the risk factors and clinical impact of elevated MV gradients following valve repair for degenerative disease remain scarce.

The aim of this study was to analyse the risk factors of elevated post-repair MV gradients and the effect here of on patient- and valve-related outcomes in a cohort of patients who underwent successful MV repair for degenerative disease.

METHODS

Patients

All adult patients (≥18 years of age) who underwent surgical intervention (n=528) for MR due to degenerative disease between January 2004 and December 2015 at our institution were eligible for inclusion. We excluded patients with a history of previous cardiac surgery (n=18) and patients in whom MV replacement was performed (n=9). Of the remaining 501 patients, 17 additional patients were excluded for the following reasons: early mortality (n=6), non-use of annuloplasty ring (n=4) or missing predischarge echocardiogram (n=7). The final study cohort compromised 484 patients who all underwent successful MV repair with a complete annuloplasty ring.

Measurements of MV gradients were acquired from continuous wave Doppler acquisitions of the diastolic inflow of the MV. Mean MV gradient was calculated as the average of 3 and 5 cycles or patients in sinus rhythm and atrial fibrillation, respectively. All acquisitions were performed according to a standardized protocol of our echo lab to ensure data reproducibility. All measures were performed by experienced echocardiographists.

Study endpoints

All endpoints were defined according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions [6]. Primary endpoints included all-cause mortality and freedom from MV reintervention. Secondary endpoints included freedom from atrial fibrillation. We excluded other types of atrial tachycardias (e.g. atrial flutter or incisional atrial tachycardia) because of etiological differences associated with the development post-repair atrial tachycardias [7]. Only patients in preoperative sinus rhythm (n=312) were included in the latter analysis.

Surgical technique and perioperative care

When indicated, anterior MV leaflet prolapse was addressed with chordal replacement. Posterior MV leaflet prolapse was addressed with a combination of leaflet resection and chordal replacement techniques. The decision on which technique to use was based on the extent of leaflet prolapse and excessive tissue in height and/or width. Earlier in this series, annular plication was more frequently used to help restore the continuity of the posterior MV leaflet. Later, leaflet sliding techniques were employed. Commissural prolapse was primarily addressed with papillary muscle head repositioning.

All patients included in the current study underwent full annuloplasty ring implantation. Ring sizing was standardly based on the surface area of the anterior MV leaflet and was not influenced by the type of anterior and/or posterior MV leaflet repair technique used. No over- or downsizing was performed in any of the patients.

Intraoperative transoesophageal echocardiography was performed by an experienced cardiologist to document the intraoperative result of MV repair. Additionally, predischarge transthoracic echocardiography (performed on postoperative day 4-7) was performed to exclude any significant residual MR. Systolic anterior motion was observed in 2 patients and treated conservatively. Oral anticoagulation was initiated for a period of 3 months with a target Internationalized Normalized Ratio of 2.0-3.0. In presence of other indications, the target Internationalized Normalized Ratio range and treatment duration were adjusted accordingly.

Follow-up

Preoperative, intraoperative and postoperative data were retrospectively collected from our computerized database. Follow-up survival, clinical and echocardiographic data were collected through regular clinical visits at our institution or affiliated clinics and hospitals, and through questionnaires to patients. Patient follow-up was based on the available recommendations [8]. Records pertaining to reported office visits, echocardiography and rhythm information, operations, cardioversions, catheter ablation or hospitalizations were obtained and analysed. Rhythm follow-up was based on electrocardiograms obtained during regular follow-up. Additional rhythm monitoring (e.g. 24-h Holter monitoring) was performed on clinical grounds (e.g. complaints of heart palpitations) and the indication for this was left at the discretion of the attending cardiologist. A total of 1126 (mean 2.3/patient, range 0-8) follow-up echocardiograms were available for analysis. The study was approved by our Institutional Ethics Committee Follow-up was completed in February 2017.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile range (IQR) when not normally distributed. Categorical data are presented as counts and percentages. The distribution of variables was evaluated using the Kolmogorov-Smirnov test.

A univariable and multivariable linear regression model, with post-repair MV gradient as a dependent continuous variable, was built to explore the factors associated with post-repair MV gradient. Variable inclusion was based on the previously established effect on MV gradient. To assess for the presence of violations in model assumptions, residuals were plotted versus fitted values and investigated graphically. Univariable and multivariable Cox proportional hazards regression analysis was used to explore risk factors for the occurrence of time-to-event outcomes. Based on known clinical validity and taking into account the ratio of events to risk factors, the following factors were included in respective multivariate models: *for mortality*: age, gender, chronic pulmonary disease, renal impairment, left ventricular function, symptomatic MR, atrial fibrillation and post-repair MV gradient; *for reintervention*: anterior MV leaflet repair and post-repair MV gradient; and *for atrial fibrillation*: age, tricuspid valve repair, preoperative left atrial diameter and post-repair MV gradient. Cubic third-degree splines were used to adjust for possible non-linear association of mean MV gradient with time-to-event outcome in the proportional hazards model. The Wald test was used to test for the presence of a non-linear effect. In addition to P-value-based hypothesis testing, non-linearity of mean MV gradient was assessed graphically by plotting the fitted splines for mean MV gradient, together with 95% confidence intervals (CIs) on the log-hazard scale versus mean MV gradient.

