European Journal of Cardio-Thoracic Surgery 50 (2016) 882–889
doi:10.1093/ejcts/ezw139 Advance Access publication 28 April 2016

ORIGINAL ARTICLE

Cite this article as: De Bonis M, Lapenna E, Barili F, Nisi T, Calabrese M, Pappalardo F *et al*. Long-term results of mitral repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: does the technique matter? Eur J Cardiothorac Surg 2016;50:882–9.

Long-term results of mitral repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: does the technique matter?[†]

Michele De Bonis[a,*], Elisabetta Lapenna[a], Fabio Barili[b], Teodora Nisi[a], Mariachiara Calabrese[a], Federico Pappalardo[a], Giovanni La Canna[a], Alberto Pozzoli[a], Nicola Buzzatti[a], Andrea Giacomini[a], Emanuela Alati[a] and Ottavio Alfieri[a]

[a] Department of Cardiac Surgery, IRCCS San Raffaele Hospital, Vita e Salute San Raffaele University, Milan, Italy
[b] Department of Cardiac Surgery, Santa Croce Hospital, Cuneo, Italy

* Corresponding author. Department of Cardiac Surgery, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy. Tel: +39-0226437102; fax: +39-0226437125; e-mail: michele.debonis@hsr.it (M. De Bonis).

Received 15 September 2015; received in revised form 27 February 2016; accepted 4 March 2016

Abstract

OBJECTIVES: An isolated undersized annuloplasty was used to treat mitral regurgitation (MR) secondary to dilated cardiomyopathy (DCM) if the baseline coaptation depth (CD) was <1 cm. In the presence of significant tethering of the mitral leaflets (CD ≥1 cm), the edge-to-edge (EE) technique was combined with annuloplasty to improve the durability of the repair. The long-term results of this approach are unknown and represent the objective of this study.

METHODS: To obtain long-term outcome data, we included in the study population the first 105 consecutive patients with severe left ventricular dysfunction (ejection fraction 29 ± 6.6%) and secondary MR submitted to mitral valve repair. Forty patients underwent isolated undersized annuloplasty and 65 patients received the EE technique combined with annuloplasty. Preoperative and postoperative data were prospectively entered into a dedicated database. Clinical and echocardiographic follow-ups were performed in our institutional outpatient clinic.

RESULTS: Follow-up was 90% complete. The median follow-up time was 7.2 years (interquartile range 4.3;10.4). The longest follow-up time was 16.5 years. A comparative analysis between the annuloplasty group and the EE group was performed. Baseline LV dimensions and function were slightly worse in the EE group, but only the severity of tethering was significantly more pronounced than in the annuloplasty group. Hospital mortality (3 vs 2.5%, $P = 1.0$) and 10-year overall survival (42 ± 6.7 vs 55 ± 8.5%, $P = 0.2$) were not significantly different in the EE and annuloplasty group, respectively. Cumulative incidence functions of cardiac death were similar as well (at 10-years, 34.3 ± 8.1 vs 37.9 ± 6.4%, respectively, $P = 0.4$). At 10 years, cumulative incidence function of recurrence of MR ≥3+ was lower in the EE patients (10.3 ± 4.1 vs 30.8±8.0%, $P = 0.01$). Isolated annuloplasty [hazard ratio (HR) 4.84, 95% confidence interval (CI) 1.46–16.1, $P = 0.01$] and residual MR >1+ at hospital discharge (HR 5.25, 95% CI 2.00–13.8, $P < 0.001$) were significantly related to the development of MR ≥3. Failure of repair was associated with recurrence of New York Heart Association III or IV symptoms ($P < 0.001$).

CONCLUSIONS: In patients with end-stage DCM and secondary MR, the association of the EE technique to the undersized annuloplasty significantly decreases the rate of recurrent MR at long-term. This higher repair durability did not translate into a better long-term prognosis in this series.

Keywords: Secondary mitral regurgitation • Mitral valve repair • Undersized annuloplasty • Edge-to-edge repair

INTRODUCTION

The choice of treatment in the secondary mitral regurgitation (MR) remains controversial [1–3]. Surgical correction can improve symptoms and quality of life, and reverse left ventricular (LV) remodelling in selected patients [4, 5]. However, a clear prognostic benefit in comparison with optimal medical therapy has not been demonstrated [6]. Mitral repair performed with an undersized rigid complete ring has been considered the reference standard for many years [7]. The main disadvantage is the risk of recurrent MR [3, 8, 9], which may underlie the lack of observed survival benefit. Several predictors of recurrent MR have been identified over the years and should be considered during patient selection [10]. In particular, more advanced leaflet tethering is an important predictor of repair failure and recurrent MR and concomitant

[†]Presented at the 29th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Amsterdam, Netherlands, 3–7 October 2015.

techniques to improve durability have been described [11–13]. These include resection of secondary chordae, suturing of the posteromedial papillary muscle to the aorto-mitral continuity, infarct plication, papillary muscle imbrication or sling, posterior LV restoration and the edge-to-edge (EE) technique. At the beginning of our study, one of the few predictors of repair failure which had already been identified was a coaptation depth (CD) of the mitral valve (MV) leaflets ≥1 cm. At that time, therefore, the policy followed in our institution was to treat secondary MR by an isolated undersized annuloplasty if the CD was <1 cm. On the other hand, in the presence of significant tethering of the mitral leaflets (CD ≥1 cm), the EE technique was routinely combined with the annuloplasty procedure, with the aim of improving the durability of the repair [14]. We previously reported the early result of this approach [14]. However, since the comparative outcome at long-term of those two techniques remains unknown, we decided to look at the late clinical and echocardiographic data of the first series of consecutive patients treated with this strategy in our institution.

