EDITORIAL

Mitral regurgitation and left ventricular dyssynchrony: implications for treatment

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Cardiac resynchronisation therapy may provide an alternative treatment for mitral regurgitation in patients unsuitable for surgery

Mitral regurgitation is frequently encountered in patients with dilated cardiomyopathy and severely depressed left ventricular (LV) function. Data from the Duke Cardiovascular Databank have shown that 30% of these patients had severe mitral regurgitation.¹ In dilated cardiomyopathy the mitral valve is usually normal and valvular incompetence is referred to as functional or secondary mitral regurgitation.^{2,3} The mechanism underlying this regurgitation is multifactorial and related to abnormalities in:

- LV volumes
- LV function
- LV shape.^{2,3}

In patients with LV dilatation, the papillary muscles are displaced towards the apex, thereby increasing the chordal tethering forces on the structurally normal mitral leaflets, leading to incomplete leaflet coaptation and mitral regurgitation. The LV dilatation also results in annular dilatation, with further mitral regurgitation. A concomitant decrease in systolic LV function (as encountered in cardiomyopathy) results in a decrease in systolic closing force of the mitral leaflets. Moreover, in patients with ischaemic cardiomyopathy, wall motion abnormalities and scar formation involving the papillary muscles lead to leaflet dysfunction and retraction. Finally, changes in the shape of the LV further exacerbate mitral regurgitation.

MITRAL REGURGITATION

In these patients mitral regurgitation is associated with a worsening in clinical symptoms, a decrease in exercise capacity and a poor prognosis.⁴ Indeed, natural history studies have reported one-year survival of only 30–40% when patients were treated conservatively.⁴ The natural history studies also revealed that mitral regurgitation is a progressive disorder, in which the regurgitation-induced volume overload results in further LV dilatation, which in turn induces further mitral regurgitation (“mitral regurgitation begets mitral regurgitation”).^{2,4}

The treatment of mitral regurgitation in dilated cardiomyopathy remains challenging. As indicated, survival on medical treatment is poor,

with mortality increasing in parallel to severity of mitral regurgitation.⁴ Recent studies have demonstrated the feasibility of mitral valve repair in patients with dilated cardiomyopathy and severely reduced LV function. Bolling *et al*⁵ initially reported on the feasibility of mitral valve repair in this subset of patients by downsizing the annulus using a flexible ring; in subsequent studies the authors demonstrated a one- and two-year survival of 82% and 71%, respectively, after surgical correction of mitral regurgitation.⁶ Similar results were obtained by Szalay *et al*⁷ who reported an 85% survival at two-year follow-up in 91 patients with ischaemic cardiomyopathy who underwent surgical mitral valve repair. Moreover, Bolling *et al* demonstrated absence of mitral regurgitation in 81% of patients after surgery.⁵

SURGICAL CORRECTION

The surgical correction of mitral regurgitation was associated with reverse LV remodelling.^{8,9} In 51 patients with ischaemic cardiomyopathy who underwent restrictive annuloplasty, serial echocardiographic studies were performed and the results revealed a significant reduction in LV end-systolic dimension (from mean (SD) 51 (10) mm to 43 (12) mm, $p < 0.001$) and LV end-diastolic dimension (from 64 (8) mm to 58 (11) mm, $p < 0.001$) at 1.5 year follow-up.⁸ These observations were strengthened by recent data confirming the reverse LV remodelling, but this time assessed by magnetic resonance imaging, which may be superior over echocardiography in assessment of LV dimensions and volumes.¹⁰ Bolling *et al*¹¹ hypothesised that stabilisation of the mitral annulus and unloading of the LV may be responsible for the reverse LV remodelling as observed in the aforementioned studies.

Clinically, the LV reverse remodelling was associated by an improvement in symptoms, with a significant reduction in New York Heart Association functional class from 3.4 (0.8) at baseline to 1.3 (0.4) at two-year follow-up ($p < 0.01$).⁸

Although these results are promising, surgery of patients with depressed LV function and severe mitral regurgitation is associated with high risk for perioperative mortality and morbidity and a general reluctance exists to refer these patients for surgery. In particular, data from the EuroHeart Survey on valvular heart disease demonstrated that many patients with severe valvular heart disease (including severe mitral regurgitation) are frequently not referred for surgery.¹² Also, recent data have shown that

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surgical restrictive mitral valve repair may only result in reverse LV remodelling if the LV is not too dilated.⁹

CARDIAC RESYNCHRONISATION THERAPY

From this end, it may be of interest to consider the recent results of cardiac resynchronization therapy (CRT) that also have shown an improvement in mitral regurgitation. Breithardt *et al*¹³ studied 24 patients with CRT on and off, in order to evaluate the effect of CRT on mitral regurgitation. The authors demonstrated an acute, significant reduction in severity of mitral regurgitation after CRT. The effective regurgitant orifice area decreased from 25 (19) mm² to 13 (8) mm² after CRT, and the changes in mitral regurgitation severity were directly related to the changes in LV systolic function (LV peak positive rate of pressure rise, LV+dP/dt_{max}). Various studies confirmed these findings and demonstrated that CRT immediately reduced the mitral regurgitant volume by 30–40%.^{13–14}

These results suggest that CRT could be considered as an alternative therapeutic option for mitral regurgitation when surgery is not preferred. The beneficial effect of CRT on mitral regurgitation is not well understood. However, strain rate imaging suggested that reduction of dyssynchrony of the posterior papillary muscle after CRT resulted in an immediate reduction in mitral regurgitation.¹⁴ Evidence for this hypothesis is provided indirectly by Brandt *et al*¹⁵ who demonstrated that interruption of CRT resulted in acute deterioration of mitral regurgitation severity.