To study the evolution of mean MV gradients during the follow-up period, a mixed-model based linear regression analysis of MV gradient on follow-up time which accounts for repeated within-patient observation was carried out. To account for potential heteroscedasticity or non-normality, bootstrap-based standard errors were investigated. In addition, a *post hoc* exploration of model residuals was explored to investigate these same model assumptions as well as the linearity assumption of MV gradient decent versus follow-up time. No evidence of serious model deviations was found and hence the regular standard errors and hypothesis test are reported.

All tests were 2-tailed and a P-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM Statistics for Windows, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) and R, version 3.5.1 using the Survival package, version 2.43-3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and MV repair details

Baseline characteristics of the whole study group is presented in **Table I**. Median patient age was 66.5 (IQR 57.8-73.8) years and the majority of patients were male. The repair and procedure details are presented in **Table II**. A full-ring was used in all patients; the majority of patients (n=456; 94.2%) underwent either a Physio I (n=223; 46.1%) or Physio II (n=233; 48.1%) ring (Edwards Lifesciences, Irvine, CA, USA) implantation. In 42 (8.7%) patients, a ring size 30 or smaller was implanted.

TABLE I. Baseline characteristics.

	n=484
Age (years)	66.5 (IQR 57.8-73.8)
Gender (female)	171 (35.3)
Body surface area (m^2)	1.93±0.22
NYHA	
I	146 (30.2)
II	243 (50.2)
III-IV	95 (19.6)
Hypertension	221 (45.7)
Atrial fibrillation	172 (35.5)
Renal impairment (mL/min/1.73 m^2)	
Moderate (CC 50-85)	226 (46.7)
Severe (CC <50)	41 (8.5)
Diabetes mellitus	22 (4.5)
Chronic lung disease	42 (8.7)
Mitral annular calcification	49 (10.1)
Echocardiographic characteristics	
LVEF ≤60%	134 (27.7)
LVEDD (mm)*	54±7
LVESD (mm)*	33±7
LAD (mm)*	45.0 (IQR 40.0-49.0)
EuroSCORE II	1.76 (IQR 0.99-3.24)
Degenerative disease subtype	
Barlow's disease	140 (28.9)
Forme fruste Barlow's disease	51 (10.5)
Site of leaflet prolapse	
Posterior leaflet	299 (61.8)
Single scallop prolapse	234 (48.3)
Anterior leaflet	41 (8.5)
Bileaflet	144 (29.7)

*Data are presented as n (%) and means ± SD or medians (IQR). Abbreviations: CC: creatinine clearance; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure. *Available for ≥95% of patients.*

TABLE II. Mitral valve repair details.

	n=484
Mitral valve annulus	
Plication	102 (21.1)
Anterior mitral valve leaflet repair (neochords)	125 (25.8)
Posterior mitral valve leaflet	
Resection	321 (66.3)
Leaflet sliding	222 (45.9)
Neochords	206 (42.6)
Chordal transfer	9 (1.9)
Indentation closure	85 (17.6)
Commissural repair	111 (22.9)
Annuloplasty ring type	
Physio I ring	223 (46.1)
Physio II ring	233 (48.1)
Other	28 (5.8)
Annuloplasty ring size	
≤28	42 (8.7)
30	62 (12.8)
32	112 (23.1)
≥34	268 (55.4)
Intraoperative mitral valve gradient (mmHg)	1.66 (IQR 1.16-2.40)
Concomitant procedures	
Tricuspid valve repair	321 (51.4)
Radiofrequency ablation for atrial fibrillation	148 (30.6)
Coronary artery bypass surgery	96 (19.8)
Aortic valve intervention	28 (5.8)

Data are presented as n (%) and medians (IQR).

Post-repair MV gradient

A moderate positive correlation (r=0.356, n=391, P<0.001) between the intraoperative and predischarge MV gradient was seen (**Supplementary material, Figure S1**). The haemodynamic results of valve repair are demonstrated in **Table III**. As expected, post-repair MV gradients decreased with the size of annuloplasty ring implanted (**Figure 1**).

TABLE III. Postoperative echocardiographic results.

	n=484
Predischarge mitral valve gradient (mmHg)	3.46±1.43
Predischarge heart rate (min^{-1})	80±15
Predischarge stroke volume (ml)*	74 (IQR 58-93)
Predischarge cardiac index (L/m^2)*	5.7 (IQR 4.6-7.4)
Predischarge haemoglobin value (mmol/L)	6.4±0.8

*Data are presented as means ± standard deviations and medians (IQR). *Available for ≥90% of patients.*

On linear regression analysis, increasing patient age (coefficient -0.11, standard error 0.005, P-value 0.034) and annuloplasty ring size (coefficient -0.181, standard error 0.018, P-value<0.001) were correlated with lower post-repair MV gradients (**Table IV)**. On the other hand, increasing body surface area (coefficient 0.905, standard error 0.340, P-value 0.008) and, interestingly, use of the Physio I ring (coefficient 0.414, standard error 0.122, P-value <0.001) were correlated with higher post-repair MV gradients. The linear regression model demonstrated good fit with no evidence of heteroscedasticity or non-linearity (**Supplementary material, Figure S2**).