MATERIALS AND METHODS

Study population

For the purpose of this study, we included in this series the first 105 consecutive patients with advanced dilated cardiomyopathy (DCM) and severe or moderately severe secondary MR refractory to medical therapy who underwent mitral repair from 1998 to 2007 (Fig. 1).

The patients enrolled in this analysis were treated at a time when the MitraClip was not yet available and, therefore, surgery was the only treatment option, even for cases at high surgical risk due to severe LV remodelling and dysfunction.

The aetiology of DCM was ischaemic in 69 cases (65.7%) and idiopathic in 36 (34.2%). All patients had severe LV dysfunction with ejection fraction (EF) ≤35% and had been hospitalized one to five times for congestive heart failure (CHF) in the previous 6 months despite maximal medical therapy. The severity of secondary MR was established by transthoracic (TTE) and transoesophageal echocardiography (TEE) using an integrative approach, and defined as mild (1+/4+), moderate (2+/4+), moderate-to-severe (3+/4+) and severe (4+/4+). The severity of tricuspid regurgitation (TR) was graded as mild, 1+/4+ (jet area/right atrial area <10%); moderate, 2+/4+ (jet area/right atrial area 10–20%); moderately severe, 3+/4+ (jet area/right atrial area 20–33%) and severe, 4+/4+ (jet area/right atrial area >33%). Dilatation and respiratory variation of the inferior vena cava as well as reduction or reversal of systolic flow in the hepatic veins were also used as supportive signs to define the severity of TR [15]. Patients with primary MR, recent myocardial infarction (≤6 months), papillary muscle rupture or severe right ventricular (RV) dysfunction were excluded. Patients with multiple organ failure and those undergoing concomitant LV reconstruction or aortic valve procedures were not included as well. In patients without atrial fibrillation, sinus tachycardia or inducible ventricular arrhythmias, dobutamine stress echocardiography was performed to assess the presence of a contractile reserve, to better define the surgical risk and, in patients with ischaemic DCM, to distinguish those who could benefit from concomitant myocardial revascularization (presence of viability) from those who required only MV surgery (absence of viability) [16].

Depending on the MV CD (<1 or ≥1 cm), 40 patients with a CD of <1 cm received an isolated undersized annuloplasty (annuloplasty group) and 65 patients with a CD of ≥1 cm were treated with the EE technique combined with annuloplasty (EE group). The Institutional Ethical Committee approved this study and waived individual consent for this retrospective analysis.

Follow-up

A dedicated outpatient clinic for patients undergoing surgical treatment of secondary MR has been there in our institution since the year 2000 and has been used to follow regularly those patients. Physical examination, electrocardiography, TTE and arrhythmology consultation are routinely performed. All data are prospectively entered in a dedicated database and are reviewed and compared for the purpose of this study.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) for Windows (Microsoft Corp, Redmond, WA, USA) and R 3.2.1 software [R Development Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/]. The distribution of variables was evaluated using the Shapiro–Wilk test. Continuous data were expressed as mean + standard deviation or as median and interquartile range (IQR). Categorical data were reported as number and percentage. If continuous data were normally distributed, comparison between two groups was performed with the Student's *t*-test for (un)paired samples, as indicated. If they were not normally distributed, the Mann–Whitney *U*-test or the Wilcoxon signed-rank test was employed for independent or related samples, respectively. χ^2 test was used for categorical data and Fisher's exact test was used when the minimum cell size requirements for the χ^2 was not satisfied. New York Heart Association (NYHA) functional class and grade of MR were treated as ordinal variables and compared with the Wilcoxon signed-rank test (related samples) or with the Mann–Whitney *U*-test (independent samples). Kaplan–Meier estimates were employed for analysing long-term survival. Fine and Gray models were used in competing risk analysis for time-to-cardiac death, with non-cardiac death as competing risk, and time-to-MR ≥3+ recurrence, with death as competing risk. Non-parametric analyses of the outcome variables of interest were computed with the cumulative incidence function (CIF) and sub-distribution hazards and comparisons were computed by means of Fine and Gray test. Direct regression modelling of the effect of covariates on CIF was performed through the semiparametric proportional hazard model for the sub-distribution hazards proposed by Fine and Gray, allowing for time-varying effect of the covariates. Hazard proportionality and time-dependent effects were checked with the analysis of Schoenfeld residuals, the Kolmogorov–Smirnov test and the Cramer-von Mises test.

RESULTS

Patient characteristics

All patients had secondary MR 3+ or 4+ and severe LV dysfunction with a mean EF of 29 ± 6.6% and left ventricular end-diastolic

