

ORIGINAL ARTICLE

The Role of Ischemic Mitral Regurgitation in the Pathogenesis of Acute Pulmonary Edema

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ABSTRACT

BACKGROUND

Acute mitral regurgitation may cause pulmonary edema, but the pathogenetic role of chronic ischemic mitral regurgitation, a dynamic condition, has not yet been characterized.

METHODS

We prospectively studied 28 patients (mean [\pm SD] age, 65 ± 11 years) with acute pulmonary edema and left ventricular systolic dysfunction and 46 patients without a history of acute pulmonary edema. The two groups were matched for all baseline characteristics. Patients underwent quantitative Doppler echocardiography during exercise. Exercise-induced changes in the left ventricular volume, the ejection fraction, the mitral regurgitant volume, the effective regurgitant orifice area, and the transtricuspid pressure gradient were compared in patients with and without acute pulmonary edema.

RESULTS

The two groups had similar clinical and baseline echocardiographic characteristics. They also had similar exercise-induced changes in heart rate, systolic blood pressure, and left ventricular volumes. In the univariate analysis, patients with recent pulmonary edema had a much higher increase than did the patients without pulmonary edema in mitral regurgitant volume (26 ± 14 ml vs. 5 ± 14 ml, $P<0.001$), the effective regurgitant orifice area (16 ± 10 mm² vs. 2 ± 9 mm², $P<0.001$), and the transtricuspid pressure gradient (29 ± 10 mm Hg vs. 13 ± 11 mm Hg, $P<0.001$). In the multivariate analysis, exercise-induced changes in the effective regurgitant orifice area ($P<0.001$), in the transtricuspid pressure gradient ($P=0.001$), and in the left ventricular ejection fraction ($P=0.02$) were independently associated with a history of recent pulmonary edema.

CONCLUSIONS

In patients with left ventricular systolic dysfunction, acute pulmonary edema is associated with the dynamic changes in ischemic mitral regurgitation and the resulting increase in pulmonary vascular pressure.

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ACUTE CARDIOGENIC PULMONARY EDEMA is a dramatic and sometimes recurrent manifestation of heart failure. Its pathogenesis is not fully understood. Acute coronary syndromes, tachyarrhythmias, valvular lesions,¹ and exacerbation of diastolic dysfunction by hypertension are possible causes.² Unrecognized mitral regurgitation may also be a contributor to this syndrome.³ Acute mitral regurgitation — for example, rupture of chordae tendineae or a papillary muscle — is usually considered a potential cause of pulmonary edema. However, in patients with chronic ischemic mitral regurgitation, the regurgitant orifice area can change dynamically in response to loading conditions, to changes in mitral annular or left ventricular dimensions, and more specifically, to increased leaflet tethering and a reduced closing force of the mitral valve.^{4,5} Patients can have transient episodes of increased regurgitant volume that lead to increased pulmonary vascular pressure, acute dyspnea, and orthopnea. Therefore, evaluation of patients at rest cannot reveal the full effect of ischemic mitral regurgitation. Exercise echocardiography provides a better appreciation of the dynamic characteristics of mitral regurgitation.⁶ Quantifying functional mitral regurgitation during exercise is feasible in patients with heart failure. Exercise-induced increases in mitral regurgitation are accompanied by increases in systolic pulmonary-artery pressure.⁷

We hypothesized that patients with acute pulmonary edema in association with left ventricular systolic dysfunction may have transient increases in the severity of ischemic mitral regurgitation. To test this hypothesis, we prospectively performed Doppler echocardiography during exercise in a consecutive series of patients a few days after the resolution of acute pulmonary congestion. We studied another group of patients who had ischemic left ventricular systolic dysfunction but no history of acute pulmonary edema. The two groups were matched for clinical and baseline echocardiographic characteristics.

METHODS

PATIENT POPULATION

We screened consecutive patients admitted with acute pulmonary edema for inclusion in this prospective study. Pulmonary edema was defined as a clinical syndrome of acute respiratory distress associated with pulmonary rales and radiographic

evidence of alveolar pulmonary edema. During a 36-month period, 223 consecutive patients were identified for further evaluation. Eligible patients were those with left ventricular systolic dysfunction without an obvious cause of acute pulmonary congestion. Exclusion criteria included an age of more than 80 years (14 patients), acute coronary syndrome (71 patients), tachyarrhythmias (33 patients), valvular lesions (18 patients), and early death (17 patients). Of the 70 remaining patients, 29 had echocardiographic evidence of preserved left ventricular systolic function (ejection fraction >45 percent); 9 remained in New York Heart Association functional class IV, precluding exercise testing; and in 4 the quality of the echocardiogram was inadequate to provide reliable quantitative information. The study population consisted of the 28 remaining patients.

