Asynchronous Movement of Mitral Annulus: An Additional Mechanism of Ischaemic Mitral Regurgitation

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Summary

In-coordinate mitral annulus movement might participate in the pathogenesis of functional mitral regurgitation. We evaluated a relationship between indices of mitral annulus systolic asynchrony and mitral regurgitation in patients after myocardial infarction in order to determine independent determinants of effective regurgitant orifice (ERO) area in a multivariate regression model.

Tissue Doppler echocardiographic studies and quantitative analysis of mitral regurgitation were performed in 40 patients (33 men, 7 women, mean age 60.1 ± 9.2 years) with a history of Q-wave myocardial infarction, with and without significant functional mitral regurgitation.

A multivariate regression model showed that mitral annulus movement asynchrony index—difference between the longest and the shortest time from the R wave in the electrocardiogram to the cessation of systolic movement of the four aspects of mitral annulus, is an independent from ejection fraction, sphericity index, tenting, annulus diameter and infarct location, determinant of mitral regurgitation ERO area (r^2 change 0.72, $p \leq 0.01$). The only other independent predictor of ERO area was mitral annulus diameter (r^2 change 0.79, $p \leq 0.01$). Other variables were predictors of ERO only in univariate analyses: ejection fraction (r^2 change 0.59,

$p \leq 0.01$), tenting area (r^2 change 0.76, $p \leq 0.01$) and sphericity index (r^2 change 0.75, $p \leq 0.01$).

In conclusion, mitral annulus asynchrony is an additional mechanism contributing to the development of functional mitral regurgitation. This suggests, that cardiac resynchronization might be considered, either as a first line intervention in patients with mitral regurgitation not considered for mitral surgery or as a supplementary measure, when results of surgery are suboptimal.

Key words: ischaemic mitral regurgitation, mitral annulus, asynchrony

Clin. Cardiol. 2007; 30: 512–516.

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Introduction

Ischaemic cardiomyopathy is associated with left ventricular remodeling.^{1,2} Tethering of mitral leaflets restricts their effective closure and, together with mitral annular dilatation, reduces the coaptation reserve.^{3–5} Any further imbalance of the mitral-ventricular complex may aggravate mitral regurgitation (MR).^{6,7}

In animals with ischaemic MR both systolic leaflet “loitering” and regional interscallop malcoaptation were described.^{4,8} Asynchronous left ventricular long axis function is present also in humans. It might cause disorganized tethering of subvalvular mitral valve apparatus, with subsequent in-coordinate leaflet coaptation and functional MR. To prove this association we evaluated a relationship between indices of mitral annulus systolic asynchrony and qualitative and quantitative measures of MR after myocardial infarction.

Methods

We prospectively enrolled consecutive outpatients after Q-wave myocardial infarction, without and with functional MR, defined as regurgitation occurring in the presence of structurally normal valve.

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Received: January 10, 2007

Accepted: February 28, 2007

Published online in Wiley InterScience

(www.interscience.wiley.com).

DOI:10.1002/clc.20131

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Inclusion criteria were: (i) a history of Q-wave myocardial infarction; (ii) structurally normal mitral valve apparatus; (iii) sinus rhythm; (iv) feasibility of assessment of MR and anatomic analysis of mitral valve. Patients with: (i) atrioventricular conduction abnormalities; (ii) bundle branch block; (iii) ventricular pacing; (iv) atrial fibrillation or other arrhythmia preventing appropriate qualitative assessment of MR; (v) organic heart and valve disease, other than coronary heart disease; as well as (vi) suboptimal echocardiographic windows, were excluded from the study.

The protocol of the study was approved by the Ethics Committee at our institution. All patients gave informed consent to participate in the study.

Echocardiographic Evaluation

Left ventricular end-systolic and end-diastolic volumes, as well as ejection fraction were measured with biplane Simpson disk method.⁹ Left ventricular sphericity index was calculated as a ratio of left ventricular long to short axis dimension.¹⁰ The degree of MR was expressed qualitatively as 1+ to 4+ (3+ and 4+ was considered significant MR) and quantitatively as effective regurgitant orifice area (ERO), quantified as feasible, either with proximal isovelocity surface area method or with quantitative Doppler volumetric method.^{11,12} Significant mitral regurgitation was defined as $ERO > 0.2 \text{ cm}^2$. In patients with trace mitral regurgitation ERO was considered null. Mitral valve annulus diameter was measured in the apical 4-chamber and 2-chamber views and averaged.¹³ Tenting area was defined as the area between the leaflets and the annular plane at mid-systole.¹⁴ Regional contractile abnormalities were described as inferoposterior, anterolateral and combined, depending on their site, according to the 16-segment model recommended by the American Society of Echocardiography.⁹

Tissue velocities of the mitral annular septal, lateral, anterior and posterior regions were recorded from the apical views with tissue Doppler imaging.¹⁵ Heart cycles with variable RR intervals, differing by more than 200 msec were excluded from analyses. Time intervals from the upstroke of the R wave in the electrocardiographic tracing to the peak velocity and cessation of left ventricular shortening during left ventricular ejection (S2 phase) respectively, were measured (Fig. 1). Two indexes of mitral annulus asynchrony were calculated: the difference between the longest and the shortest time to the peak and end of the S2 wave respectively, and standard deviation of the average time intervals of movement of mitral annulus.¹⁶ All echocardiographic measurements were made by a single observer (PS).