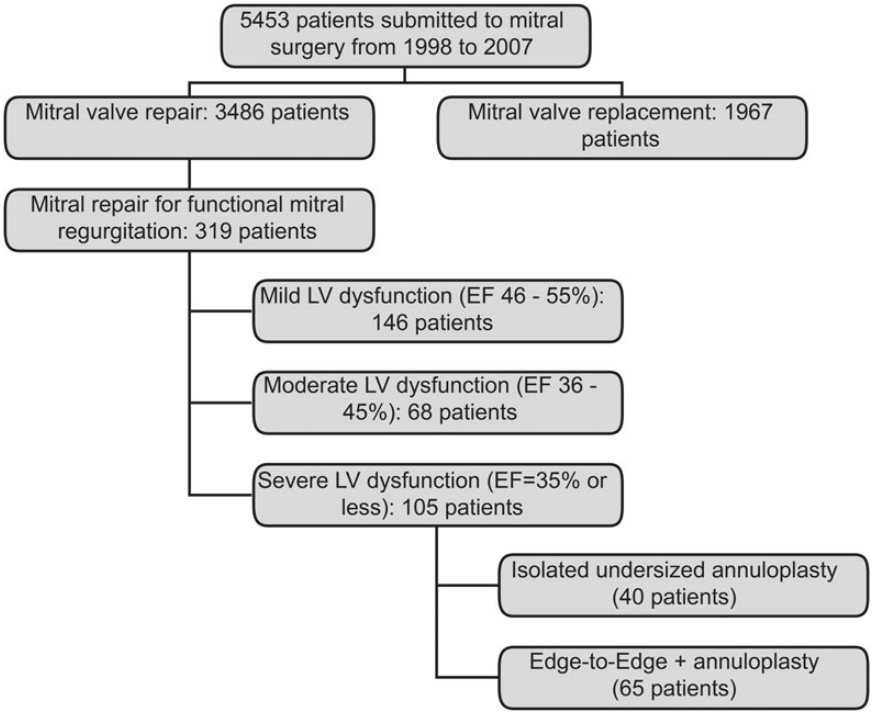

Figure 1: Consort flow diagram showing how the study population was recruited. LV: left ventricular; EF: ejection fraction.

diameter (LVEDD) 68 ± 7.1 mm. The mean left ventricular end-diastolic volume approached 200 ml. The majority of patients had pulmonary hypertension and about one-third of them was in atrial fibrillation. As given in Table 1, the preoperative clinical and echocardiographic characteristics of the two groups were similar with the only exception of the CD ($P = 0.0001$) and tented MV area ($P = 0.01$) which were obviously significantly higher in the patients who underwent EE repair. LV dimensions and function were slightly worse in the EE group, but the difference was not statistically significant. Most of the patients were in NYHA functional class III or IV and all were receiving heart failure medication at the maximal tolerated dose without significant differences between the two groups.

Table 1: Clinical and echocardiographic preoperative data in the edge-to-edge and isolated annuloplasty groups

	EE + annuloplasty $N = 65$	Annuloplasty $N = 40$	*P*-value
Male gender (*n*, %)	45 (69)	29 (72)	0.7
Age (years)	63 ± 10	63 ± 10.2	0.8
Ischaemic DCM (*n*, %)	43 (66)	26 (65)	0.9
NYHA class (*n*, %)			0.5
II	9 (14)	8 (20)	
III	40 (61)	23 (58)	
IV	16 (25)	9 (22)	
AF (*n*, %)	14 (21)	14 (35)	0.9
LVEF (%)	29 ± 6.6	31 ± 6	0.09
LVEDD (mm)	68 ± 6.3	67 ± 8.1	0.3
LVESD (mm)	52 ± 8.2	50 ± 7.4	0.4
LVEDV (ml)	203 ± 59.8	188 ± 54.2	0.2
SPAP (mmHg)	48 ± 13.3	44 ± 14.1	0.1
Tented area (cm^2)	2.9 ± 0.88	2.1 ± 0.84	0.01
Coaptation depth (cm)	1.2 ± 0.27	0.8 ± 0.15	0.0001

AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; SPAP: systolic pulmonary artery pressure; EE: edge-to-edge; DCM: dilated cardiomyopathy; NYHA: New York Heart Association.

Procedural data

All patients, with and without EE repair, received an undersized complete ring. The annuloplasty rings were semirigid (Seguin, St. Jude Medical) or rigid (Carpentier–Edwards, Classic) in 90.5% of the cases (95/105) and flexible (Duran, Medtronic, Inc. or Tailor, St. Jude Medical) in 9.5% (10/105). The flexible rings were used exclusively at the beginning of our experience and then abandoned. In the EE group, the mean ring size was significantly higher (28.9 ± 2.34; median 28, IQR 28;30) than that in patients undergoing restrictive annuloplasty alone (27 ± 1.6; median 26, IQR 26;28) ($P = 0.0001$). In the EE group, a short EE suture was added to the ring annuloplasty in correspondence of the site of origin of the regurgitant jet as assessed by echocardiography: centrally (in case of central jet, 58/65 patients, 89.2%) or posteromedially (when the regurgitant jet was in correspondence of the posterior commissure, 7/65 patients, 10.7%). When more than one jet was identified, the EE was applied on the largest one, relying on the undersized ring for the resolution of the others. Concomitant coronary artery bypass graft (CABG) was performed in 49 of 69 patients (71%) with ischaemic DCM (29 in the EE group and 20 in the isolated undersized annuloplasty one). In the remaining 20 ischaemic patients (29%), myocardial revascularization was not performed because of unsuitable coronary anatomy or the presence of scar in the target region. The distribution of those 20 patients was not significantly different between the 2 groups

Table 2: Postoperative complications

	EE + annuloplasty *N* = 65	Annuloplasty *N* = 40	*P*-value
Low output syndrome (*n*, %)	5 (7.6)	3 (7.5)	0.7
Acute renal failure with need for CVVH (*n*, %)	2 (3)	0	0.7
Sepsis (*n*, %)	4 (6.1)	1 (2.5)	0.7
Tracheostomy for respiratory failure (*n*, %)	2 (3)	0	0.7
Stroke (*n*, %)	1 (1.5)	0	0.8
AMI (*n*, %)	0	0	–
Retroperitoneal haematoma (*n*, %)	0	1 (2.5)	0.8
Re-exploration for bleeding (*n*, %)	0	1 (2.5)	0.8
Mediastinitis (*n*, %)	2 (3)	2 (5)	0.9

CVVH: continuous veno-venous haemofiltration; AMI: acute myocardial infarction; EE: edge-to-edge.

