Mechanisms and Clinical Implications of Asymptomatic Mitral Regurgitation in Patients With Left Ventricular Dysfunction

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Background Functional mitral regurgitation (MR) is common in patients with chronic heart failure (CHF). During exercise, hemodynamic changes such as elevation of blood pressure and an increase in the left ventricular end-diastolic dimension may increase MR. Severity of CHF is reflected by exercise tolerance and, therefore, MR during exercise is supposed to indicate the severity of heart failure. The degree of MR increase and left ventricle (LV) shape was quantified during exercise in CHF patients and were compared with exercise tolerance. **Methods and Results** Twenty patients with CHF (mean age: 63 years) underwent dynamic cycle exercise at steady-state levels of 80% and 150% of the anaerobic threshold (AT). The MR jet area and left atrial (LA) area were measured during exercise and the ratio of MR/LA was calculated. The LV shape was assessed by calculating the ratio of the major to the minor axis. The MR/LA ratio increased during exercise (rest: $16.9 \pm 6.5\%$, 80% AT: $21.9 \pm 8.9\%$, 150% AT: $30.9 \pm 11.2\%$; $p < 0.01$) and the LV shape became more spherical (rest: 1.34 ± 0.10 , 80% AT: 1.31 ± 0.10 , 150% AT: 1.23 ± 0.11 ; $p < 0.05$). There was a negative correlation between MR/LA ratio and the ratio of the major to the minor axis (-0.722 , $r < 0.01$).

Conclusions MR during exercise increases as the severity of CHF increases. Functional MR is correlated with the shape of the LV. (Circ J 2008; 72: 115–119)

Key Words: Echocardiography; Exercise; Heart failure

Mitral regurgitation (MR) is often observed in patients with left ventricular (LV) dysfunction despite the absence of organic changes in the mitral valve leaflet, papillary muscle rupture, and chordae tendinae rupture. This MR, also called functional MR, becomes more severe during exercise, as previously reported¹

Most previous studies on the determinants of exercise capacity in patients with heart failure have focused on the relative contribution of the heart and the periphery in limiting O₂ transport to and uptake by the exercising muscles^{2–7}. Although the mechanisms of exercise intolerance have multiple factors, they depend, at least in part, on the maximal pumping capacity of the heart; that is, the maximal stroke volume and cardiac output.

It is generally accepted that, in the absence of significant MR, the increase in stroke volume during dynamic exercise is largely brought about by a combined increase in preload and contractility^{3,8}. In the presence of MR, dynamic changes in the severity of regurgitation during exercise may compromise the normal increase in forward stroke volume and, hence, reduce maximal cardiac output and exercise capacity^{9–12}.

During exercise, various hemodynamic changes—peripheral vascular resistance increases to maintain blood pressure throughout the contracting skeletal muscles, vascular flow increases to improve the oxygen supply, and ventricular size increases to increase the stroke volume—may occur. Some of these factors might affect functional MR.

The mechanisms of functional MR are poorly understood. Previous studies have suggested that several factors, including LV size, extent of emptying, mitral annular diam-

Table 1 Clinical Characteristics and Baseline LV Function

<i>Clinical data</i>	
Age (years)	63±8
MR grade at rest	Mild: 9, Moderate: 11
<i>LV function</i>	
Ejection fraction (%)	33±13
End-diastolic dimension (mm)	62±9
<i>Cardiopulmonary exercise test</i>	
Anaerobic threshold ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)	10.2±2.2 (5.1–14.5)
Peak $\dot{V}\text{O}_2/\text{HR}$ (ml/beat)	7.2±2.7 (3.6–13.3)
$\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope	38.3±8.5 (26.1–49.8)
<i>Cause of heart failure</i>	
Ischemic heart disease	6
Dilated cardiomyopathy	11
Hypertensive heart disease	3
<i>Medication</i>	
-blocker	9
ACEI or ARB	13

Data are expressed as the mean±SD.

