Effects of Valve Replacement for Aortic Stenosis on Mitral Regurgitation

Philippe Unger, MD, PhD[a,*], Danièle Plein, MD[d], Guy Van Camp, MD, PhD[e], Bernard Cosyns, MD[f], Agnès Pasquet, MD, PhD[g], Valérie Henrard, MD[h], Didier de Cannière, MD, PhD[b], Christian Melot, MD, PhD[c], Luc A. Piérard, MD, PhD[h], and Patrizio Lancellotti, MD, PhD[h]

We aimed to prospectively and quantitatively assess the effects of aortic valve replacement (AVR) for aortic stenosis (AS) on mitral regurgitation (MR) and to examine the determinants of the changes in MR. Fifty-two patients with AS scheduled for AVR were included if holosystolic MR not being considered for replacement or repair was detected. MR was quantified using the proximal isovelocity surface area method before and 8 ± 4 days after surgery. Mitral valvular deformation parameters did not change significantly, but the mitral effective regurgitant orifice (ERO) and regurgitant volume decreased from 11 ± 6 mm^2 to 8 ± 6 mm^2 and from 20 ± 10 ml to 11 ± 9 ml, respectively (both $p < 0.0001$). Using multiple linear regression analysis, preoperative severity of MR, mitral leaflet coaptation height, and end-diastolic volume decrease were independently associated with postoperative reduction in MR, whereas changes in mitral valve morphology after surgery were not. MR etiology did not predict the reduction in MR. In conclusion, the decrease in MR observed in most patients after AVR is associated with the magnitude of acute left ventricular reverse remodeling. As the reduction in left ventricular systolic pressure contributes to the decrease in regurgitant volume, the preoperative quantitative assessment of MR should best be performed by measurement of the ERO. **(Am J Cardiol 2008;102:1378–1382)**

Mitral regurgitation (MR) is a common finding in patients with aortic stenosis (AS). The severity of the MR increases over time in relation to the increase in transaortic pressure gradient.[1] At the time of aortic valve replacement (AVR), up to two-thirds of patients with AS exhibit varying degrees of MR.[2] Because combined aortic and mitral valve replacement markedly increases the operative risk and affects long-term morbidity and mortality,[3,4] it has been suggested that MR does not require specific treatment because downgrading of MR usually occurs after isolated AVR. In fact, AVR for AS, by reducing left ventricular (LV) afterload, might have the potential to improve mitral valve competence through reverse LV remodeling and reduced mitral annular size. Several authors[2,5-13] have attempted to determine predictive factors for MR changes after surgery. However, these studies, mostly limited by their retrospective nature and/or by the qualitative or semi-quantitative assessment of MR, have given conflicting results. Indeed, the percentage of patients with reduced MR ranges from >80%[9] to <30%.[8] No study has used a quantitative method for assessing MR in this setting. The extent and determinants of changes in MR after AVR, therefore, remain to be determined. Whether postoperative changes in MR reflect LV hemodynamics or LV and mitral valve geometric changes is unknown. We therefore aimed to prospectively and quantitatively assess the effects of AVR on MR severity and to examine the determinants of postoperative changes in MR.

Methods

Patients were included in this multicenter study if they presented with severe AS and were scheduled for AVR and had at least mild holosystolic MR. Patients with MR being considered for a concomitant mitral valve procedure were excluded, as were patients with previous mitral valve surgery, technically inadequate echocardiogram, or greater than moderate aortic regurgitation (vena contracta width >6 mm). Patients were also subsequently excluded from the study if any surgical procedure on the mitral valve (repair or replacement) was performed. The final study group consisted of 52 patients. Coronary angiography was performed in all patients. Significant coronary artery disease was considered to be present if ≥50% narrowing of ≥1 coronary artery was present. Patients gave their informed consent, and the protocol was approved by the ethics committee of each institution.

Echocardiographic examinations were performed using either a Vivid 7 system (GE Healthcare, Little Chalfont,

[a]Department of Cardiology, [b]Department of Cardiac Surgery, and [c]Intensive Care Unit, ULB-Erasme Hospital, Brussels, Belgium; [d]Department of Cardiology, Clinique Saint-Jean, Brussels, Belgium; [e]Department of Cardiology, Universitair Ziekenhuis-UZ Brussel, Brussels, Belgium; [f]Department of Cardiology, CHIREC-Hôpital de Braine-l'Alleud; [g]Department of Cardiology, UCL-Cliniques Universitaires Saint-Luc, Brussels, Belgium; and [h]Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium. Manuscript received May 21, 2008; revised manuscript received and accepted July 13, 2008.