(*P* = 0.5). Other associated procedures were tricuspid valve repair in 14 patients who had concomitant secondary tricuspid regurgitation 3+ or 4+ regardless of the size of the annulus (13.3%), bipolar radiofrequency ablation of permanent atrial fibrillation in 15 (14.2%) and cardiac support device (CorCap, ACORN Cardiovascular) implant in 2 (1.9%). To decrease the afterload in the early phase after mitral repair, prophylactic support with intra-aortic balloon pump was used in 75 patients (71.4%), with no significant differences between the 2 groups (*P* = 0.6).

Clinical hospital outcomes

Overall hospital mortality was 2.8% (3/105 patients) with no significant differences between the EE (3%, 2/65) and the isolated annuloplasty groups (2.5%, 1/40) (*P* = 1.0). The cause of death was ventricular arrhythmia in 1 and low cardiac output in 2 patients. Postoperative complications are reported in Table 2. No significant differences were observed in terms of acute renal failure requiring continuous veno-venous haemofiltration, low output syndrome, cerebrovascular accident, respiratory failure requiring tracheostomy, acute myocardial infarction, sepsis and mediastinitis between the two groups.

Echocardiography at hospital discharge

A TTE was performed at discharge in all hospital survivors. For the 3 surgical patients who died in the hospital, the last TTE before death was considered. No or mild MR was present in 94 patients (94/105, 89.5%) and moderate MR (2+/4+) in 11 patients (10.4%). Out of those 11 patients with residual 2 + MR, 5 (5/65, 7.6%) belonged to the EE group and 6 (6/40, 15%) to the annuloplasty one (*P* = 0.3).

Follow-up

Clinical outcomes. All patients had periodical echocardiographic and clinical follow-up. The last assessment was performed within the previous 12 months in all surviving patients with the exception of 11 patients who had their last evaluation performed more than 12 months before the year of the study (2014) and who were

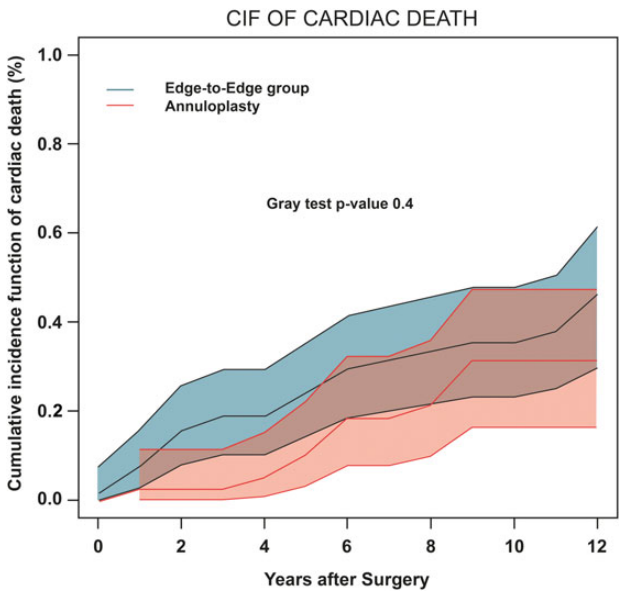

Figure 2: Cumulative incidence function of cardiac death in the two groups.

therefore considered lost to follow-up (follow-up completeness 90%). The mean length was 7 ± 3.9 years (median 7.2 years, IQR 4.3;10.4). At 10 years, overall survival was not significantly different in the annuloplasty and in the EE groups (55 ± 8.4 vs 42 ± 6.7%, *P* = 0.2). Cumulative incidence functions of cardiac death were similar as well (at 10 years, 34.3 ± 8.1 vs 37.9± 6.4%, respectively, Gray test *P*-value 0.4) (Fig. 2). During follow-up, 18 patients died in the annuloplasty group and the cause was cardiac related in 11 of them: CHF (6 patients), sudden death (1 patient), RV failure following heart transplantation (1 patient), stroke due to MV endocarditis (1 patient), cerebral bleeding after percutaneous transluminal coronary angioplasty (PTCA) (1 patient), aortic dissection following pulmonary valve replacement (1 patient). In the EE group, 34 patients died and 22 deaths were cardiac related: CHF (12 patients), sudden death (5 patients), acute myocardial infarction (2 patients), RV failure following heart transplantation (2 patients) and RV failure after left ventricular assist device (LVAD) implantation (1 patient).

The semiparametric proportional hazard model for the subdistribution hazards proposed by Fine and Gray was used to

identify potential predictors of cardiac mortality in the overall study population. After adjusting for the preoperative variables of Table 1 significantly associated with the event in univariate analysis, NYHA class III–IV was the only factor related to cardiac death, with an adjusted hazard ratio (HR) of 3.61 [95% confidence interval (CI) 0.94–13.90, *P*-value 0.06].

Eleven patients required a new cardiac operation during follow-up: 7 in the annuloplasty group (7/39, 17.9%) and 4 in the EE one (4/63, 6.3%) ($P = 0.09$). Three patients underwent conventional MV replacement, 2 patients transapical Sapient XT valve-in-ring implantation, 1 patient with recurrent MR after a 27-mm flexible ring underwent a rerepair with an undersized Carpentier rigid ring. In addition, 1 patient underwent pulmonary valve replacement, 3 patients heart transplantation and 1 patient LVAD implantation.

