Systematic evaluation of the flexible and rigid annuloplasty ring after mitral valve repair for mitral regurgitation

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Abstract

Objectives: Mitral annulus reconstruction is now a common surgical procedure for the treatment of mitral regurgitation. However, there are still controversies in the selection of materials for annuloplasty in the clinical controlled studies available. The purpose of the present systematic review of the literature is to address whether a flexible ring is superior to a rigid ring in terms of improvement in clinical and echocardiographic outcomes.

Methods: A systematic literature search was undertaken of all clinical control trials comparing the outcomes of mitral annuloplasty surgery with the flexible and rigid ring in MEDLINE, EMBASE, and the Cochrane Library.

Results: Overall, 12 published trials were identified as being eligible for overview and were included in the meta-analysis study between 1966 and 2010: four prospective randomized and eight case-control studies. Combined hazard ratios suggested that the flexible annuloplasty ring had no favorable impact on survival: the mean (95% confidence interval (CI)) was 1.24 (0.24—2.24). From the mortality data at maximum follow-up ranging 35—61 months, there was no significant difference on mortality, reoperation, and significant recurrent mitral regurgitation between the two rings. Also, we were not able to find an improvement by flexible rings on shortening fraction, left ventricular end-diastolic volume, end-systolic volume, and end-diastolic and end-systolic diameter. There was a significantly higher ejection fraction in arms for flexible rings relative to rigid rings with pooled standardized mean deviation (SMD) 0.29, 95% CI: 0.06—0.52, \( p = 0.015 \). Finally, compared to the rigid annuloplasty ring, patients implanted with flexible ones presented significantly a far better effect preserving the mitral valve area: SMD 0.54, 95% CI: 0.13—0.95, \( p = 0.01 \), and less constrictive for blood flow across the mitral valve, with the pooled SMD of peak velocity (flexible vs rigid: \( /C0.63, 95% CI: /C0.12 to /C0.13, p = 0.013 \).

Conclusions: Except for the improvement in ejection fraction and preserving the mitral valve area effects in the flexible cases, it remains comparable with regard to overall survival, mortality, reoperation, regurgitant recurrence, and left ventricular performance between the flexible and rigid ring.

Keywords: Mitral valve insufficiency; Mitral valvuloplasty; Annuloplasty ring; Meta-analysis

1. Introduction

Mitral valve repair (MVR) is the favorite procedure chosen for the surgical treatment of pure mitral regurgitation [1]. Reparative procedures on the regurgitant mitral valve show better outcomes compared to mitral valve replacement in terms of operative mortality, late survival, and freedom from thromboembolic accidents and quality life, with an excellent long-term freedom from reoperation and recurrent significant regurgitation [2—4]. The annuloplasty ring is the most widely applied and reliable procedure among various MVR techniques, which restores the mitral annulus to its normal size and shape. Basically, there are two types of annuloplasty rings: the rigid and flexible ring. The flexible ring is developed for reducing the annular size but for allowing it to continuously change during the cardiac cycle, it is better to comply with the physiological configuration of the mitral annulus [5]. Thus, flexible rings are supposedly, convincing replacement for rigid rings. However, comparative studies between rigid and flexible rings, with regard to postoperative clinical outcomes and left ventricular function, performed in limited clinical settings, have produced some confusing and controversial results even in the prospective randomized trials [6,7]. Therefore, a systematic review of the literature has been performed to assess MVR effects in relation to the type of annuloplasty ring used.

2. Material and methods

2.1. Search strategy

A systematic literature search was undertaken of MEDLINE (1966 to July 2010), EMBASE (1974 to July 2010), and the Cochrane Library 2010. We employed the keywords ‘Mitral valve repair, mitral valve reconstruction or mitral valvuloplasty’ and ‘annuloplasty’ with limits of ‘Clinical trial’ and
‘Humans’. In order to broaden the sensitivity of the search strategy, we aimed to identify all published and unpublished clinical trials of mitral annuloplasty surgery with different annuloplasty rings. Where available, abstracts from major cardiology and cardiothoracic surgery scientific meetings from 2003 to 2010 were manually searched. Reference lists of all relevant studies were reviewed irrespective of language, and even attempts were made to correspond with authors of relevant trials.