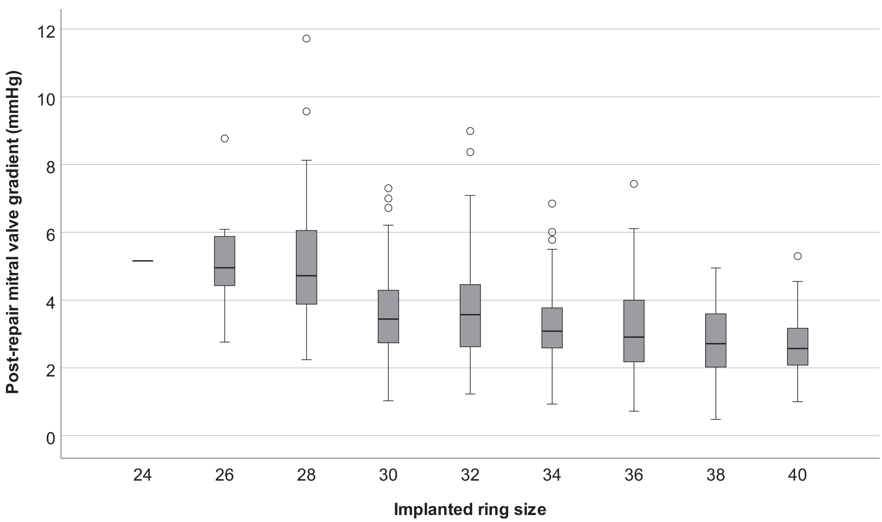

FIGURE 1. Post-repair resting mitral valve gradients in relation to the implanted annuloplasty ring size. Smallest size rings (≤size 28) had the most pronounced effect on post-repair gradients. The middle horizontal line presents the median and the upper and lower borders of the box present the upper and lower quartiles. The upper and lower whiskers present the maximum and minimum values of non-outliers. Extra dots present the outliers.

TABLE IV. Univariable and multivariable linear regression analysis on risk factors associated with post-repair mitral valve gradients.

	Univariable analysis			**Multivariable analysis**		
	Coefficient	**Standard error**	**P-value**	**Coefficient**	**Standard error**	**P-value**
Gender (female)	0.114	0.137	0.40	0.069	0.153	0.65
Age (years)	0.000	0.006	0.98	-0.110	0.005	0.034
Body surface area	0.294	0.302	0.33	0.905	0.340	0.008
Atrial fibrillation	-0.137	0.136	0.32	-0.008	0.121	0.95
Posterior mitral annular plication	0.347	0.160	0.030	0.109	0.155	0.48
Annular decalcification	-0.682	0.223	0.002	-0.235	0.195	0.23
PMVL resection	0.028	0.139	0.84	0.188	0.126	0.14
PMVL indentation closure	-0.154	0.172	0.37	-0.123	0.149	0.41
Annuloplasty ring size	-0.164	0.017	<0.001	-0.181	0.018	<0.001
Annuloplasty ring type						
Physio I ring	0.486	0.129	<0.001	0.414	0.122	0.001
Postoperative blood haemoglobin value	-0.288	0.082	<0.001	-0.301	0.071	<0.001
Postoperative heart rate	0.029	0.004	<0.001	0.024	0.004	<0.001

Abbreviations: AMVL: anterior mitral valve leaflet; PMVL: posterior mitral valve leaflet.

Late clinical results

From cubic spline-based analyses, no evidence of non-linearity for post-repair MV gradient was found for all time-to-event outcomes (**Supplementary material, Figures S3-S5**). Hence, post-repair MV gradient was entered into the Cox proportional hazards regression analysis models as a continuous variable for all subsequent analyses.

During a median follow-up period of 5.8 (IQR 3.4-9.3) years (99.5% complete, 2 patients were lost to follow-up due to emigration), 84 patients died. When corrected for patient age, gender, chronic pulmonary disease, renal impairment, left ventricular function, symptomatic MR and atrial fibrillation, post-repair MV gradient was not associated with patient survival (HR 1.034, 95% CI 0.889-1.203, P=0.66; **Supplementary material, Table S1**).

Follow-up on clinical related events was 90% complete with a mean duration of 5.2 (IQR 2.7-8.8) years. When adjusted for patient age, tricuspid valve repair and preoperative left atrial diameter, post-repair MV gradient was not associated with late atrial fibrillation occurrence (HR 0.849, 95% CI 0.682-1.057, P=0.14; **Supplementary material, Table S1**).

When adjusted for anterior MV leaflet repair, post-repair MV gradient was associated with a higher risk of MV reintervention (HR 1.378, 95% CI 1.033-1.838, P=0.029; **Supplementary material, Table S1**). A total of 11 late reinterventions were performed. The indication for reintervention was recurrent MR in 9 patients and elevated MV gradient in the remaining 2 patients. In both of the latter patients, a post-repair gradient of ≥5 mmHg (5.88 mmHg and 5.23 mmHg, respectively) was seen on pre-discharge echocardiography, despite an acceptable gradient seen on intraoperative echocardiography (2.53 mmHg and 4.23 mmHg, respectively). In the first of the latter patients, an annuloplasty ring size 26 was initially implanted and a re-repair due to heart failure symptoms (no significant MR or other explanation for this observation were found) was performed 1.3 years after the initial operation. Upon reoperation, the annuloplasty ring was explanted, resolving the problem of elevated gradient. In the other patient, an annuloplasty ring size 32 was implanted during the initial operation. Severe pannus formation occurred and the patient underwent a valve replacement 1.1 years after the initial operation.