Statistics

Data were expressed either as percentages or mean $\pm$ standard deviation. A value of $p < 0.05$ was considered

FIG. 1 Correlations between standard deviation of the average of time intervals from the R wave in the electrocardiogram to the cessation of systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus (SDRES) and ERO as well as between the difference between the longest and the shortest time from the R wave in the electrocardiogram to the cessation of systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus (DIFFRES) and ERO area.

significant. Groups with and without significant mitral regurgitation on qualitative analysis ($ERO > 0.2 \text{ cm}^2$ vs. $ERO \leq 0.2 \text{ cm}^2$ or absent), were compared with either Students-*t* or chi-square tests where appropriate. Pearson's correlation coefficients were calculated to evaluate the relationship between indices of asynchrony and ERO area. Multivariate stepwise logistic regression analyses were performed with ERO as dependent and: ejection fraction, sphericity index, tenting area, mitral annulus diameter and regional contractile abnormalities as independent variables. Variables defining long axis asynchrony: standard deviation of the average of time intervals from the upstroke of the R wave in the electrocardiogram to the end of the velocity tracing of the

systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus (SDRES), and differences between the longest and the shortest time from the upstroke of the R wave in the electrocardiogram to end of the velocity tracings of four annular regions (DIFFRES), were separately added to the model. Intraobserver variability of tissue Doppler data was assessed on 2 series of 20 measurements. Correlation coefficient between the results of two series was $r = 0.83$ ($p = 0.02$).

Results

Fourty patients (33 men, 7 women, mean age $\pm$ standard deviation 60.1 ± 9.2 years, range 38 to 78 years) were included in the study. All patients had a history of Q-wave myocardial infarction (including 16 after multiple myocardial infarctions). There were 8 patients with a history of diabetes, 21 patients with hypertension, and 24 patients with a history of heart failure, 11 patients underwent coronary artery bypass grafting and 14 patients percutaneous coronary interventions in the past. In a qualitative colour Doppler assessment mitral regurgitation was absent in 10 patients (25%), 13 patients (33%) had insignificant ($\leq 2+$) and 17 patients (42%) significant (15 patients $3+$ and 2 patients $4+$) mitral regurgitation. ERO could be calculated in 23 out of 30 patients (77%) with mitral regurgitation on colour Doppler mapping. In 7 patients out of 13 patients (54%) with $1+$ or $2+$ mitral regurgitation on colour Doppler mapping, ERO could not be calculated, either due to the absence of regurgitant jet, lack of reliable Doppler tracing of the jet or very small size of proximal isovelocity surface area. Quantitative analysis was feasible in all patients with significant regurgitation on colour Doppler mapping. ERO exceeded 0.2 cm^2 in 10 out of 23 patients (43%) with calculable ERO. Compared to patients with $\text{ERO} \leq 0.2 \text{ cm}^2$ or absent, patients with $\text{ERO} > 0.2 \text{ cm}^2$ differed with respect to the history of heart failure (15% vs. 29%, $p \leq 0.03$) and presence of anterolateral segmental abnormalities (66% vs. 100%, $p \leq 0.04$). There was a statistically borderline difference in the frequency of percutaneous coronary interventions (43% vs. 10% respectively; $p = 0.058$). Differences in their echocardiographic variables are presented in Table 1.

There were significant correlations between SDRES and ERO, as well as between DIFFRES and ERO (Fig. 1). Mitral annulus asynchrony was also related to the degree of mitral regurgitation assessed qualitatively (Fig. 2).

A multivariate regression model showed that mitral annulus movement asynchrony (DIFFRES), was a determinant of mitral regurgitation ERO area, independent from ejection fraction, sphericity index, tenting, annulus diameter and infarct location (r^2 change 0.72, $p \leq 0.01$). The only other independent predictor of ERO area was mitral annulus diameter (r^2 change 0.79, $p \leq 0.01$).

Fig. 2 Relationship between the degree of mitral regurgitation and difference between the longest and the shortest time from the R wave in the electrocardiogram to the cessation of systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus (DIFFRES).

Other variables were predictors of ERO only in univariate analyses: ejection fraction (r^2 change 0.59, $p \leq 0.01$), tenting area (r^2 change 0.76, $p \leq 0.01$) and sphericity index (r^2 change 0.75, $p \leq 0.01$).