Two reviewers independently extracted data from each study on study title, first author, year of publication, institution, population characteristics, type of annuloplasty ring, study design, follow-up, inclusion and exclusion criterion, and main outcomes of clinic or echocardiography: mortality, 5-year survival, left ventricular performance, recurrent rate, and mitral valvular area. If the same author published multiple studies reporting outcomes at different follow-up points, we abstracted patient characteristics from the first study, with data for outcomes of interest at subsequent follow-up times extracted from the later studies. When two studies by the same institution reported the same outcomes at similar follow-up periods, we included in our analysis either the better quality or the most informative publication. Discordances were resolved by re-review or consensus review.

### 2.2. Study selection

All clinical controlled trials, evaluating mitral annuloplasty surgery with different annuloplasty rings (rigid vs flexible, prosthetic, or autologous), were enrolled. Trials were included without limitation to subject population, year, type of conference proceedings, or language. We excluded studies if the flexible and rigid rings were allocated to the same group as a prosthetic arm and if the outcomes of interest were not reported or it was impossible to calculate these from the published results. No control group, of course, was within our exclusion criteria.

### 2.3. Quality assessment of individual studies

We used predetermined criteria to assess the quality of included randomized trials as the following three categories from A (high quality) to C (low quality) [8]. These quality criteria included the randomization procedure, the use of intention-to-treat analysis, the report of dropout rates, allocation concealment, and the extent to which valid outcomes were described.

### 2.4. Statistical analysis

We carried out our meta-analysis in line with the Cochrane Collaboration recommendations of meta-analyses guidelines [9]. For categorical variables, the relative risk as the summary statistics was employed, demonstrating the adverse ratio in the study group (flexible annuloplasty ring) relative to control group (rigid annuloplasty ring). A relative risk of less than 1 was in favor of the study group, and the point estimate of the relative risk was taken of statistical significance if the 95% confidence interval did not include the value 1. Continuous data were expressed as standardized mean difference (SMD) and on overall SMD was calculated. The actual measures of the effect of all continuous variables were the differences from baseline to end point. For the quantitative aggregation of the survival results, the annuloplasty ring effect was measured by the hazard ratio (HR) between the two survival distributions. By convention, an observed HR > 1 implied a worse survival for the study group. A fixed-effects model was chosen on the presumption that variation in the individual trial results occurred about a true mean. Conversely, the randomized model was adopted. We assessed heterogeneity for summary effects by calculating the chi-square and \( I^2 \) statistics. Quantification of the effect of heterogeneity will be assessed by means of \( I^2 \), ranging from 0% to 100%. \( I^2 \) demonstrates the percentage of total variance across studies due to heterogeneity and will be used to judge the consistency of evidence.

### Table 1. Characteristics of 12 clinical controlled trials, comparing the flexible mitral annuloplasty ring with the rigid one.