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*Corresponding author: Tel: +3225553907; fax: +3225554609.

E-mail address: philippe.unger@erasme.ulb.ac.be (P. Unger).

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Table 1
Hemodynamic and geometric changes after aortic valve replacement

Parameters	Preoperative n = 52	Postoperative n = 52	p Value
Maximal transaortic pressure gradient (mm Hg)	71 ± 25	25 ± 10	<0.0001
Mean transaortic pressure gradient (mm Hg)	42 ± 16	13 ± 6	<0.0001
Aortic valve area (cm^2)	0.59 ± 0.19	1.41 ± 0.27	<0.0001
Heart rate (beats per minute)	80 ± 17	82 ± 16	0.34
Systolic arterial pressure (mm Hg)	124 ± 19	124 ± 21	0.85
Sinus rhythm/Atrial fibrillation	42/10	40/12	0.81
Left ventricular end-diastolic diameter (cm)	5.06 ± 0.67	4.79 ± 0.69	0.0001
Left ventricular end-systolic diameter (cm)	3.65 ± 0.94	3.36 ± 0.80	0.0004
Left ventricular end-diastolic volume (ml/m^2)	94 ± 37	80 ± 32	<0.0001
Left ventricular end-systolic volume (ml/m^2)	53 ± 35	40 ± 27	<0.0001
Left ventricular ejection fraction (%)	49 ± 16	54 ± 14	0.0003
Left ventricular mass (g)	279 ± 111	258 ± 93	0.005
Left atrial area (cm^2)	21 ± 5	21 ± 6	0.94
Ratio of regurgitant jet area to left atrial area (%)	29 ± 15	18 ± 13	<0.0001
Time velocity integral of mitral regurgitant jet*	181 ± 34	137 ± 3	<0.0001
Maximal velocity of mitral regurgitant jet*	591 ± 69	508 ± 63	<0.0001
Mitral regurgitant volume (ml)	19.6 ± 10.0	11.3 ± 8.9	<0.0001
Mitral effective regurgitant orifice (mm^2)	11.2 ± 6.1	8.1 ± 6.3	<0.0001
Mitral tenting area (cm^2)	2.73 ± 0.92	2.61 ± 0.77	0.27
Mitral coaptation height (cm)	0.90 ± 0.31	0.84 ± 0.32	0.07

* Analysis restricted to 46 patients because 6 patients had no postoperative MR.

United Kingdom) or a Philips IE33 system (Philips Medical System, Andover, Massachusetts). Data were recorded in digital format and stored on optical or digital video disks for off-line analysis and were sent to a core echocardiographic laboratory (Erasme Hospital). Quantitation of MR was performed by the proximal isovelocity surface area method as previously described.[14] Briefly, the radius was measured from frames with optimal flow convergence. The largest radius, usually in midsystole, was selected for analysis. The mitral valve effective regurgitant orifice (ERO) was calculated as the ratio of regurgitant flow to peak regurgitant velocity, and the regurgitant volume as the product of the ERO and the time velocity integral of the regurgitant flow. For the postoperative examination, we assumed that regurgitant flow was zero when holosystolic proximal isovelocity surface area or MR continuous wave Doppler signal was absent. LV end-diastolic and end-systolic volumes and ejection fraction were measured by the biapical modified Simpson disk method. The valvular tenting area—the area enclosed between the annular plane and the mitral leaflets—was obtained from the parasternal long-axis view at midsystole.[15] The distance between leaflet coaptation and the mitral annulus plane (coaptation height) was measured in the apical 4-chamber view.

Left atrial area and regurgitant jet area were measured by planimetry from the apical 4-chamber view, allowing calculation of the ratio of regurgitant jet area to the left atrial area. Systolic pulmonary artery pressure was estimated from the systolic transtricuspid pressure gradient (in mm Hg) using the modified Bernoulli equation ($\Delta P = 4\ V^2$, where V = maximal tricuspid insufficiency velocity in m/s).