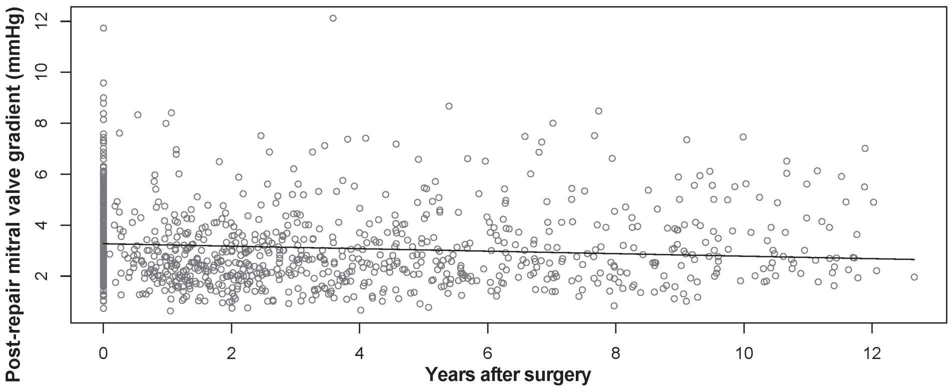

FIGURE 2. Longitudinal changes in mean resting mitral valve gradients. During the follow-up period, a slight decrease, when compared with the predischarge post-repair mean mitral valve gradient, can be observed.

Late echocardiographic results

On mixed-model linear regression analysis on the evolution of mean MV gradient during the follow-up period, a slight decline in MV gradients was seen (estimate=-0.05, 95% CI = -0.07- -0.02, P<0.001) during the follow-up period (**Figure 2**).

DISCUSSION

The results of our study are in line with previous studies, and demonstrate that, following valve repair for degenerative disease, high post-repair gradients are of important clinical relevance. However, repair technique (in particular posterior MV leaflet resection) did not show a significant effect on post-repair gradients and no effect of post-repair gradients on the occurrence of late atrial fibrillation was observed.

The mechanism of elevated post-repair MV gradients is poorly understood, but is in our opinion related to fixation of the posterior annular perimeter length. Indeed, in an adult sheep model, Dagum et al. have shown that cyclic changes in the MV annular area, reaching a maximum in late diastole, are correlated with length changes of the posterior annular perimeter [9]. After implantation of a true-sized partial or complete flexible annuloplasty device, complete fixation of the MV annular area, posterior and anterior annular perimeters throughout the cardiac cycle was observed. Similarly, Bothe et al. reported that MV annuloplasty results in a significant reduction of the maximal MV opening area [10], independent of the type of annuloplasty device used (partial or full ring; flexible, semi-rigid or rigid). Moreover, the Physio I ring (as well as the majority of other full rings implanted) did not impair posterior MV leaflet motion. Additionally, while the Physio I ring did increase the excursion of the annular and belly region of the anterior MV leaflet, it did not affect the excursion of the anterior leaflet at the leaflet edge. No effect on anterior leaflet motion was seen after the implantation of a partial Cosgrove-Edwards band (Edwards Lifesciences, Irvine, CA, USA). Their results suggest that no diastolic flow obstruction due to changes in anterior leaflet motion is to be expected after implantation of the majority of annuloplasty devices tested.

In a study on 107 patients after MV repair for degenerative disease, Mesana et al. suggested that full rings may be associated with higher post-repair gradients when compared to partial bands [5]. Their results need to be interpreted with caution as the Duran ring (Medtronic Inc., Minneapolis, MN, USA), notoriously prone to significant pannus formation [11, 12], was used in most patients who underwent full ring implantation. As MV gradients were measured several years after the initial operation, the high gradients observed in this group are most likely related to pannus formation and not implanted annuloplasty device type. Murashita et al. explored post-repair gradients in 1147 patients after MV repair for degenerative disease [13]. In most patients, a standard 63 mm flexible band was implanted, irrespective of annular perimeter length or anterior leaflet size. In the first median follow-up period (124.5 days after operation), a mean gradient of 3.7±1.6 mmHg was reported that declined to a mean gradient of 3.3±1.8 mmHg in the second median follow-up period (600 days after operation). The gradients in the first median follow-up period seem somehow higher than early post-repair gradients observed in our population. On longitudinal analysis, a decline similar to the one observed by Murashita et al. was also observed in our population. While clearly limited, amongst others, by the unadjusted differences in patient populations, such observations challenge the alleged superiority of partial bands in terms of post-repair gradients. On the other side, excessive shortening of the posterior annular perimeter (resulting from downsizing described by the authors) is bound to have resulted in smaller MV areas than would have been achieved with a true-sized ring.