A comparison group was selected by means of a review of our data set of patients who had ischemic left ventricular dysfunction. On the basis of this data set, 134 patients met the following inclusion criteria: no history of pulmonary edema, at least mild mitral regurgitation, and quantitative echocardiographic measurements of left ventricular volume, the ejection fraction, mitral regurgitation, and the transtricuspid pressure gradient at rest and during exercise. The patients were selected on the basis of the sampling method and the range of clinical and baseline echocardiographic factors calculated in the 28 patients who had pulmonary edema. The factors used in matching were age, left ventricular end-diastolic volume, end-systolic volume, ejection fraction, transtricuspid pressure gradient, and mitral regurgitant volume. Of the 134 patients initially selected from our sample, those who had one or more baseline values outside the range observed in the group of patients with pulmonary edema were excluded. Since systolic blood pressure, left atrial area, mitral deceleration time, and peak velocity of the A wave differed significantly between the groups, the ranges of those factors were also considered.

The process of selecting the comparison group was performed in such a way that the prespecified characteristics of the pulmonary-edema group did not differ significantly, on average, from those of the comparison group. The process was blinded and computerized and resulted in a total of 46 patients in the comparison group, all of whom consented to participate in the study. The protocol was approved by the institutional review board of the

University Hospital of Liege, and all patients gave written informed consent.

EXERCISE ECHOCARDIOGRAPHY

Symptom-limited, graded, bicycle exercise testing was performed with the patients in a semisupine position on a tilting exercise table. Beta-blockers were given neither on the day before the test nor on the morning of the test. After an initial workload of 25 W maintained for six minutes, the workload was increased every two minutes by 25 W. Every two minutes, blood pressure was measured and a 12-lead electrocardiogram was obtained. Two-dimensional and Doppler echocardiographic recordings were obtained throughout the test.

ECHOCARDIOGRAPHIC MEASUREMENTS

Echocardiographic examinations were performed with the use of a phased-array Acuson Sequoia imaging device. Two-dimensional and Doppler echocardiographic data were obtained in digital format and stored on optical disks for off-line analysis. For each measurement, at least three cardiac cycles were averaged. The same experienced observer analyzed all exercise Doppler echocardiograms. The reader did not know whether the patient had acute pulmonary edema.

We quantified mitral regurgitation with the use of both the quantitative Doppler method — using mitral and aortic stroke volumes — and the proximal isovelocity surface area method, as previously described.⁷ The proximal isovelocity radius was measured from at least three frames with optimal flow convergence. The largest radius, usually in mid-systole, was selected for analysis. The regurgitant volume and effective regurgitant orifice area were calculated with use of standard formulas. When the proximal isovelocity surface area method could be used both at rest and during stress, the results of the two methods were averaged. The reproducibility of the quantification of mitral regurgitation at rest and during exercise in our laboratory has been reported previously.⁷ The area of valvular tenting was evaluated on the basis of the parasternal long-axis view at mid-systole and included the area enclosed between the annular plane and the mitral-valve leaflets. Systolic pulmonary-artery pressure (in millimeters of mercury) was estimated from the systolic transtricuspid pressure gradient with the use of the modified Bernoulli equation ($\Delta P=4v^2$, where ΔP is the tricuspid pressure gradient in millimeters of mercury and v is the

maximal velocity of the tricuspid regurgitant jet in meters per second). The characteristics of left ventricular diastolic function that we measured included the peak velocities of the E wave (early diastole) and the A wave (late diastole), the ratio of these velocities, the isovolumic relaxation time, and the E-wave deceleration time.

STATISTICAL ANALYSIS

Continuous variables are expressed as means \pm SD. Student's t-test was used to assess differences between mean values. Categorical variables were compared with Fisher's exact test. All reported P values were calculated on the basis of two-sided tests, and a P value of less than 0.05 was considered to indicate statistical significance. To identify independent variables associated with a history of recent pulmonary edema, a stepwise logistic-regression analysis was performed with the use of Statistica software, version 5 (StatSoft).