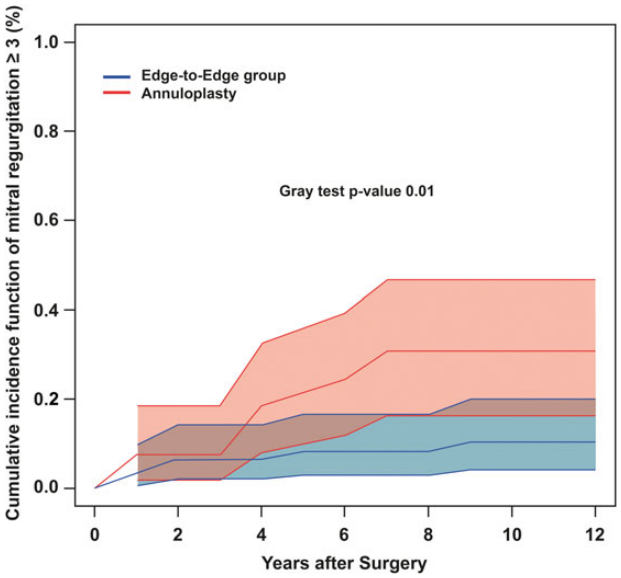

Figure 3: Cumulative incidence function of recurrent mitral regurgitation ≥3+ in the two groups.

Recurrence of mitral regurgitation. At 10 years, cumulative incidence function of recurrence of MR ≥3+ was lower in the EE patients compared with those treated with the annuloplasty alone (10.3±4.1 vs 30.8±8.0%, $P = 0.01$) (Fig. 3). After adjusting for preoperative variables of Table 1 significantly associated with the event in univariate analysis, isolated annuloplasty (HR 4.84, 95% CI 1.46–16.1, $P = 0.01$) and residual MR >1+ at hospital discharge (HR 5.25, 95% CI 2.00–13.8, $P < 0.001$) were significantly related to the development of MR ≥3 (Table 3). The assumption of hazard-proportionality was considered fulfilled based on the analysis of Schoenfeld residuals and the tests for time-invariant effect (Kolmogorov–Smirnov test and Cramer-von Mises test; $P = 0.21$ and 0.19, respectively).

In both the groups, the presence at follow-up of MR at least 3+/4+ was associated with recurrence of NYHA III or IV symptoms ($P < 0.001$).

Follow-up echocardiographic data. At the last echocardiogram, 54.92% of the patients (56/102 patients) had no or mild MR, and 28.4% (29/102 patients) showed moderate (2+/4+) mitral insufficiency. Recurrence of 3–4+ MR occurred in 17 patients (16.6%): 11 in the annuloplasty group (11/39, 28.2%) and 6 in the EE group (6/63, 9.5%; $P = 0.03$) (Fig. 4).

In both groups, an improvement in LVEF and LVEDD was observed. In particular, LVEF increased from 29 ± 6.6 to 34 ± 12.5% in the EE group ($P = 0.001$) and from 31 ± 6 to 36 ± 8.3% in the annuloplasty group ($P = 0.006$). The LVEDD decreased from 68 ± 6.3 to 62 ± 9.4 mm in patients who underwent EE repair ($P = 0.001$) and from 67 ± 8.1 to 58 ± 8.8 mm in patients who underwent isolated annuloplasty ($P = 0.0001$). Finally, a more pronounced decrease in the SPAP was documented in the EE group (from 48 ± 13.3 to 38 ± 9.2 mmHg, $P = 0.0001$) than in the annuloplasty group (from 44 ± 14.1 to 40 ± 9.8 mm, $P = 0.08$).

At last follow-up, a significant clinical improvement was also noted in both groups. In the EE group, NYHA III or IV was reported in 86.1% of the patients (56/65) at baseline and in 25.3% (16/63) at follow-up ($P < 0.0001$). In the isolated annuloplasty group, NYHA class III or IV was present preoperatively in 80% of

Table 3: Predictors of recurrence of mitral regurgitation ≥3+ in the overall study population

Preoperative variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.0 (0.9–1.1)	0.6		
Atrial fibrillation	1.1 (0.6–2)	0.5		
Idiopathic DCM	0.84 (0.30–2.4)	0.75		
NYHA class III or IV	1.2 (0.26–5.5)	0.81		
LVEF	0.98 (0.93–0.99)	0.008	0.94 (0.87–1.01)	0.09
SPAP	1.05 (1–1.11)	0.05	1.06 (1–1.14)	0.06
LVEDD	1.04 (0.97–1.12)	0.27		
Isolated annuloplasty	3.35 (1.24–9.04)	0.02	4.84 (1.46–16.1)	0.01
MR >1+ at discharge	4.04 (2.17–7.52)	<0.001	5.25 (2.00–13.8)	<0.001

LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure; LVEDD: left ventricular end-diastolic diameter; DCM: dilated cardiomyopathy; HR: hazard ratio; CI: confidence interval; MR: mitral regurgitation; NYHA: New York Heart Association.