The results of our analyses suggest that the post-repair gradient is partially associated with patient characteristics (relation of patient age and body surface area to post-repair gradient likely reflect the relation of these parameters to systemic metabolic needs and hereto related cardiac output). Moreover, our results demonstrate that the choice of annuloplasty device used might affect post-repair gradients. This likely correspondent to the differences in the ratio between the anterior-posterior diameter (reflecting anterior MV leaflet surface area to which the ring is sized) and the length of the "posterior perimeter" of the annuloplasty ring between different annuloplasty devices. We are unaware of any studies demonstrating that the increased saddle shape of the Physio II ring is related to improved diastolic MV opening properties when compared to annuloplasty devices with less pronounced saddle-shape. Because of the lack of evidence, we cannot exclude the possibility that the Physio II ring results in superior diastolic opening properties of the anterior leaflet that might explain our observation. For the time being, this should, however, be seen as a theory and properly designed studies will need to be conducted in the future.

In a recent meta-analysis, Mazine et al. have speculated that in cases of posterior MV leaflet prolapse, chordal replacement techniques will result in lower MV gradients when compared to leaflet resection techniques [14]. Our results failed to demonstrate any significant effect of posterior leaflet resection on post-repair gradient. This is likely related to the fact that we primarily used leaflet resection techniques to address excessive posterior MV leaflet tissue and structurally avoided excessive resection. Should this be avoided, no significant shortening of the posterior leaflet free edge, that could at least theoretically limit diastolic leaflet mobility, is to be expected. Functional MV stenosis should not present a reason not to perform adequate leaflet resection when this is indicated, an opinion previously emphasized by our group and others [15-18].

We did not observe any effect of elevated MV gradients on freedom from atrial fibrillation. On the contrary, elevated post-repair MV gradient was identified as a risk factor for late atrial fibrillation occurrence in recent studies by Kawamoto et al. [19] as well as Ma et al. [20]. We included only patients in sinus rhythm who did not undergo any ablation procedures, a characteristic that could provide an explanation for the differences observed between our results and the results by Kawamoto et al. [19]. More importantly, we differentiated between atrial fibrillation and other types of atrial tachycardias as the mechanisms associated with the development of different atrial tachycardias after MV operations are known to fundamentally differ [7]. To adjust for potential unadjusted bias, future studies should include information on the type of incision made to expose the MV when exploring the effect of other factors on early and late atrial tachycardias. Previous studies also demonstrated that an elevated post-repair MV gradient impairs left atrial reverse remodelling [21]. Nevertheless, atrial fibrillation is most likely related to left atrial fibrosis that develops because of long-standing volume overload prior to the operation and is present even in patients in preoperative sinus rhythm [22]. More studies, with longer follow-up, are also needed to explore weather left atrial reverse remodelling in the presence of elevated post-repair gradient is decreased or only delayed. The results of our study do, however, suggest that the clinical burden of elevated post-repair gradient might be lower than previously suggested.

The observation that the risk of reintervention might be related to post-repair MV gradient has not previously been reported. The incidence of reoperation for MV stenosis after previous repair is known to be low [13, 23] but reflects only the patients most affected by this condition. Other studies have additionally shown that high post-repair gradients will result in decreased exercise tolerance and quality of life [3, 5]. We followed the established concepts of valve repair for degenerative disease that include annular remodelling and stabilization. As fixation of the maximal posterior perimeter length, and hereto related maximal MV area, are likely inevitable with any type of annuloplasty device used, elevated post-repair gradients might not be avoidable in all patients. Omitting annuloplasty device implantation is controversial as this is known to result in a higher risk of recurrent MR [24]. Possibly, new annuloplasty device design and identification of patients in whom annular characteristics are sufficiently preserved to support valve sufficiency in the long-term even without annular stabilization would help reduce the burden of this problem.

LIMITATIONS

This is a single-centre retrospective study with study limitations inherent to the study design. The results are applicable to the type of MV repair techniques described only and further studies are needed to evaluate the effect or other repair techniques (e.g. edge-to-edge repair) and annuloplasty devices on the occurrence of elevated post-repair gradients. During the study period, the MV repair techniques have evolved with, in particular, annular plication being performed less often. As the type of leaflet repair did not affect the sizing of the annuloplasty device implanted, no relevant effect on the results presented is to be expected. Moreover, the number of reinterventions was low and prevented us to explore the risk factors for MV reintervention specified to the indication for reintervention (i.p. recurrent MR vs. elevated MV gradient). While we failed to identify a relation between post-repair MV gradient and survival or atrial fibrillation, we cannot exclude the possibility that a correlation does exist but we were unable to detect it due to an insufficient number of patients and events. Our results should thus be seen as hypothesis forming and will need to be confirmed in future studies. We have performed cubic spline analyses but failed to identify a cut-off value that would ease the identification of patient a risk for complications related to elevated post-repair MV gradient in the clinical setting. Identification of a cut-off value should be pursued in future studies. Nevertheless, in line with previous studies, our results do support the efforts aimed at securing the lowest possible post-repair MV gradient.

CONCLUSION

Following MV repair with a semi-rigid annuloplasty ring, increased resting MV gradients are not uncommon. This is, among others, related to the implanted ring size and patient body surface area. Elevated post-repair MV gradients might result in poorer freedom from reintervention due to the added risk of reintervention for MV stenosis while survival and incidence of late atrial fibrillation development do not seem to be affected.