Additional evidence for the relation between LV dyssynchrony and the severity of mitral regurgitation is presented in the current issue of *Heart*. Agricola *et al*¹⁶ evaluated 74 patients with chronic LV dysfunction (LV ejection fraction 32 (7)%, 53% ischaemic aetiology) and varying degrees of mitral regurgitation. The authors subsequently evaluated the univariate determinants of the severity of mitral regurgitation and confirmed the contribution of the established parameters, including LV volumes (particularly LV end-systolic volume), function (LV ejection fraction) and shape (sphericity index), to the presence of mitral regurgitation. Of interest, the dyssynchrony index assessed by tissue Doppler imaging, which included the dyssynchrony of the posterior mitral leaflet, was also a determinant for the presence of mitral regurgitation. Unfortunately, patients in the current study did not undergo CRT and therefore the effect of resynchronisation on (reduction in) mitral regurgitation could not be evaluated.

When the patients were divided into ischaemic and non-ischaemic heart failure, it became evident that the dyssynchrony index was only a determinant of mitral regurgitation in patients with non-ischaemic aetiology underlying heart failure.

CRT: AN ALTERNATIVE TO SURGERY?

These findings are clinically relevant, since these observations suggest that CRT may be considered a potential alternative treatment for mitral regurgitation in patients who may not be ideal candidates for surgery. Based on the observations in the study by Agricola *et al*,¹⁶ it appears that mitral regurgitation is (at least in part) related to the presence of LV dyssynchrony that involves the posterior mitral leaflet. Moreover, the data from Breithardt *et al*¹³ and Kanzaki *et al*¹⁴ suggest that resynchronisation of the posterior leaflet results in reduction of mitral regurgitation. Thus, CRT may be an alternative treatment for mitral regurgitation if LV dyssynchrony is present and if the posterior leaflet is involved. However, the precise criteria (precise location and magnitude of LV dyssynchrony) remain to be determined. Moreover, the current observations suggest that mainly non-ischaemic heart failure patients may benefit, although the studies by

Breithardt *et al*¹³ and Kanzaki *et al*¹⁴ included a substantial number of patients with ischaemic cardiomyopathy and demonstrated LV dyssynchrony both in patients with ischaemic and non-ischaemic cardiomyopathy.

Besides the acute effect of CRT on mitral regurgitation, an additional 10–20% reduction in mitral regurgitant volume has been shown at long-term follow-up; data from the MIRACLE trial and other large trials have shown a significant reduction in average mitral regurgitation jet area and mitral regurgitation severity index after CRT.^{17–18} The improvement at long-term follow-up is most likely secondary to the reverse LV remodelling. In these long-term follow-up studies, the reduction of mitral regurgitation was observed in patients with ischaemic but also non-ischaemic cardiomyopathy.

In summary, the work by Agricola *et al*¹⁶ provides further (indirect) support for the proposal that CRT may be beneficial in subsets of heart failure patients who are not candidates for surgery. It appears that the LV dyssynchrony including the posterior mitral leaflet is an important determinant of the presence of mitral regurgitation, and preliminary data indicate that CRT may improve mitral regurgitation in these patients.

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REFERENCES

- 1 Trichon BH, Felker GM, Shaw LK, *et al*. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003;**91**:538–43.
- 2 Carabello BA. Ischemic mitral regurgitation and ventricular remodeling. *J Am Coll Cardiol* 2004;**43**:384–5.
- 3 Yiu SF, Enriquez SM, Tribouilloy C, *et al*. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation* 2002;**102**:1400–6.
- 4 Grigioni F, Enriquez-Sarano M, Zehr KJ, *et al*. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;**103**:1759–64.
- 5 Bolling SF, Deeb GM, Brunsting LA, *et al*. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg* 1995;**109**:676–82.
- 6 Bolling SF, Pagani FD, Deeb GM, *et al*. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;**115**:381–6.
- 7 Szalay ZA, Civelek A, Hohe S, *et al*. Mitral annuloplasty in patients with ischemic versus dilated cardiomyopathy. *Eur J Cardiothorac Surg* 2003;**23**:567–72.
- 8 Bax JJ, Braun J, Somer ST, *et al*. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation* 2004;**110**(suppl 1):II-103–8.
- 9 Braun J, Bax JJ, Versteegh MIM, *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.
- 10 Westenberg JMM, Van der Geest RJ, Lamb HJ, *et al*. MRI to evaluate left atrial and ventricular reverse remodeling after restrictive mitral annuloplasty in dilated cardiomyopathy. *Circulation* 2005;**112**(suppl 1):I-437–42.
- 11 Bolling SF, Smolens IA, Pagani FD. Surgical alternatives for heart failure. *J Heart Lung Transplant* 2001;**20**:729–33.
- 12 Iung B, Baron G, Butchart EG, *et al*. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on valvular heart disease. *Eur Heart J* 2003;**24**:1231–43.
- 13 Breithardt OA, Sinha AM, Schwammenthal E, *et al*. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol* 2003;**41**:765–70.
- 14 Kanzaki H, Bazaz R, Schwartzman D, *et al*. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. *J Am Coll Cardiol* 2004;**44**:1619–25.
- 15 Brandt RR, Reiner C, Arnold R, *et al*. Contractile response and mitral regurgitation after temporary interruption of long-term cardiac resynchronization therapy. *Eur Heart J* 2006;**27**:187–92.
- 16 Agricola E, Oppizzi M, Galderisi M, *et al*. Role of regional mechanical dyssynchrony as a determinant of functional mitral regurgitation in patients with left ventricular systolic dysfunction. *Heart* 2006;**92**:1390–5.
- 17 St John Sutton MG, Plappert T, Abraham WT, *et al*. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;**107**:1985–90.
- 18 Saxon LA, De Marco T, Schafer J, *et al*. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. *Circulation* 2002;**105**:1304–10.