<table>
<thead>
<tr>
<th>Study et al.</th>
<th>Year</th>
<th>Country</th>
<th>Type of annulus</th>
<th>Study design</th>
<th>Number (F/R)</th>
<th>Inclusion criteria</th>
<th>Follow-up (month)</th>
<th>Age (year, F/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. [6]</td>
<td>2007</td>
<td>Korea</td>
<td>Carpenter/Duran</td>
<td>Prospective/random</td>
<td>170/187</td>
<td>Pure MR</td>
<td>46.6 ± 32.6</td>
<td>50.3 ± 16/49.4 ± 1.53</td>
</tr>
<tr>
<td>Chung et al. [10]</td>
<td>2007</td>
<td>Korea</td>
<td>Carpenter/Duran</td>
<td>Case–control</td>
<td>141/153</td>
<td>Degenerative MV</td>
<td>42.7 ± 26.5</td>
<td>53 ± 13/53 ± 13</td>
</tr>
<tr>
<td>Bevilacqua et al. [13]</td>
<td>2003</td>
<td>Italy</td>
<td>Carpenter/pericardium</td>
<td>Case–control</td>
<td>56/77</td>
<td>Degenerative MV</td>
<td>35.6 ± 18.7</td>
<td>64.4 ± 9.7/61.7 ± 12.6</td>
</tr>
<tr>
<td>Dall’Agata et al. [12]</td>
<td>1998</td>
<td>Netherlands</td>
<td>Carpenter/Cosgrove</td>
<td>Case–control</td>
<td>15/4</td>
<td>Pure MR</td>
<td>2–3</td>
<td>Immediate</td>
</tr>
<tr>
<td>Yamaura et al. [16]</td>
<td>1997</td>
<td>Japan</td>
<td>Carpenter/Duran</td>
<td>Case–control</td>
<td>10/10</td>
<td>Pure MR</td>
<td>Unavailable</td>
<td></td>
</tr>
<tr>
<td>Okada et al. [5]</td>
<td>1995</td>
<td>Japan</td>
<td>Carpenter/Duran</td>
<td>Case–control</td>
<td>15/11</td>
<td>Degenerative MV</td>
<td>2–3</td>
<td>51.3 ± 8.7/53.5 ± 11.5</td>
</tr>
<tr>
<td>Yamaura et al. [17]</td>
<td>1995</td>
<td>Japan</td>
<td>Carpenter/Duran</td>
<td>Case–control</td>
<td>10/10</td>
<td>Pure MR</td>
<td>Unavailable</td>
<td></td>
</tr>
<tr>
<td>David et al. [15]</td>
<td>1989</td>
<td>Canada</td>
<td>Carpenter/Duran</td>
<td>Prospective/random</td>
<td>15/10</td>
<td>Degenerative MV</td>
<td>2–3</td>
<td>Unavailable</td>
</tr>
</tbody>
</table>

MV, mitral valve; MR, mitral regurgitation; F/R, flexible ring/rigid ring.
and considered $I^2$ statistics in excess of 50% to indicate heterogeneity. All statistical analyses were carried out with Stata 10 (StataCorp, College Station, TX, USA).

3. Results

3.1. Trial flow and characteristics

Our searches for clinical trials comparing the efficacy of mitral annuloplasty surgery with different annuloplasty rings yielded 86 potentially relevant articles, of which 70 articles were excluded for using percutaneous mitral annuloplasty device as the surgery procedure, concentrating robotic-assisted operation or any other valvuloplasty technique without any annuloplasty ring used. Four were excluded for not including a control arm. Then, a total of 12 articles [5—7,10—18] reporting on clinical trials met our inclusion criterion initially. The results from the 12 published trials were identified as being eligible for overview and were included in the meta-analysis study between 1966 and 2010. There was a total of 1165 patients in these studies. The mean age of trial enrollment ranged from 38 to 62 years. The proportion of women included in the trials ranged from 35% to 44%. The study designs were prospective randomized in four groups [6,7,14,15], and case-control study in the remaining eight studies. Table 1 lists the main characteristics of these studies.

The overall quality was roughly assessed on a 3-point scale according to the Cochrane handbook. All the included articles scored B (moderate quality).

3.2. Outcomes of interest

3.2.1. Survival parameters at maximum follow-up

The individual HRs of the five evaluated studies were calculated from the graphical representations of the survival distributions with overall 5-year survival. The aggregation did not produce a statistically significant HR with a better survival prognosis in cases of implanting flexible annuloplasty ring (Fig. 1A). The test for heterogeneity gave a significant result ($p < 0.01$), but it was impossible to go further in the

Fig. 1. Forest plot showing results from meta-analysis of trials reporting survival data, comparing the flexible mitral annuloplasty ring with the rigid one. (A) Hazards ratio on 5-year survival. (B) Relative ratio of mortality.
categorization of the trials, namely, to treat articles reporting on overall 5-year survivals separately. The use of a random-effects model obtained the conclusion with a combined HR of 1.24 (95% CI: 0.24—2.24).

Six groups reported on mortality at maximum follow-up after mitral annuloplasty surgery with variable follow-up ranging from $35.6 \pm 18.7$ to $61.4 \pm 20.1$ months. Meta-analysis of the studies did not show any significant difference in mortality at maximum follow-up between the two annuloplasty rings (relative risk 1.12, 95% CI 0.73—1.71, no statistical heterogeneity, $p = 0.205$) (see Fig. 1B).