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SUPPLEMENTARY MATERIAL

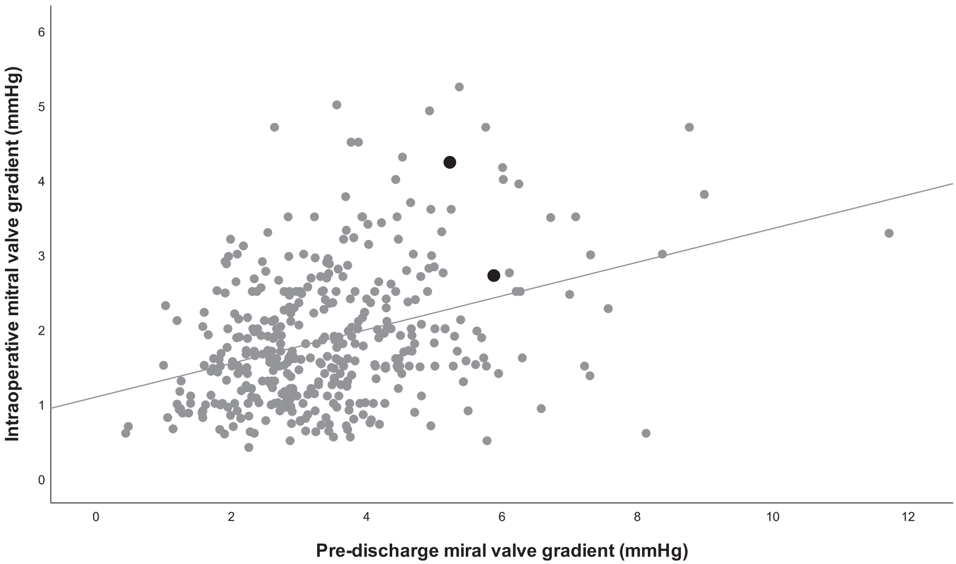

FIGURE S1. Pearson's correlation analysis demonstrated a moderate positive correlation (r=0.356, n=391, P<0.001) between the intraoperative and pre-discharge post-repair MV gradient. Patients in whom a late reintervention was performed a highlighted in red. An intraoperative gradient of 2.53 mmHg and 4.23 mmHg, and pre-discharge gradient of 5.88 mmHg and 5.23 mmHg, respectively, was present in these patients.

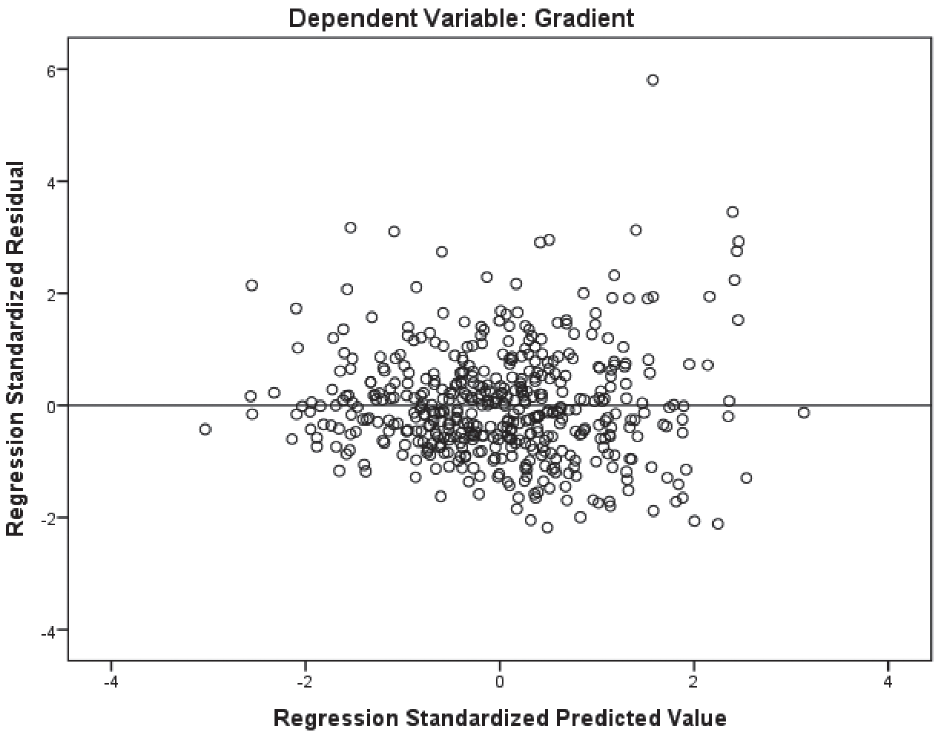

FIGURE S2. Model fit analysis for the linear regression analysis model on the risk factors associated with post-repair mitral valve gradient.