RESULTS

CHARACTERISTICS OF THE PATIENTS

The acute pulmonary edema in all 28 study patients was treated with oxygen, nitrates, and furosemide. Eight patients (29 percent) were admitted between 8 a.m. and 8 p.m., and the 20 remaining patients (71 percent) between 8 p.m. and 8 a.m. A systolic murmur of mitral regurgitation was reported in 13 of the 28 patients. Before the acute episode, 21 patients were in New York Heart Association functional class II, 4 were in class III, and 3 were in class I. All 28 patients underwent exercise Doppler echocardiography 7 ± 2 days (range, 4 to 11 days) after the acute episode. Heart rate and systolic blood pressure were higher at the time of hospital admission than before the exercise test: 89 ± 7 beats per minute vs. 75 ± 11 beats per minute ($P<0.001$), and 164 ± 19 mm Hg vs. 127 ± 15 mm Hg ($P<0.001$), respectively. The clinical characteristics of these patients and of the 46 patients in the comparison group are shown in Table 1. There were no significant differences between the groups in any characteristic.

QUANTITATIVE DOPPLER ECHOCARDIOGRAPHY AT REST

All 74 patients had at least trivial functional mitral regurgitation. All baseline echocardiographic variables were similar in the two groups (Table 1). Figure 1 shows the correlation between the effective

Table 1. Baseline Characteristics of the Patients.*

Variable	Pulmonary Edema (N=28)	No Pulmonary Edema (N=46)	P Value
Age — yr	65±11	66±10	0.97
Male sex — no. (%)	20 (71)	31 (67)	0.79
Smoking — no. (%)	17 (61)	31 (67)	0.62
Diabetes mellitus — no. (%)	7 (25)	12 (26)	1.00
Hypertension — no. (%)	13 (46)	21 (46)	1.00
Infarct site — no.			0.81
Inferior	11	20	
Anterior	11	20	
Both	6	6	
NYHA functional class — no.			0.21
I	3	7	
II	21	27	
III	4	12	
History of CABG — no. (%)	3 (11)	10 (22)	0.35
Drug therapy — no. (%)			
Furosemide	15 (54)	18 (39)	0.24
ACE inhibitor	25 (89)	40 (87)	1.00
Beta-blocker	23 (82)	34 (74)	0.57
Spironolactone	7 (25)	14 (30)	0.79
Nitrate	12 (43)	19 (41)	1.00
Systolic arterial pressure — mm Hg	127±15	131±16	0.39
Heart rate — beats/min	75±11	77±14	0.57
Left ventricular end-diastolic volume — ml/m ²	149±22	140±22	0.16
Left ventricular end-systolic volume — ml/m ²	98±20	89±23	0.08
Left ventricular ejection fraction — %	35±7	37±6	0.13
Left atrial area — cm ²	19±5.5	19±4.4	0.58
Tenting area — cm ²	6.3±1.2	5.9±1.4	0.28
Left ventricular wall-motion index	1.7±0.23	1.6±0.22	0.12
Regurgitant volume — ml	23±11	21±12	0.78
Effective regurgitant orifice area — mm ²	18±9	16±9	0.33
Transtricuspid pressure gradient — mm Hg	26±9	25±10	0.72
Isovolumic relaxation time — msec	94±15	99±14	0.12
E-wave velocity — cm/sec	78±22	83±23	0.43
A-wave velocity — cm/sec	55±22	63±25	0.16
Ratio of E-wave:A-wave velocities	1.66±0.81	1.53±0.83	0.56
Mitral E-wave deceleration time — msec	188±51	183±55	0.66

* Plus-minus values are means ±SD. NYHA denotes New York Heart Association, CABG coronary-artery bypass grafting, and ACE angiotensin-converting enzyme.

regurgitant orifice area and the transtricuspid pressure gradient at rest.

EXERCISE TEST

The patients with recent pulmonary edema exercised for an average of 9.7±2.8 minutes and those

in the comparison group for an average of 10.6±3.4 minutes (P=0.24). Heart rate and systolic arterial pressure increased about the same amount in both groups. During testing, no chest pain, ischemic electrocardiographic changes, important arrhythmias, or echocardiographic evidence of exer-

cise-induced ischemia developed in any patients. Of the 74 patients, 25 stopped exercise because of dyspnea and 49 because of fatigue. The test was stopped more frequently because of dyspnea in the case of patients with a history of recent pulmonary edema than in that of patients in the comparison group (17 of 28 patients [61 percent] vs. 8 of 46 patients [17 percent], $P = 0.001$).