Discussion

Segmental and temporal nonuniformity of wall movement can be demonstrated in the normal human left ventricle.¹⁷ It increases with regional myocardial contractile abnormalities in ischaemic cardiomyopathy and impairs left ventricular function.^{18,19} We demonstrated that this in-coordination, represented by the asynchronous long axis movement of mitral annulus, was associated with an increase in the degree of MR.

Previous studies suggested a number of mechanisms responsible for ischaemic MR, such as tethering of the leaflets by the displaced papillary muscles,³ annular dilatation and other geometric changes,^{5,20,21} global and local left ventricular remodeling and sphericization.^{1,2} Clearly, isolated changes, such as isolated annular dilatation, are not able to cause important functional MR.¹⁴ However acting in concert, geometric distortions of mitral valvular—ventricular complex lead to diminished leaflet coaptation and MR.²¹

Surgery of functional MR aims mainly at reduction of mitral annular size.²⁰ However MR may persist or recur in spite of ring implantation.²² Ring annuloplasty increases the coaptation reserve, but it frequently fails, if other mechanisms, such as restricted leaflet motion or alterations of papillary muscle geometry, play a dominant role.²³

TABLE 1 Comparison of echocardiographic variables in patients with and without significant effective mitral regurgitant orifice area (ERO > 0.2 cm² vs. ERO ≤ 0.2 cm²)

	ERO>0.2 (mean ± std. deviation)	ERO ≤ 0.2 (mean ± std. deviation)	p
Ejection fraction	33 ± 14	46 ± 18	0.049
Tenting area (mm)	15 ± 4	9 ± 6	0.004
Annulus diameter (mm)	38 ± 5	33 ± 5	0.01
Sphericity index	0.7 ± 0.1	0.6 ± 0.1	0.01
SDR (msec)	31 ± 8	24 ± 8	0.02
SDRES (msec)	34 ± 10	30 ± 8	0.002
DIFFRS (msec)	70 ± 17	52 ± 17	0.006
DIFFRES (msec)	75 ± 24	42 ± 17	0.002

ERO = effective orifice area, SDR = standard deviation of the average of time intervals from the R wave in the electrocardiogram to the peak velocity systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus, SDRES = standard deviation of the average of time intervals from the R wave in the electrocardiogram to the cessation of systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus, DIFFRS = difference between the longest and the shortest time from the R wave in the electrocardiogram to the peak to the peak velocity systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus, DIFFRES = difference between the longest and the shortest time from the R wave in the electrocardiogram to the cessation of systolic movement of septal, lateral, anterior and posterior aspects of mitral annulus.

Biventricular pacing acutely decreases mitral regurgitation severity. Breithardt *et al.* directly ascribed the beneficial effect of cardiac resynchronization to improved myocardial performance and increased mitral valve closing forces.²⁴ Other effects of cardiac resynchronization might be of significance. Papillary muscle disco-ordination was observed in animals.²⁵ Glasson *et al.* demonstrated that discoordinate papillary muscle shortening was associated with systolic mitral leaflet “loitering” and participated in the development of functional MR.⁴ Ahmad *et al.* demonstrated that ischaemic MR was associated with altered annular motion amplitude.²⁶ The results of these studies are in agreement with the present analysis, showing relationship between quantitatively assessed MR and in-coordinate annular movement. Therefore mitral annulus and papillary muscle asynchrony, recently described by Kanzaki *et al.*²⁷ may be considered an additional mechanism contributing to the development of functional MR, especially in patients with reduced “coaptation reserve.”

We acknowledge several limitations of the study. The data were obtained by routine two-dimensional echocardiographic examinations, supplemented with tissue Doppler imaging. Therefore we did not evaluate the three-dimensional geometry of mitral valvular—ventricular complex. Tissue velocities at the different aspects of mitral annulus were not recorded simultaneously but in separate cardiac cycles. Hence, although we paid an attention to exclude heart cycles with varying RR intervals from the analyses, synchronicity of tissue velocities was evaluated relative to the upstroke of preceding electrocardiographic R waves, rather than in absolute terms. Although previous reports supported the adequacy of two-dimensional echocardiography for the measurement of papillary muscle displacement, we

considered tissue Doppler imaging of papillary muscles not feasible, so the data concerning the relative in-coordination of papillary tips—annulus complex are lacking. Also Doppler methods used to quantify MR have some limitations. Measurements of mitral apparatus deformation were performed at a single time point, therefore physiologic variation of tenting area and mitral annulus during the cardiac cycle was not evaluated. The measurements were made by a single observer and inter-observer variability data were not available.

Conclusions

Mitral annulus asynchrony may be considered an additional mechanism contributing to the development of functional mitral regurgitation. Further studies should establish whether, following careful assessment of asynchrony, cardiac resynchronization therapy might be the option for patients with functional MR not considered for surgery or when MR recurs after surgery.

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