The etiology of MR was determined on the preoperative echocardiogram and categorized as (1) functional, if occurring without valvular morphologic abnormality (except minor an-

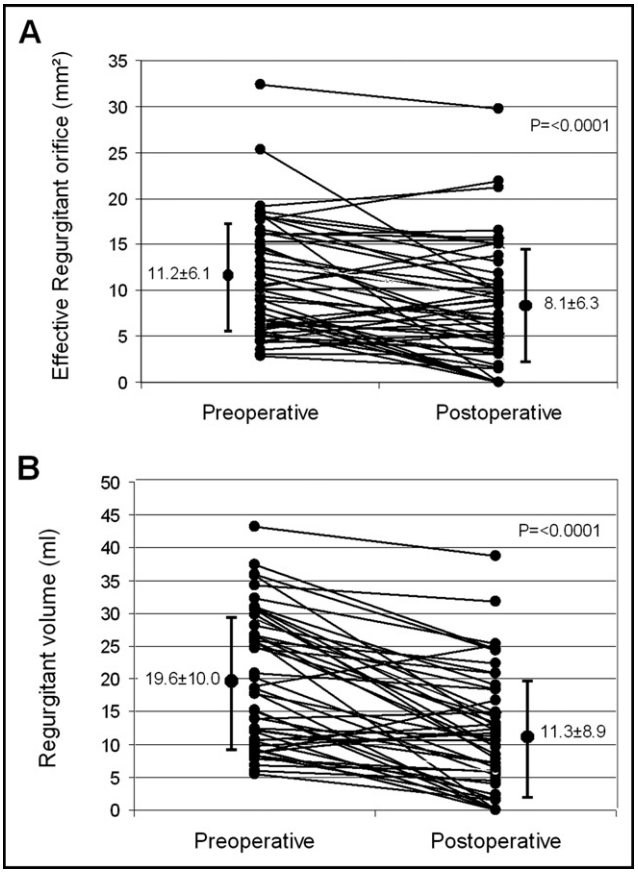

Figure 1. Changes in quantified mitral regurgitation after aortic valve replacement. Effective regurgitant orifice *(Panel A)*; regurgitant volume *(Panel B)*.