3.2.2. Significant recurrent mitral regurgitation at maximum follow-up

Recurrence of significant mitral regurgitation (MR) was equal to or greater than grade 3 during the follow-up period. Six clinical trials, focusing on the significant recurrent mitral regurgitation, demonstrated that there was no significantly higher recurrence in patients with flexible annuloplasty ring relative to that with rigid ring. Fixed effects (Mantel—Haenszel) pooled relative risk was 1.66 (95% CI: 0.93—2.96), $p = 0.085$. No heterogeneity was detectable, $p = 0.634$. There is a case—control study excluded by the system because of reporting negative recurrence in both the arms (see Fig. 2).

3.3. Reoperation

Of the 12 studies, six provided data on reoperation for mitral valves, with an outcome assessment time varying from $35.6 \pm 18.7$ to $61.4 \pm 20.1$ months. The pooling analysis obtained a relative risk of reoperation comparing the flexible annuloplasty ring and rigid ring of 1.75 (95% CI: 0.76—3.98; $p = 0.186$), with no evidence to suggest statistical heterogeneity ($p = 0.587$). The variation in relative risk attributable to heterogeneity ($I^2$) was 0 (see Fig. 3).
3.4. Left ventricular performance

Most studies reported on the stable postoperative left ventricular ejection fractions. Compared to the rigid annuloplasty ring, patients treated with flexible rings reported significantly a better effect: SMD 0.29, 95% CI: 0.06–0.52, p = 0.015. Heterogeneity was not significant, p = 0.051 (see Fig. 4A). We wanted to further confirm the left ventricular contraction function with the shortening fraction (FS), but this parameter was rarely reported exactly. Only two studies provided data for the comparison on FS, and no statistically significant differences were found: SMD 0.43, 95% CI: −0.05 to 0.91, p = 0.081 (Fig. 4B).

Data from studies that compared the flexible annuloplasty ring with rigid ring in decreasing preload were scarce. The details on left ventricular end-diastolic volume (EDV) and left ventricular end-systolic volume (ESV) postoperation were available in only three articles. Pooling of results yielded an insignificant advantage for flexible ring with respect to EDV and ESV: SMD −0.13, 95% CI: −0.54 to 0.28, p = 0.53; SMD −0.26, 95% CI: −0.67 to 0.15, p = 0.208 respectively. There was no statistical heterogeneity (Fig. 4C and D).

The five studies that assessed left ventricular function improved mostly the used left ventricular end-diastolic diameter (EDD) and left ventricular end-systolic diameter.
(ESD) for this purpose. We found that flexible rings had no statistically significant effect on EDD levels compared to rigid annuloplasty rings (SMD $-0.19$, 95% CI: $-0.51$ to $-0.12$, $p = 0.23$) (Fig. 4E) and a non-statistically significant decreasing effect on ESD levels (SMD $-0.05$, 95% CI: $-0.22$ to $-0.12$, $p = 0.546$). No statistical heterogeneity occurred (Fig. 4F).

### 3.5. Mitral valve orifice

Patient data recorded during echocardiographic monitoring are the main assessment about the mitral valve orifice, the peak velocity of trans-mitral blood flow (PV) and the mitral valve area in diastole (MVA) focused commonly besides any backflow. Compared to the rigid annuloplasty ring, patients implanted with flexible rings presented significantly a far better effect preserving the MVA: SMD 0.54, 95% CI: 0.13–0.95, $p = 0.01$ (Fig. 5A). This effect could be reflected by the PV reported by other studies with the pooled SMD (flexible vs rigid: $-0.63$, 95% CI: $-1.12$ to $-0.13$, $p = 0.013$) (see Fig. 5B).

### 4. Discussion

In this systematic review, we found no statistically significant effect in using flexible annuloplasty ring on mortality, reoperation, recurrence at maximum follow-up, and 5-year survival in patients with isolated mitral insufficiency. Compared to that in the rigid annuloplasty ring group, the area of the mitral annulus with the flexible ring significantly increased during the cardiac cycle. As a result, a significant difference was drawn for the velocity of trans-mitral blood flow, with a lower velocity in the flexible group relative to that in the rigid one. However, we found no clinically relevant effects on the mitral annuloplasty type and cardiac preload, that is, EDV, ESV, or left ventricular contraction parameters, that is, FS, EDD, and ESD. It indicated that patients treated with flexible rings reported a little better effect, compared to those treated with rigid rings.