LV, left ventricular; MR, mitral regurgitation; mild MR, MR/left atrial (LA) <20%; moderate MR, MR/LA=20–40%; $\dot{V}\text{O}_2$, oxygen consumption; $\dot{V}\text{E}$, minute ventilation; $\dot{V}\text{CO}_2$, CO₂ production; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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Fig 1. Echocardiographic examples of dynamic changes in severity of functional mitral regurgitation (MR) during exercise in a patient with heart failure. LV, left ventricle; LA, left atrial.

eter, papillary muscle function, and left atrial (LA) size, are implicated!^{13–16} Also, recent studies have suggested that remodeling of the LV is one of the main mechanisms of functional MR!^{17,18}

Here, we investigated LV deformation and studied how it relates to functional MR during exercise in patients with chronic heart failure (CHF).

Methods

Study Population

The study population comprised 20 consecutive male patients with heart failure (mean age: 63 ± 8 years, range: 58–73 years) who met the following inclusion criteria: (1) symptoms of New York Heart Association class I or II; and (2) mild-to-moderate MR as determined by color Doppler echocardiography under resting conditions (Table 1). Patients with primary mitral valve disease, prosthetic mitral valves, evident inducible myocardial ischemia, chronic obstructive pulmonary disease, or other non-cardiac conditions that limit exercise capacity were excluded. In 6 patients, heart failure was caused by ischemic heart disease, non-ischemic dilated cardiomyopathy was the cause in 11 patients, and hypertensive heart disease with LV dilatation in 3 patients. Ischemic heart disease was defined by the presence of a documented previous myocardial infarction, or a previous luminal narrowing ($>50\%$) of a proximal major epicardial coronary artery that had undergone successful coronary intervention. Each patient was informed about the nature of the study, which was approved by the ethics committee of our institution.

Exercise Testing

All patients underwent a symptom-limited dynamic exercise test and 2 constant work rate studies, using a stationary cycle ergometer (Rehcor 500P; Lode, Groningen, The Netherlands). None of the patients experienced angina pectoris or syncope, or showed ischemic ST changes or severe arrhythmia during exercise testing. Oxygen consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were continuously measured using a breath-by-breath gas analyzer (Minato AE300S; Minato Ikagaku, Osaka, Japan). The first test was used to determine the anaerobic

threshold (AT), peak $\dot{V}O_2$, peak $\dot{V}O_2/HR$, and $\dot{V}E/\dot{V}CO_2$ slope, as described elsewhere!¹⁹ AT was determined by the V-slope method²⁰ and $\dot{V}E/\dot{V}CO_2$ slope was determined by linear regression analysis!²¹ During this test, the initial workload was set at 0 W and the intensity of exercise was increased by 1 W every 6 s. All patients were encouraged to perform maximal exercise. To evaluate changes of MR during exercise, 2 steady-state exercise tests were performed 1 week later. The first test was performed at an intensity of 80% of AT and the second test was at 150% of AT. All tests were performed in the upright position. As the state of heart disease is stable and subjects performed no physical training during this period, there was no training effect at the second test.

Echocardiographic Study

Echocardiographic studies (SONOS 5500; Philips Medical Systems, Andover, MA, USA) were performed 2 min after the beginning of exercise. The MR jet area and the LA area at the time of the mid-systolic phase (Fig 1) were measured by the area trace method on a 4-chamber view and their ratio (MR/LA) was calculated as described elsewhere!²² The degree of MR is determined by the MR/LA ratio, whereby $<20\%$ is mild, 20–40% is moderate, and $>40\%$ is severe. The MR/LA ratio at rest and during exercise was obtained from the same view.

LV shape was calculated using the ratio of the major to the minor axis at end-diastole on the 4-chamber view!²³ In the present study, the ratio of the major to the minor axis of the end-diastole LV ventricle is defined as the sphericity index.