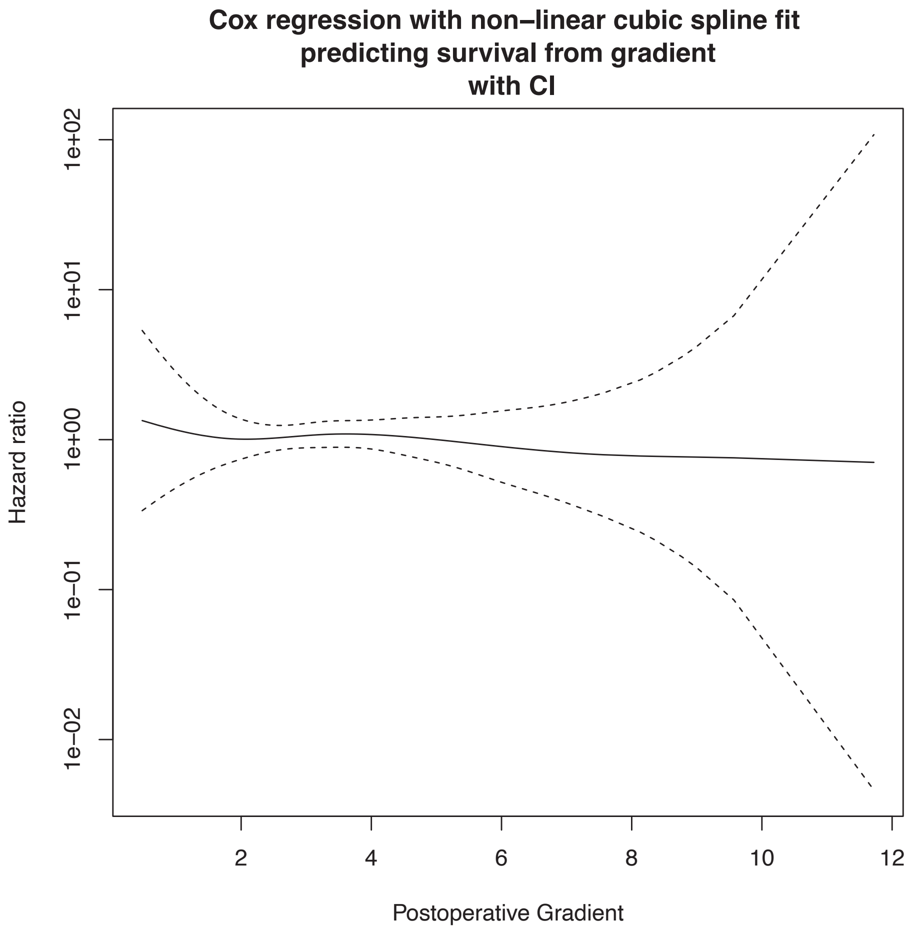

FIGURE S3. Univariate cubic spline regression analysis for the outcome mortality. No evidence of for non-linearity was found. Test for non-linearity: P=0.68.

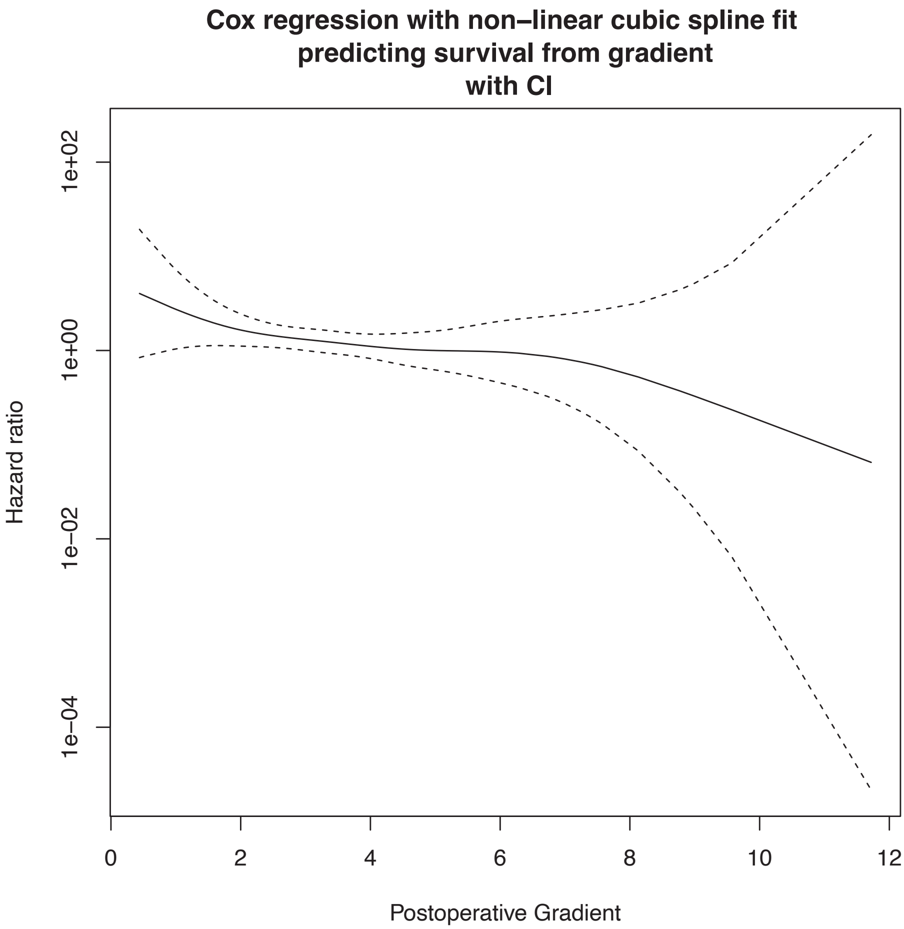

FIGURE S4. Univariate cubic spline regression analysis for the outcome atrial fibrillation. No evidence of for non-linearity was found. Test for non-linearity: P=0.56.