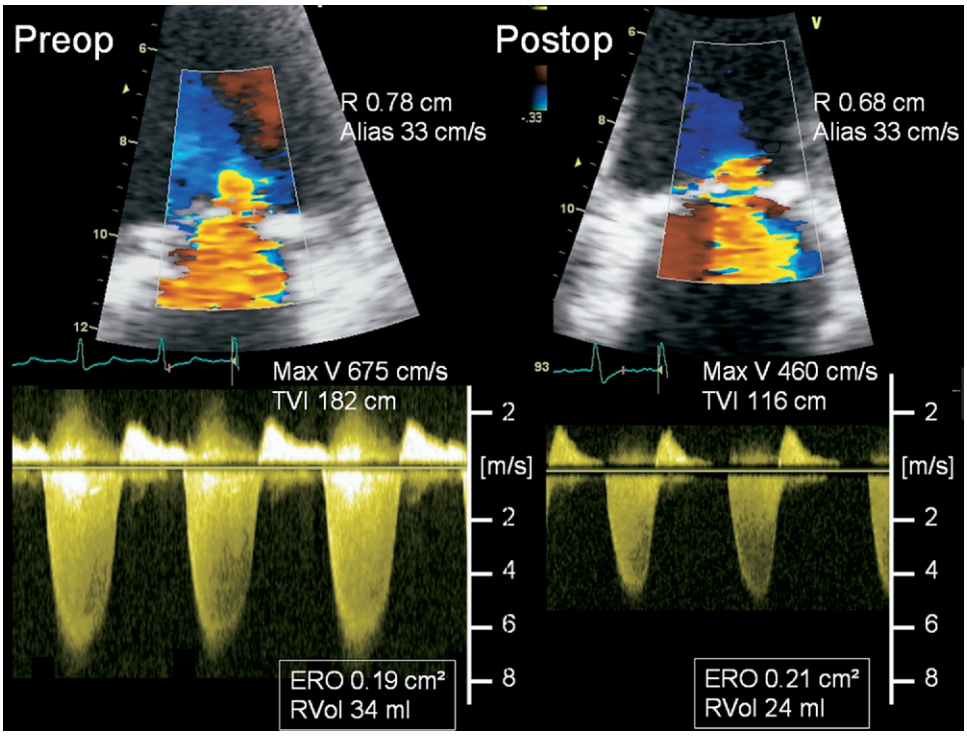

Figure 2. Example of changes in mitral regurgitation induced by aortic valve replacement. Apical 4-chamber view showing proximal flow-convergence region at baseline *(Preop)* and after aortic valve replacement *(Postop)*, and typical pattern of regurgitant volume *(Rvol)* reduction. There is no significant change in calculated effective regurgitant orifice *(ERO)*, whereas regurgitant volume markedly decreases as a result of reduction in the time velocity integral *(TVI)* of regurgitant jet. R = proximal isovelocity surface area (PISA) radius; Alias = aliasing velocity; Max V = maximal regurgitant flow velocity.

nular calcifications), with or without wall motion abnormalities or LV dysfunction; or (2) organic, if associated with evidence of leaflet, annular, chordal, or papillary muscle pathology. Patients were categorized by 2 independent observers (PU, PL) and in cases of discordance, by consensus.

Continuous variables were reported as means and SD and compared with a Student's *t* test. One-way analysis of variance (for repeated measurements, when appropriate) was used to compare more than 2 groups. If continuous variables were not normally distributed, comparisons were made using a Wilcoxon rank sum test and Kruskal-Wallis nonparametric tests. Categorical variables were reported as percentages and were compared using the Fisher's exact test. A value of $p < 0.05$ was considered significant. Simple and multiple regression analysis using backward elimination were used to study the relationship between changes in ERO and in regurgitant volume (dependent variables) after AVR, and preoperative clinical and echocardiographic variables (independent variables). A value of $p < 0.10$ was considered significant to enter the variable into the multivariate model. A similar analysis was performed to study the determinants of AVR-induced changes in ERO and in regurgitant volume by examining the relationship between changes in ERO and in regurgitant volume (dependent variables) and perioperative changes in echocardiographic variables (independent variables).

Results

The mean age was 77 years and the men/women ratio was 22/30. Echocardiography was performed 6.3 ± 10.8 days (median 1.5 days) before and 8.3 ± 4.1 days (median 7 days) after surgery. Functional MR was observed in 28 patients; 24 patients had organic (or mixed) MR, which consisted in moderate to severe calcific mitral valve disease in all patients except 1 with mitral valve prolapse. Twenty-eight patients had coronary artery disease, among whom 19 underwent concomitant coronary bypass grafting (3 other patients had had previous coronary artery revascularization and the remaining 6 had distal lesions, considered unsuitable for revascularization). Forty-seven patients received a bioprosthetic and 5 a mechanical aortic valve. Atrial fibrillation was observed preoperatively in 10 subjects and postoperatively in 12.

The hemodynamic and geometric changes after AVR are listed in Table 1. Mitral ERO and regurgitant volume both decreased (Figure 1). After surgery, there was a decrease in the average individual percentage decrease in ERO (25% ± 46%) and in regurgitant volume (40 ± 41%), and in the ratio of the regurgitant jet to left atrial area (37% ± 38%). The difference in reduction was significant between ERO and regurgitant volume ($p < 0.0001$) and between ERO and the ratio of regurgitant jet to left atrial area ($p = 0.034$). In addition, the degree of change in MR was highly variable from patient to patient. An example is presented in Figure 2. Thirty-six patients (69%) experienced a decrease in ERO (mean decrease 5.4 ± 3.9 mm^2, range 0.5 to 18.2 mm^2), 45 patients (87%) a decrease in regurgitant volume (mean decrease 10.1 ± 6.6 ml, range 0.1 to 25.9 ml), and 43 (83%) a decrease in the regurgitant jet to left atrial area ratio (mean decrease 51% ± 25%). For those who had either no change or an increase in MR, the

Table 2
Preoperative predictors of decrease in mitral regurgitation after aortic valve replacement