Statistical Analysis

All data are expressed as the mean $\pm$ SD. Values of $p < 0.05$ were considered statistically significant. Correlation coefficients were calculated by regression analysis. One-way analysis of variance was used to determine the statistical significance and Bonferroni analysis was used for post-hoc analysis.

Table 2 Doppler Echocardiographic Changes During Exercise

	Rest	80% AT	150% AT
LV end-diastolic dimension (mm)	62.1±8.9	63.5±9.2	67.7±9.5*†
MR jet area/LA area (%)	16.9±6.5	21.9±8.9*	30.9±11.2**†
LV sphericity index	1.34±0.10	1.31±0.10	1.23±0.11**†

* $p<0.05$ vs AT; ** $p<0.01$ vs rest; † $p<0.05$ vs 80% AT.

Data are expressed as the mean±SD.

AT, anaerobic threshold; LV sphericity index, LV major axis/LV minor axis. Other abbreviations see in Table 1.

Fig 2. Relationship between changes in severity of functional mitral regurgitation (MR) during exercise at 150% anaerobic threshold and peak oxygen consumption ($\dot{V}O_2$)/HR.

Fig 3. Relationship between changes in severity of functional mitral regurgitation (MR) during exercise at 150% anaerobic threshold and changes in end-diastolic sphericity index (whereby left ventricle (LV) sphericity index = LV major axis/LV minor axis).

Results

Patient Characteristics and Exercise Tolerance

All patients performed cardiopulmonary exercise testing until exhaustion. No patient showed myocardial ischemia during the tests. As shown in Table 1, their exercise tolerance was moderately impaired. Although they varied from Weber class A to D, most of the subjects were class C. Peak $\dot{V}O_2$ /HR, which reflects the stroke volume during exercise, was also moderately impaired. Mean body height and age in the present study were 170 cm and 63 years, and the average value of peak $\dot{V}O_2$ /HR was approximately 12 ml/beat.²⁴ Therefore, these patients' cardiac function during exercise was about 60% of normal.

Echocardiographic Changes During Exercise

As shown in Table 2, the ratio of MR jet area to LA area increased significantly during exercise at 80% AT (rest: 16.9±6.5%, 80% AT: 21.9±8.9%; $p<0.05$) and increased further during exercise at 150% AT (30.9±11.2%; $p<0.01$).

To determine the effect of morphological factors on the increase of MR during exercise, we quantified the LV end-diastolic dimension and end-diastolic sphericity index. The LV end-diastolic dimension remained constant at 80% AT; however, it increased at an exercise intensity of 150% AT (Table 2). The end-diastolic sphericity index showed a similar result, remaining constant at 80% AT and decreasing at 150% AT (Table 2).

The degree of exercise-induced MR change (Δ MR) correlated negatively ($r=-0.500$, $p<0.01$) with peak $\dot{V}O_2$ /HR (Fig 2). This result suggests that, as MR worsens, the increase of stroke volume is attenuated. Δ MR correlated positively with $\dot{V}E/\dot{V}CO_2$ slope, although the correlation was small ($r=0.242$). Exercise-induced changes in MR showed no correlation with ejection fraction or AT.

The exercise-induced changes of MR severity was found to correlate with exercise-induced changes of end-diastolic sphericity index ($r=-0.722$, $p<0.01$; Fig 3).

Discussion

In the present study, we found the following: (1) The severity of functional MR increased in almost all patients during exercise, both at the work intensity of the AT and at an intensity greater than the AT. The increase in MR was greater when the exercise intensity was greater. (2) The exercise-induced changes in the severity of functional MR affected exercise capacity. (3) The exercise-induced changes in the severity of functional MR were related to the sphericity of the LV.

We have reported that functional MR increases as exercise intensity increases. Although previous studies have also described the relationship between MR and exercise, almost all used only single work rate exercise. The present study is the first to investigate the relationship between exercise intensity and functional MR severity.