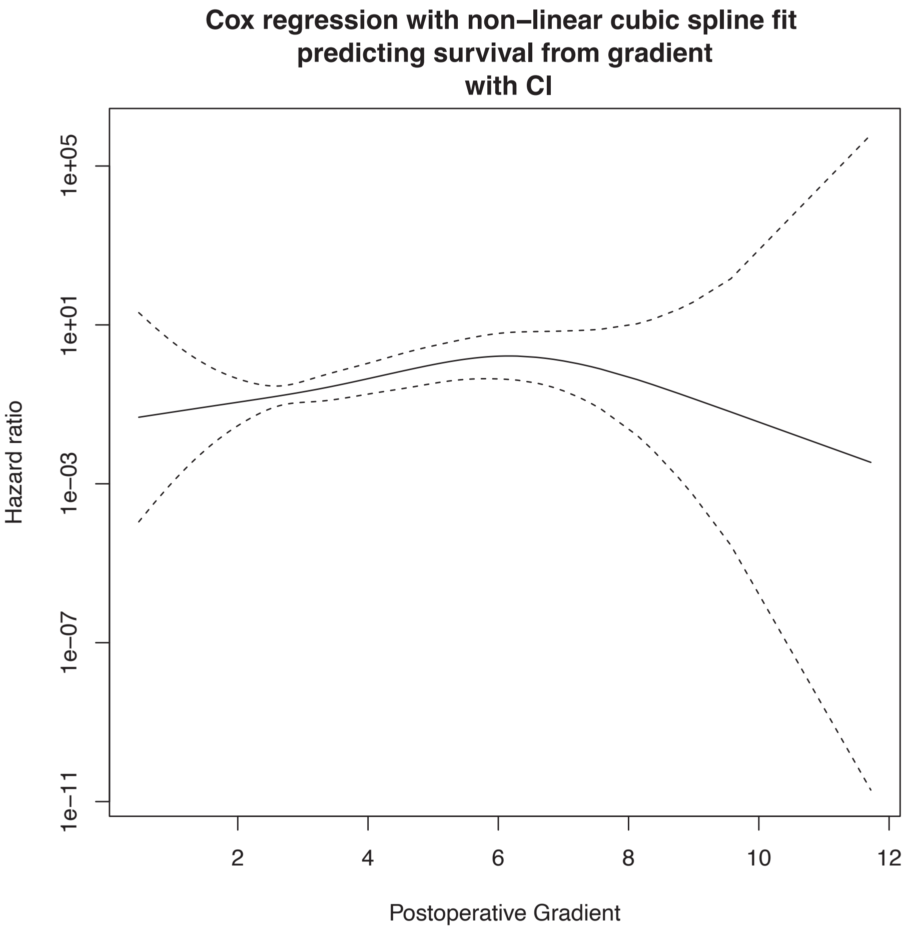

FIGURE S5. Univariate cubic spline regression analysis for the outcome reintervention. No evidence of for non-linearity was found. Test for non-linearity: P=0.30.

TABLE S1. Univariate and multivariate Cox proportional hazards regression analysis results for time-to-event outcomes of interest. Post-repair mitral valve gradient was included as a continuous variable.

	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
All-cause mortality						
Age (continuous)	1.084	1.058-1.111	<0.001	1.065	1.033-1.098	<0.001
Gender (female)	1.322	0.852-2.050	0.21	0.826	0.508-1.342	0.44
Chronic obstructive pulmonary disease	2.654	1.463-4.813	0.001	1.992	1.078-3.682	0.028
Impaired left ventricular function	1.608	1.025-2.524	0.039	1.515	0.952-2.410	0.080
Renal impairment						
Moderate (CC <85 ml/min)	2.824	1.626-4.906	<0.001	1.533	0.825-2.851	0.18
Severe (CC ≤50 ml/min)	5.641	2.905-10.954	<0.001	1.834	0.793-4.243	0.16
Atrial fibrillation	2.148	1.399-3.299	<0.001	1.362	0.867-2.139	0.18
Symptomatic mitral regurgitation	1.814	1.051-3.131	0.032	1.020	0.574-1.811	0.95
Postoperative mitral valve gradient (continuous)	0.970	0.834-1.128	0.69	1.034	0.889-1.203	0.66
Atrial fibrillation						
Age (continuous)	1.082	1.048-1.116	<0.001	1.085	1.048-1.123	<0.001
Tricuspid valve repair	1.737	0.964-3.132	0.066	1.193	0.648-2.196	0.57
Left atrial diameter (continuous)	1.018	0.973-1.064	0.44	1.035	0.986-1.087	0.16
Postoperative mitral valve gradient (continuous)	0.831	0.668-1.034	0.097	0.849	0.682-1.057	0.14
Mitral valve reintervention						
Anterior mitral valve leaflet repair	0.910	0.241-3.444	0.89	0.964	0.255-3.646	0.96
Postoperative mitral valve gradient (continuous)	1.380	1.035-1.840	0.028	1.378	1.033-1.838	0.029

Abbreviation: CC: creatinine clearance; CI: confidence interval; HR: hazard ratio.