Predictors	Univariate Analysis	
	p	R
Mitral effective regurgitant orifice reduction		
Left ventricular mass	0.01	0.35
Left ventricular end-diastolic volume	0.02	0.32
Left ventricular end-systolic volume	0.02	0.31
Left ventricular ejection fraction	0.046	−0.28
Mitral effective regurgitant orifice	0.009	0.36
Mitral regurgitant volume	0.049	0.27
Left atrial surface	0.03	0.30
Mitral coaptation height	0.008	0.37
Transtricuspid systolic pressure gradient	0.095	0.25
Mitral regurgitant volume reduction		
Diastolic arterial blood pressure	0.07	−0.26
Left ventricular mass	0.02	0.31
Left ventricular end-diastolic volume	0.09	0.23
Mitral effective regurgitant orifice	0.0005	0.46
Mitral regurgitant volume	0.0001	0.53
Left atrial area	0.002	0.43
Mitral coaptation height	0.03	0.30
Mitral tenting area	0.02	0.32

Only parameters with a value of $p < 0.10$ are presented.

Table 3
Postoperative echocardiographic parameters associated with mitral regurgitation decrease (expressed as preoperative minus postoperative values)

Determinants	Linear Regression	
	P	R
Reduction in effective regurgitant orifice		
Reduction in left ventricular end-diastolic volume	<0.0001	0.56
Reduction in left ventricular end-systolic volume	0.0001	0.52
Reduction in regurgitant volume		
Reduction in left ventricular end-diastolic volume	0.0009	0.45
Reduction in left ventricular end-systolic volume	0.02	0.32

increase in ERO was 2.1 ± 1.6 mm^2 (range 0.1 to 4.8 mm^2), the increase in regurgitant volume was 3.4 ± 2.9 ml (range 1.1 to 8.1 ml), and the increase in the regurgitant jet to left atrial ratio was 27 ± 19% (range 5% to 69%). Thirteen patients (25%) had an ERO ≥15 mm^2 preoperatively, compared with 8 (15%) postoperatively ($p = 0.33$); 23 patients (44%) had a regurgitant volume ≥20 ml preoperatively, and 9 (17%) postoperatively ($p = 0.005$).

MR etiology did not affect the magnitude of ERO changes ($p = 0.31$), but the change in regurgitant volume was larger in patients with organic MR (6.2 ± 6.4 ml vs 10.6 ± 8.6 ml for functional and organic MR, respectively; $p = 0.04$). Changes in MR were not predicted by the presence of coronary artery disease ($p = 0.52$ and 0.66 for ERO and regurgitant volume, respectively), or the need for revascularization by bypass grafting ($p = 0.76$ and 0.74 for ERO and regurgitant volume, respectively). The preoperative predictors of decrease in MR are listed in Table 2. Using multiple linear regression analysis, preoperative ERO ($p = 0.036$) and mitral coaptation height ($p = 0.03$) were independently associated with the decrease in ERO; only preoperative regurgitant volume ($p = 0.0001$) remained associated with the decrease in regurgitant volume. In multiple linear regression analysis, MR etiology was no longer an independent predictor of the regurgitant volume reduction.

The decreases in ERO and in regurgitant volume were associated with a reduction in LV volumes (Table 3) but not with an improvement in mitral tenting area ($p = 0.26$ and $p = 0.21$, respectively) or in coaptation height ($p = 0.29$ and $p = 0.18$, respectively). By multivariable analysis, only the reduction in LV end-diastolic volume was associated with a decrease in ERO and in regurgitant volume ($p < 0.001$ for both variables).

Discussion

The main findings of this prospective study are (1) after isolated AVR for AS, most patients exhibit a significant reduction in the quantified degree of MR; (2) the improvement in regurgitant volume is more pronounced than the reduction in ERO, the latter being a true marker of lesion severity; (3) this postoperative improvement in MR is mainly related to the severity of preoperative MR and the extent of mitral valvular deformation (coaptation height); and (4) the reduction in MR is associated with the magnitude of LV acute reverse remodeling, namely the decrease in LV end-diastolic volume.