This study was attempted to compare the long-term clinical results between rigid and flexible rings. The overall

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**Fig. 5. Forest plot showing results from meta-analysis of trials reporting mitral valve orifice comparing the flexible mitral annuloplasty ring with the rigid one. (A) Standardized mean difference on mitral valve area. (B) Standardized mean difference on peak velocity.
survival and mortality for the long-term period are always concentrated upon in any clinical trial; also, it is the eventual goal that all the medical practitioners pursue. The aggregation of the survival data was performed by using the results reported in the five varied studies only. The pooling result did not produce a statistically significant HR with a better survival prognosis in cases where the flexible annuloplasty ring was implanted. However, the test for heterogeneity gave a significant result. A possible explanation of this outcome may be as follows. The types of study available were heterogeneous, of the five concerning survival data articles, only two were prospective randomized design. Moreover, population inclusion-derived heterogeneity was often oriented to particular groups of patients, such as those with mitral incompetence originated from degenerative disease, ischemic heart disease, or rheumatic lesion. However, the degenerative disease was claimed predominantly. For this reason, a global meta-analysis was not performed and the analysis concentrated on more homogeneous subgroups of patients by aggregating the data of studies conducted in similar patient populations. However, it was impossible to go further to treat articles reporting overall 5-year survivals in subgroups due to limited study. This result of the meta-analysis should encourage the development of adequately designed prospective studies, with an appropriate statistical methodology including multivariate analysis, in order to demonstrate the relationship between annuloplasty ring and survival. After all, the overall survival outcome can be mirrored by another assessment, mortality. In accordance with the HR, we did not obtain any significant difference in mortality at maximum follow-up between the two annuloplasty rings, with no heterogeneity. Although at short-term follow-up, a flexible annuloplasty was proved to be beneficial, first reported on this effect of annular dynamics. However, this type of study is of low force, due to limited study. This result of the meta-analysis was not found. Only the slight superiority of the flexible ring was observed on the aspect of EF.

Our present pooled data suggested that mitral repair with a flexible ring produced EF superior to those associated with the use of a rigid ring in patients with isolated MR, and aggregation of PV and MVA was suggestive of a more restrictive pattern of blood flow across the mitral valve in patients with rigid annuloplasty. The mitral annulus is a dynamic structure, providing an active contribution to the mechanics of the mitral valve apparatus, owing to a sphincter-like action achieved by the contraction and relaxation of basoconstrictor muscles surrounding the annulus posteriorly. A possible disadvantage of the rigid fixation of the mitral annulus is the reduction of such a dynamic annular motion; on the contrary, flexible prosthetic devices have been proposed to own the advantages of being more physiological (nonplanar configuration of mitral annulus, reduced area in systole) and better preserving left ventricular function, at least with regard to EF. Moreover, in the cardiac preloading characteristics such as LVEDD, LVESD, LVEDV, and LVESV, no significant difference in the pooled analysis between the flexible and rigid ring was not found. Only the slight superiority of the flexible ring was detected on the aspect of EF.
This is the first systematic review and meta-analysis on the topic of mitral annuloplasty ring. It offers an up-to-date and complete overview of all human clinical trials involving flexible and rigid mitral annuloplasty ring therapy for pure MR, because it is the result of an extensive search, including gray literature [18]. In addition, maximum efforts have been undertaken to minimize missing or incomplete data by attempting to contact all authors. Although the authors of this article tried to include a high number of quality studies, it turned out that the data were consistent to a certain extent and heterogeneity occurred owing to a majority of case-control trials. It should be stressed upon that the results need to be confirmed by an adequately designed prospective study and the exact time of the long-term follow-up be assigned.

To conclude, a systematic review of current and the best available evidence suggests that in patients with a flexible annuloplasty ring compared to patients with a rigid annuloplasty ring, the significant improvement in EF pooled by this comprehensive analysis does not translate into better clinical outcomes, such as 5-year survival, overall mortality, reoperation, and regurgitant recurrence, which present comparable outcomes.

References