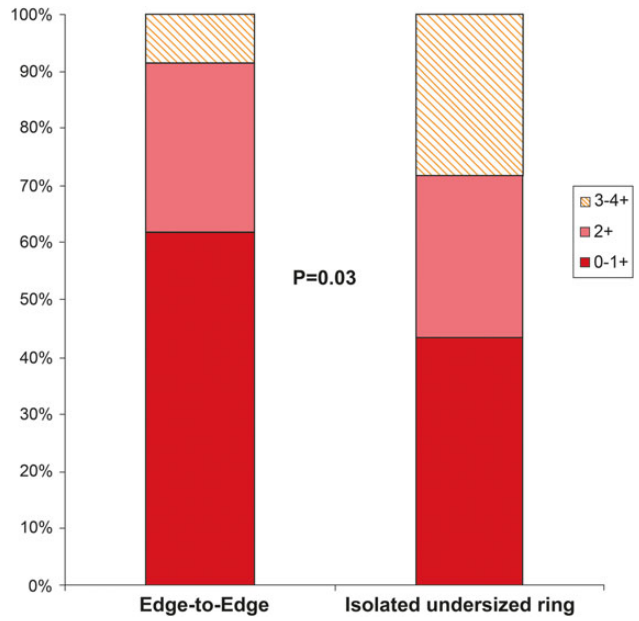

Figure 4: Grade of mitral regurgitation at the last echocardiographic assessment in the two groups.

the patients (32/40) and at last follow-up in 25.6% (10/39) of them ($P < 0.0001$).

DISCUSSION

The main finding of this study is that, in patients with end-stage DCM and secondary MR, the association of the EE technique to the undersized annuloplasty significantly decreases the rate of recurrent MR at long-term compared with restrictive annuloplasty alone.

Mitral repair performed with an undersized rigid complete ring has been considered the reference standard for functional MR for many years [7] although it has been associated with a significant rate of recurrent MR [3, 8, 9]. It is nowadays clear that patient selection should be considered in several echocardiographic predictors of failure of restrictive annuloplasty which have been identified over the years [10]. In particular, more advanced leaflet tethering is an important risk factor for recurrent MR and concomitant techniques to improve durability have been described [11–13]. At the beginning of our experience, one of the few predictors of repair failure, which had already been identified, was a CD of the MV leaflets ≥1 cm. Indeed, the CD is the ultimate mechanism of secondary MR independent of LV function and shape (sphericity index) [17]. At that time, the policy followed in our institution was to treat functional MR by an isolated undersized annuloplasty if the CD was <1 cm. On the other hand, in patients with CD ≥1 cm, the EE technique was routinely combined with the annuloplasty procedure, with the aim of counteracting the increased tethering of the MV leaflets and improving the durability of the repair. In the Cleveland Clinic experience, the EE technique combined with a posterior flexible band annuloplasty had led to disappointing results in patients with secondary MR, mainly due to redilatation of the mitral annulus [18]. To avoid this drawback, in our institution, the EE technique was on purpose always associated with an undersized complete ring (preferentially rigid or semirigid) and the site of leaflet approximation was literally guided by the TEE findings. The aim was to improve the durability of the repair in patients with more pronounced leaflet tethering and avoid MV replacement. In 2005, we first reported the early results of this approach which showed that the recurrence of MR 3+ or 4+ at 18 months was 6-fold lower with the EE compared with the isolated annuloplasty. In addition, freedom from recurrence of severe MR at 1.5 years was 20% higher in the EE group [14]. Those were preliminary results, which needed to be confirmed by a larger number of patients and a significantly longer follow-up. Recently, we compared the outcome of the surgical and percutaneous EE repair in secondary MR, but only at mid-term [19]. In this study we decided to look at the long-term results of this pure surgical strategy (isolated undersized ring versus EE + ring) in a sample size which, meanwhile, had increased about one-third compared with our initial series. It is worth noting that the patients enrolled in this analysis were treated at a time when the MitraClip was not yet available and, therefore, surgery was the only treatment option, even for cases at high surgical risk due to severe LV remodelling and dysfunction. Despite that, hospital mortality was low and similar in the two groups. Clinical and echocardiographic follow-ups were performed in a dedicated outpatient clinic which represents a strength of this study. The data prospectively collected demonstrate that the association of the EE technique with the undersized annuloplasty significantly decreased the rate of recurrent MR at long-term. The cumulative incidence function of recurrence of MR ≥3+ at 10 years was higher in the isolated annuloplasty patients. The main reason that the EE technique is more effective than annuloplasty alone both at early and long-term is most likely represented by the fact that, by ensuring leaflet coaptation exactly where the tethering is more pronounced, the EE is able to counteract or delay its tendency to recur in case of ongoing LV remodelling. Multivariate analysis confirmed that the use of the EE technique was an independent predictor of repair durability at long-term. In addition, it demonstrated that suboptimal initial result begets further MR, emphasizing the importance of patient selection and appropriate surgical technique in order to achieve an immediate perfect competence of the MV.

A surprising and apparently contradictory finding of this study was that this higher repair durability did not translate into a better long-term survival. Indeed, the 10-year overall survival and the cumulative incidence function of cardiac death were not significantly different in the EE and annuloplasty groups. This finding is not in line with previous studies showing that patients with residual or recurrent MR following MV repair for secondary MR had a lower survival compared with those left with a competent MV [8, 20]. One possible explanation might be found in the small number of patients compared. Another possible reason could be represented by the advanced stage of the disease affecting our study population and, in particular, the patients belonging to the EE group who had the more advanced degree of leaflet tethering mirroring a more advanced degree of LV remodelling and dysfunction. The lack of a statistically significant difference in LV size and function in the EE compared with the isolated annuloplasty group might simply be due to the small sample size. The negative prognostic implications of the advanced cardiomyopathy disease might have possibly nullified the survival benefit expected from the greater effectiveness of the EE repair. This hypothesis seems to be confirmed by the fact that most of the cardiac deaths were due to the CHF and by the fact that an NYHA functional class III–IV was noticed in the same proportion of patients (25%) in both the groups, despite the lower rate of repair failure in the EE group.