Several studies have described a reduction in the MR color jet area after AVR for AS, but there has been much debate regarding the magnitude of this decrease and the number of patients who improve.[2,5-13] In addition, the timing of the postoperative echocardiographic examination varied markedly among studies, ranging from the early postoperative period [6,12] to 18 months after surgery.[5] To the best of our knowledge, the present study is the first to prospectively assess the magnitude of changes in the quantified degree of MR. After AVR, MR severity, as assessed by the ERO and the regurgitant volume, decreased in most patients, although it increased slightly in a minority of the patients. The improvement was more pronounced in patients with the most severe MR, regardless of whether the MR was organic or functional. The mean reduction was greater for the regurgitant volume (40%) and the color flow mapping of the regurgitant jet (37%) than for the mitral ERO (25%), emphasizing the importance of the reduction in systolic LV pressure. About 46% of our patients with a preoperative ERO ≥10 mm^2 improved and attained an ERO <10 mm^2. Using a cut-off of 15 ml for regurgitant volume, MR improved of category in 60% of patients.

In aortic valve stenosis, MR may be functional, organic, or both. In addition to the presence of concomitant structural mitral valve abnormalities, MR has been linked to various geometric and hemodynamic changes. Preoperatively, the following parameters have been shown to be associated with a decrease in severity of MR: LV mass,[11,12] LV function,[9] left atrial diameter,[5] and the degree of MR.[7] In the present study, only the preoperative severity of MR and the extent of mitral valvular deformation as assessed by the coaptation height emerged as independent predictors of postoperative improvement in MR.

Unlike several previous reports[6,13] that described a larger surgery-induced improvement in MR in patients with functional MR, whether MR was functional or not in the present study was not predictive of improvement in MR. This discrepancy may be related to the relatively small number of patients with purely functional MR in the study by Barreiro et al.,[6] to the different time-delay of the postoperative echocardiographic study (up to 1 year in the study by Vanden Eynden et al.[13]), and to the predominance of calcific mitral valve disease in our elderly population. The coaptation height—a marker of increased tethering forces—is expected to be higher in patients with functional MR. It could thus be presumed that the larger the preoperative valvular deformation—reversible lesion—the greater would be the decrease in MR after AVR. Reduction in MR was determined by the acute reverse LV remodeling as assessed by the LV end-diastolic volume. Changes in LV shape and geometry might, thus, also contribute to improved MR through a decrease in mitral tethering forces.[16,17] However, neither the changes in mitral valve deformation parameters nor the changes in LV performance were predictive of MR improvement. Such LV remodeling is probably the consequence of correction of afterload mismatch. Whether progressive reverse LV remodeling could induce further MR reduction over time needs to be addressed by long-term serial echocardiographic studies. The decrease in regurgitant volume outweighed the reduction in ERO. The regurgitant volume is determined by the ERO, the systolic pressure gradient across the orifice and the duration of systole.[18,19] As LV cavity pressure drops early after surgery, the transmitral pressure gradient decreases, resulting in MR improvement. Indeed, the reduction of the time-velocity integral of the continuous-wave spectra of MR and of the LV to left atrial pressure difference contributed markedly to the decrease in regurgitant volume. This observation differs from the changes reported after afterload reduction induced by vasodilator therapy in heart failure patients with dynamic MR, in which the time-velocity integral and the systolic blood pressure to left atrial pressure gradient remain unaltered.[20] Taken together, these results suggest that systolic LV pressure reduction is a main contributor to the early postoperative reduction in regurgitant volume, whereas correction of mitral valve geometry plays little or no role.

The effects of changes in medical treatment after AVR were not taken into account. However, systolic blood pressure did not change significantly. Moreover, the main change was a reduction in regurgitant volume, making an effect of vasodilator therapy less likely; the pharmacological reduction of LV filling pressure and systemic vascular resistance have been shown to translate into a reduction in regurgitant volume mainly through a decrease in ERO and not through a change in the pressure gradient across the mitral valve.[20] Because of the design of the study, no patient had severe MR. Indeed, the presence of severe MR was an obvious indication to proceed to double valve surgery. A high percentage of our study population consisted of elderly patients, which is reflected by the large number of calcified mitral valve disease. Whether our results are applicable to younger patients remains uncertain; one may hypothesize that the frequent occurrence of annular calcification in our population may be associated with a more fixed regurgitant orifice. The possible effects of prosthesis–patient mismatch were not examined. Finally, long-term serial echocardiographic studies are required to assess the effects of progressive LV and mitral remodeling over time and the prognostic importance of MR quantification in this clinical setting.

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