The present study suggests that functional MR correlated negatively with peak $\dot{V}O_2$ /HR. Considering that peak $\dot{V}O_2$ /HR is determined by the peak stroke volume, an impaired increase of stroke volume due to increased MR may be the main reason for the reduction in peak $\dot{V}O_2$ /HR and for the negative correlation between functional MR and peak $\dot{V}O_2$ /HR.

There was a weak correlation between functional MR and $\dot{V}E/\dot{V}CO_2$ slope. Although the $\dot{V}E/\dot{V}CO_2$ slope partly depends on pulmonary blood flow and cardiac output, it mainly depends on physiological dead space, which in turn, is determined only by cardiac output. Therefore, this confirmed the apparently weak correlation between functional MR and $\dot{V}E/\dot{V}CO_2$ slope.

There was no correlation between MR and LV ejection fraction. The LV ejection fraction is calculated from LV diastolic and systolic cross-sectional area at rest (Simpson's method). This means that the ejection fraction does not equal the stroke volume because the stroke volume can be preserved when the LV is enlarged. Furthermore, it has been reported that the ejection fraction is not correlated with exercise tolerance.²⁵ Therefore, ejection fraction may not be a predictor of worsening MR.

Mechanisms of Worsening Functional MR During Exercise

Although functional MR is frequently observed in patients with LV dysfunction,⁴ the mechanisms that determine its presence and severity are incompletely understood. Previous studies have suggested that several factors, including LV size, extent of emptying, mitral annular diameter, papillary muscle function, and LA size, are implicated,^{13–16} although some cases do not have functional MR with dilation of the mitral annular diameter alone.¹³ Other studies have suggested that papillary muscle dysfunction worsens tethering of the mitral valve,^{15,16} even though recent studies suggest that papillary muscle dysfunction because of ischemic heart disease decreases tethering of the mitral valve.^{7,18} The present study suggests that worsening of functional MR correlated only with the shape of the LV; that is, remodeling of the LV seemed to be the main mechanism of functional MR.

It is possible that the increase in the systolic dimension caused worsening of MR. Lancellotti and colleagues reported that, as the end-systolic volume increases, the effective regurgitant orifice (ERO) increases.²⁶ However, in their paper, the correlation coefficient was greater between the ERO and the end-diastolic volume than the end-systolic volume.²⁶ Therefore, it is assumed that the impact of the systolic dimension is not great.

There is one report of a decrease in the ERO during exercise in a few subjects.²⁶ The present study's results show that no subject exhibited improved MR during exercise. The discrepancy is due to differences in the underlying disease. In the study by Lancellotti et al, a decrease in the ERO during exercise occurred mainly in patients with inferior myocardial infarction.²⁶ In the present study, there was no patient with inferior myocardial infarction and, so, no patient showed an improvement in MR during exercise.

Clinical Implications

The exercise-induced changes in the severity of functional MR correlated with peak $\dot{V}O_2$ /HR. Peak $\dot{V}O_2$ /HR reflects the stroke volume at peak exercise. The results of the present study show that worsening of functional MR during exercise contributes to the limitation of cardiac function during exercise, even in patients who exhibit only mild to moderate MR at baseline. Impaired cardiac output during exercise might contribute to the worsening of the $\dot{V}E/\dot{V}CO_2$ slope, despite the weak correlation coefficient. In contrast, functional MR worsens as peak $\dot{V}O_2$ decreases. Exercise tolerance is determined by many factors, cardiac output being one of the most important, but skeletal muscle, endothelial cell, and autonomic nervous function are also involved. Therefore, although MR worsened with exercise, and decreased the stroke volume, it did not directly regulate exercise tolerance in this situation. Worsening of functional MR is observed during exercise of a lower intensity than the AT. The AT represents moderate intensity and 50–60% of the peak workload, and is widely used for anaerobic exer-

cise in patients with heart disease. However, from the present study, it was observed that MR worsens at this intensity although exercise tolerance is not affected. Therefore, care must be taken when prescribing exercise therapy, as MR may be increased.