Indeed, a number of patients undergoing EE repair developed CHF symptoms over time due to their advanced cardiomyopathy disease despite the absence of recurrent MR.

LIMITATIONS

This study has several limitations. The number of patients is relatively small, hence we performed formal tests to check the power of the study for the main outcome of interest, the recurrence of MR at follow-up. We performed power calculations for a time-to event analysis, with recurrence of MR ≥3+ as event, null-hypothesis HR = 1, sample size = 105, proportion of sample in group EE = 62%, Type I error rate = 5% and the computed power was 91%.

The assignment of the patients to one or another technique was based on one of the few predictors of failure of the isolated undersized annuloplasty which had been identified at the time of enrolment. Indeed, we used the CD which is the ultimate mechanism of secondary MR independent of LV function and shape (sphericity index) [17]. A CD of >1 cm is a well-defined predictor of recurrent MV regurgitation and hence the adjunct of EE to annuloplasty has been conceived to reduce the increased risk of MV regurgitation in patients after surgery when compared with patients with CD <1 (annuloplasty group).

More recently, many other predictors of failure of an isolated restrictive annuloplasty have been recognized, but they were not used in the selection of the patients belonging to this series. We cannot exclude that concomitant CABG might have improved by itself ischaemic MR in some patients. However, since there were no differences between the two groups in terms of number of patients undergoing CABG and number of grafts and coronary arteries revascularized, this potential effect should have been similar in the subsets of patients.

Conflict of interest: none declared.

REFERENCES

[1] Magne J, Girerd N, Sénéchal M, Mathieu P, Dagenais F, Dumesnil JG *et al*. Mitral repair versus replacement for ischemic mitral regurgitation: comparison of short-term and long-term survival. Circulation 2009;120: S104–11.

[2] Lorusso R, Gelsomino S, Vizzardi E, D'Aloia A, De Cicco G, Lucà F *et al*. ISTIMIR Investigators. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian Study on the Treatment of Ischemic Mitral Regurgitation (ISTIMIR). J Thorac Cardiovasc Surg 2013;145:128–39.

[3] Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P *et al*. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23–32.

[4] Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg 1995;4:676–83.

[5] Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ *et al*. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. Eur J Cardiothorac Surg 2005;27:847–53.

[6] Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45: 381–7.

[7] Spoor MT, Geltz A, Bolling SF. Flexible versus nonflexible mitral valve rings for congestive heart failure. Circulation 2006;114 (suppl I):I67–71.

[8] McGee EC, Gillinov AM, Blackstone EH, Rajeswaran J, Cohen G, Najam F *et al*. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2004;128:916–24.

[9] Borger MA, Alam A, Murphy PM, David TE. Ischemic mitral regurgitation: repair, replace or revisit? Ann Thorac Surg 2006;81:1153–61.

[10] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H *et al*. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the management of valvular heart disease of the European Society of Cardiology (ECS) and the European Association for Cardio-Thoracic surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

[11] Borger MA, Murphy PM, Alam A, Armstrong S, Maganti M, David TE. Initial results of the chordal-cutting operation for ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2007;133:1483–92.

[12] Langer F, Kunihara T, Hell K, Schramm R, Schmidt KI, Aicher D *et al*. RING +STRING: successful repair technique for ischemic mitral regurgitation with severe leaflet tethering. Circulation 2009;120:S85–91.

[13] Hvass U, Joudinaud T. The papillary muscle sling for ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2010;139:418–23.

[14] De Bonis M, Lapenna E, La Canna G, Ficarra E, Pagliaro M, Torracca L *et al*. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the 'edge-to-edge' technique. Circulation 2005; 112 (9 Suppl): I402–8.

[15] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA *et al*. Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.

[16] La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O. Echocardiography during infusion of dobutamine for identification of reversibly dysfunction in patients with chronic coronary artery disease. J Am Coll Cardiol 1994;23:617–26.

[17] Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation 2000;102:1400–6.

[18] Bhudia SK, McCarthy PM, Smedira NG, Lam B, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. Ann Thorac Surg 2004;77:1598–606.

[19] De Bonis M, Taramasso M, Lapenna E, Denti P, La Canna G, Buzzatti N *et al*. MitraClip therapy and surgical edge-to-edge repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: mid-term results of a single-centre experience. Eur J Cardiothorac Surg 2016;49:255–62.

[20] Crabtree TD, Bailey MS, Moon MR, Munfakh N, Pasque MK, Lawton JS *et al*. Recurrent mitral regurgitation and risk factors for early and late mortality after mitral valve repair for functional ischemic mitral regurgitation. Ann Thorac Surg 2008;85:1537–42.

APPENDIX. CONFERENCE DISCUSSION

Dr R. Weisel *(Toronto, Canada):* I have two questions for you.

The first one, did you compare apples to apples? Did you ever do a propensity analysis to actually have two groups which had the same substrate?

Dr De Bonis: The two series were not that much different if you look at the data. The main difference was related to the tethering indexes, which are of course a marker of remodeling of the left ventricle. But nevertheless the difference in terms of both ejection fraction, diastolic diameter, end–diastolic volume and so on was not statistically different between the two groups. So the main difference was in terms of the tethering index. From that point of view, there are apples and oranges. And I agree with you. What about the propensity? That is your question. Well, I think, first of all, if you do propensity matching you will decrease the number of patients because you have to get comparable patients, and the number of patients to start with was too low to further reduce that. Also, the second point is that it is very difficult, because, per protocol, we decided that those who had more tethering were assigned to the edge–to–edge group and those with less tethering to the other one. So this variable could not really be somehow adjusted, because, per protocol, it was decided like that. So one group would always have higher tethering.