The results suggest that, as functional MR reduces exercise capacity, treatment of functional MR by diminishing remodeling of the LV might improve LV function during exercise. Pharmaceutical intervention such as β -blockers, angiotensin-converting enzyme inhibitors (ACEI) or spironolactone would seem to be important, but in the subjects of the present study functional MR remained despite taking an ACEI and/or a β -blocker. This means that pharmaceutical intervention is not sufficient to prevent LV remodeling. Surgical intervention is the next option for the treatment of functional MR when LV function worsens during exercise despite medical treatment. Mitral valve replacement can completely prevent worsening of functional MR; however, it is important to preserve the continuation of the mitral annulus, leaflet, chordae tendinae, and papillary muscle. As thrombosis and the side effects of warfarin are serious problems in mitral valve replacement, mitral valvoplasty is better. However, annuloplasty can treat coaptation of the mitral valve leaflet but cannot treat tethering of the mitral valve.²⁷ Indeed, annuloplasty worsens tethering of the posterior leaflet and is the cause of postoperative MR.²⁸ New surgical approaches to improve tethering are under development^{29–31} and are urgently needed.

Study Limitations

The present study had only 20 subjects. The color Doppler appearance of MR jets is influenced by several parameters, such as gain setting, packet size, aliasing velocity, and frame rate. Also, despite good agreement between the MR/LA ratio and MR severity under resting conditions, it has been suggested that this parameter may be less accurate during exercise. In addition, eccentric jets may vary according to the imaging plane, leading to underestimation of MR severity.³²

Conclusions

The data suggest that exercise-induced changes in the severity of functional MR may contribute to impaired exercise capacity in patients with CHF. Although the exercise training was performed at an intensity of the AT or lower, exaggeration of functional MR sometimes occurs; therefore, it must be evaluated carefully.

The data also suggest that functional MR correlated only with the shape of the LV; that is, remodeling of the LV seemed to be the main mechanism of functional MR.

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References

1. Takano H, Adachi H, Ohshima S, Taniguchi K, Kurabayashi M. Functional mitral regurgitation during exercise in patients with heart failure. *Circ J* 2006; **70**: 1563–1567.
2. Weber KT, Kinasevitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982; **65**: 1213–1223.
3. Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. *Am J Cardiol* 1983; **51**: 52–60.

4. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: Failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991; **17**: 1065–1072.
5. Sullivan MJ, Knight D, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure: Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation* 1989; **80**: 769–781.
6. Vanoverschelde JJ, Essamri B, Vanbutsele R, d'Hondt A, Cosyns JR, Detry JR, et al. Contribution of left ventricular diastolic function to exercise capacity in normal subjects. *J Appl Physiol* 1993; **74**: 2225–2233.
7. Lapu-Bula R, Robert A, De Kock M, D'Hondt AM, Detry JM, Melin JA, et al. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemia dilated cardiomyopathy. *Am J Cardiol* 1999; **83**: 728–734.
8. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986; **58**: 281–291.
9. Tanabe K, Ishibashi Y, Ohta T, Oyake N, Shimada T, Murakami R, et al. Effect of left and right lateral decubitus positions on mitral flow pattern by Doppler echocardiography in congestive heart failure. *Am J Cardiol* 1993; **71**: 751–753.
10. Stevenson LW, Brunken RC, Belil D, Grover-McKay M, Schwaiger M, Schelbert HR, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced heart failure. *J Am Coll Cardiol* 1990; **15**: 174–180.
11. Stevenson LW, Bellil D, Grover-McKay M, Brunken RC, Schwaiger M, Tillisch JH, et al. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1987; **60**: 654–658.
12. Keren G, LeJemtel TH, Zelcer AA, Meisner JS, Bier A, Yellin EL. Time variation of mitral regurgitant flow in patients with dilated cardiomyopathy. *Circulation* 1986; **74**: 684–692.
13. Borow KM, Lang RM, Neumann A, Carroll JD, Rajfer SI. Physiological mechanisms governing hemodynamic responses to positive inotropic therapy in patients with dilated cardiomyopathy. *Circulation* 1988; **77**: 625–637.
14. Ballester M, Jajoo JJ, Rickards A, Rickards A, McDonald L. The mechanism of mitral regurgitation in dilated left ventricle. *Clin Cardiol* 1983; **6**: 333–338.
15. Burch GE, De Pasquale NP, Phillips JH. Clinical manifestations of papillary muscle dysfunction. *Arch Intern Med* 1963; **112**: 112–117.
16. Burch GE, De Pasquale NP, Phillips JH. The syndrome of papillary muscle dysfunction. *Am Heart J* 1968; **75**: 399–415.
17. Messas E, Guerrero JL, Handschumacher MD, Chow CM, Sullivan S, Schwammenthal E, et al. Paradoxical decrease in ischemic mitral regurgitation with papillary muscle dysfunction: Insights from three-dimensional and contrast echocardiography with strain rate measurement. *Circulation* 2001; **104**: 1952–1957.
18. Uemura T, Otsuji Y, Nakashiki K, Yoshifuku S, Maki Y, Yu B, et al. Papillary muscle dysfunction attenuates ischemic mitral regurgitation in patients with localized basal inferior left ventricular remodeling: Insights from tissue Doppler strain imaging. *J Am Coll Cardiol* 2005; **46**: 113–119.
19. Meguro K, Adachi H, Ohshima S, Taniguchi K, Nagai R. Exercise tolerance, exercise hyperpnea and central chemosensitivity to carbon dioxide in sleep apnea syndrome in heart failure patients. *Circ J* 2005; **69**: 695–699.
20. Beaver WL, Wassermann K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60**: 2020–2027.
21. Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response exercise in patients with chronic heart failure. *Br Heart J* 1990; **63**: 281–283.
22. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: The mechanism of functional mitral regurgitation. *Circulation* 1983; **68**: 498–508.
23. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American society of echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
24. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of exercise testing and interpretation, 2nd edn. Philadelphia: Lea & Febiger; 1994.
25. Froelicher VF. Interpretation of specific exercise test responses. In: Froelicher VF, ed. Exercise and the heart, 2nd edn. Chicago, IL: Year Book Medical Publishers Inc; 1987; 83–145.
26. Lancellotti P, Lebrun F, Pierard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. *JACC* 2003; **42**: 1921–1928.
27. Hung J, Papakostas L, Tahta SA, Hardy BG, Bollen BA, Duran CM, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: Continued LV remodeling as a moving target. *Circulation* 2004; **110**(Suppl 1): 1185–1190.
28. Kuwhara E, Otsuji Y, Iguro Y, Ueno T, Zhu F, Mizukami N, et al. Mechanism of persistent ischemic mitral regurgitation following annuloplasty: Importance of augmented posterior mitral leaflet tethering. *Circulation* 2006; **114**: 1529–1534.
29. Ueno T, Sakata R, Iguro Y, Nagata T, Otsuji Y, Tei C. A new surgical approach to reduce tethering in ischemic mitral regurgitation by relocation of separate heads of the posterior papillary muscle. *Ann Thorac Surg* 2006; **81**: 2324–2325.
30. Hvass U, Chatel D, Assayag P, Ouroudji M, Pansard Y, Lenormand C, et al. Papillary muscle sling: A new functional approach to mitral repair in patients with ischemic left ventricular dysfunction and functional mitral regurgitation. *Ann Thorac Surg* 2003; **75**: 809–811.
31. Messas E, Guerrero JL, Handschumacher MD, Conrad C, Chow CM, Sullivan S, et al. Chordal cutting: A new therapeutic approach for ischemic mitral regurgitation. *Circulation* 2001; **104**: 1958–1963.
32. Chen CG, Thomas JD, Anconina J, Harrigan P, Mueller L, Picard MH, et al. Impact of impinging wall jet on color Doppler quantification of mitral regurgitation. *Circulation* 1991; **84**: 712–720.