Dr Weisel: So either you can compare them or you can't compare them?

Dr De Bonis: I think we can compare them.

Dr Weisel: So the idea of the propensity matching is you match patients individually, not by groups. Anyway it is a good idea.

The second question relates to the ischemic mitral group. We just heard a few minutes ago that they are a different group than the non-ischemic, and

what were the results in the ischemic, and was this repair just as good in ischemic as it was overall?

Dr De Bonis: Yes. The ischemic patients out of the entire population were indeed 69, so 65% of the population. The freedom from recurrent mitral regurgitation was 20% higher, in the edge-to-edge group compared to the isolated annuloplastry being at 6 year 90% in the edge-to-edge group and 70% in the isolated annuloplasty one.

Did that answer your question?

Dr Weisel: I think so. In the CTS Net trial that you talked about, we found that inferior basilar dyskinesia was the major predictor of recurrent MR. Was that in your series as well?

Dr De Bonis: Yes. That is very important. We were unable to look for that because we were unable retrospectively to identify those with a real inferior scar. We had it in some of them but not in all.

But this point is very important, because we published another specific paper on that. When we assessed the results in this setting, ischemic mitral regurgitation, of the Geoform ring, which is a saddle-shaped ring to fit ischemic mitral regurgitation the most important predictor of recurrent mitral regurgitation was inferior akinesia. When we used that ring, the tethering of the posterior leaflet by applying the ring became even worse because of the inferior akinesia, and we had a recurrent eccentric jet at follow-up. So I think it is a very important point although we were unable to assess that in this series.

Dr V. A. Subramanian *(New York, NY, USA):* Even though you talk about the CTS Net trial, there are two things that have got to be provocative in these talks, and they are very provocative. The problem is that you have a high recurrence very early, within one month. When you leave the operating room our pre-discharge echo shows only trace mitral regurgitation, and how do you explain one month early recurrence in any of these studies?

My question to you, Michele, is that it's very interesting that you had early some mitral regurgitation, whether residual or recurrent, however you want to define that, and it is at one period, and then at a prolonged period you have an increase in mitral regurgitation. So we really don't understand the mechanism of recurrence of mitral regurgitation today. We blame it on left ventricular dilatation. Absolutely no data. The data is predated like 2004; fraud data. We can go through that. So the mechanism is still not understood.

Perhaps from the Evalve work we see 2+ MR, but we have active remodeling. To me I think it will be either preventing some of the enlarging effect of the leaflet or preserving the annular function. We somehow forget the annular function is still important. Because most of the papillary muscle and chordae sits in the commissure, the force distributed from the ventricle to the annulus is very high. It is very difficult to understand, so we need to figure out our understanding.

It would be nice if you had done an edge-to-edge with no annuloplasty and shown this end result; it would have been phenomenal.

Dr De Bonis: Can I give you my impression rather than my science. Our strength point is that we have had a dedicated outpatient clinic for those patients since the year 2000. So we have been following them for 15 years. The first point I would like to make is that these are very sick patients and we should not wait that long. These are patients with 200 ml of end-diastolic volume and an ejection fraction of 29% with severe mitral regurgitation, which means 20% or 25% of true EF. So to me in these patients we don't see a difference in terms of mortality, because once those ventricles are so sick, even if you get less recurrent mitral regurgitation the history of the disease goes by itself.

And the second point I would like to make is that the edge-to-edge is able to force a cooptation more than the ring, because you suture the leaflets together. You get reverse remodeling at the beginning, but then if you get still ongoing remodeling, even the edge-to-edge is going to fail anyway.

Dr J. Obadia *(Lyon, France):* What is impressive in your study is that you have better results in the worst group. Would this lead you to add the edge-to-edge even if the tethering is below 10 mm?

Dr De Bonis: That's interesting. My answer is that is that in this population, probably too sick, today we would not consider surgery. If you wait for the patient to become so sick, then you are not really able to impact on the mortality. Probably the MitraClip is going to be less effective but even safer.

The key point is that you should do what you said in an earlier stage when you really can reverse the LV re-modelling and this is against all the guidelines we have. So we are in a vicious cycle. We have to wait because the guidelines tell us to wait; we wait; they become too sick and it is too late.

Dr A. Moritz *(Frankfurt, Germany):* You didn't refer to gradient. Sometimes these restrictive mitral valves on their own have some gradient because they don't open regularly. And the other thing, if you do the edge-to-edge repair, you resemble the MitraClip so that you slip the repair somewhat into the leaflet or do you simply perform a true edge-to-edge, sewing only the closing edges together?

Dr De Bonis: That's completely different in degenerative and in functional mitral regurgitation. If you have degenerative mitral regurgitation you have a lot of tissue and you can do what you mean. You can plicate the leaflets into the ventricle just like the MitraClip does; you can counteract prolapse. In functional MR the leaflets are completely different, and you can just do a small suture approximating the free edge. So you cannot invaginate the leaflets into the ventricle.

As far as gradients are concerned, this is a history we have asked ourselves for many, many years; we have done exercise tests in those patients. I have never seen one single patient—we have been operating like that on more than 500—one single patient with a problem of stenosis. We never had to re-operate on a patient for stenosis and no patients have ever been clinically symptomatic for stenosis. Those patients do not do marathons, and if you do an exercise test certainly you will get 5 mmhg as a mean gradient but this will not have any clinical relevance.