EXERCISE-INDUCED CHANGES

During exercise, regurgitant volume and the effective regurgitant orifice area increased (by 26 ± 14 ml and 16 ± 10 mm², respectively) in all but one patient with pulmonary edema (Fig. 2). In contrast, small exercise-induced changes were observed in the comparison group. There were highly significant differences between groups in the magnitude of exercise-induced changes in regurgitant volume ($P < 0.001$), the effective regurgitant orifice area ($P < 0.001$), the transtricuspid pressure gradient ($P < 0.001$), and the tenting area ($P = 0.001$) (Table 2). The differences were also significant for changes in ejection fraction ($P = 0.002$) and left ventricular wall-motion index ($P = 0.02$). Exercise-induced changes were similar in the two groups with respect to systolic arterial pressure, heart rate, and left ventricular end-diastolic and end-systolic volumes. Figure 3 shows the correlation between exercise-induced changes in the effective regurgitant orifice area and the transtricuspid pressure gradient in the two groups.

In the multivariate analysis (Table 3), the logistic-regression model was used to examine acute pulmonary edema as a dependent variable and found that exercise-induced changes in the effective regurgitant orifice area, in the transtricuspid pressure gradient, and in the left ventricular ejection fraction were independently associated with recent acute pulmonary edema.

DISCUSSION

These data show that patients with left ventricular systolic dysfunction presenting with pulmonary edema have a large exercise-induced increase in ischemic mitral regurgitation and pulmonary hypertension a few days after the acute episode. Functional ischemic mitral regurgitation is frequent in patients with heart failure and carries an adverse prognosis.⁸ It occurs despite a structurally normal mitral valve in the setting of leaflet tethering caused by annular dilatation and displaced papillary mus-

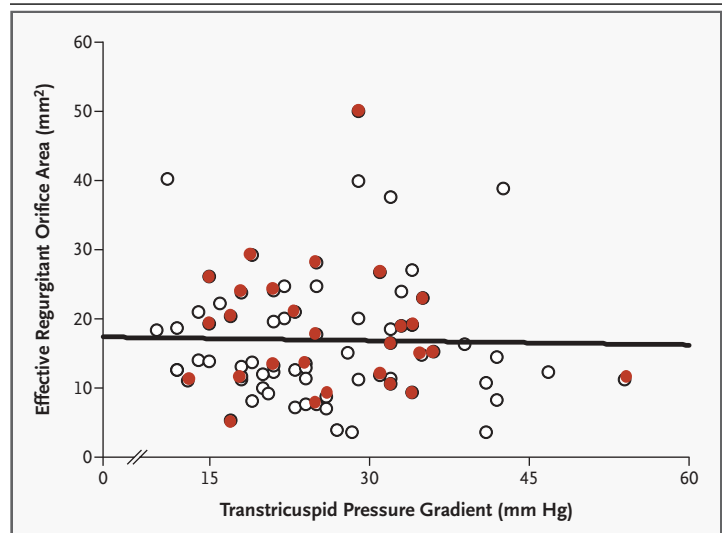


Figure 1. Correlation between the Effective Regurgitant Orifice Area and the Transtricuspid Pressure Gradient at Rest.

The correlation between the variables was not significant ($r = -0.02$). Red circles indicate patients who had pulmonary edema, and open circles patients in the comparison group, with no pulmonary edema. Some data points in the comparison group indicate values for more than one patient.

cle and of a decreased closing force of the mitral valve caused by left ventricular dysfunction.⁹

Ischemic mitral regurgitation is a dynamic lesion, and its severity may vary over time. The dynamic changes can be quantitatively measured during semisupine exercise.⁷ The degree of mitral regurgitation at rest is unrelated to exercise-induced changes.¹⁰ Large exercise-induced increases in mitral regurgitation identify patients at high risk of a poor outcome.¹¹

In ischemic mitral regurgitation, an effective regurgitant orifice area of 20 mm² or more is considered severe and is associated with excess mortality.⁸ Only 10 of the 28 patients (36 percent) in the acute-pulmonary-edema group had an orifice area of 20 mm² or more. In addition to the degree of mitral regurgitation at rest, large increases in the effective regurgitant orifice area (>13 mm²) during exercise convey an adverse prognosis.¹¹ Of the 28 patients, 19 (68 percent) had an orifice area that increased by more than 13 mm² during exercise. This finding underscores the dynamic component, rather than the severity of mitral regurgitation at rest, as the major determinant of pulmonary edema in this clinical setting.

Chronic severe mitral regurgitation progres-

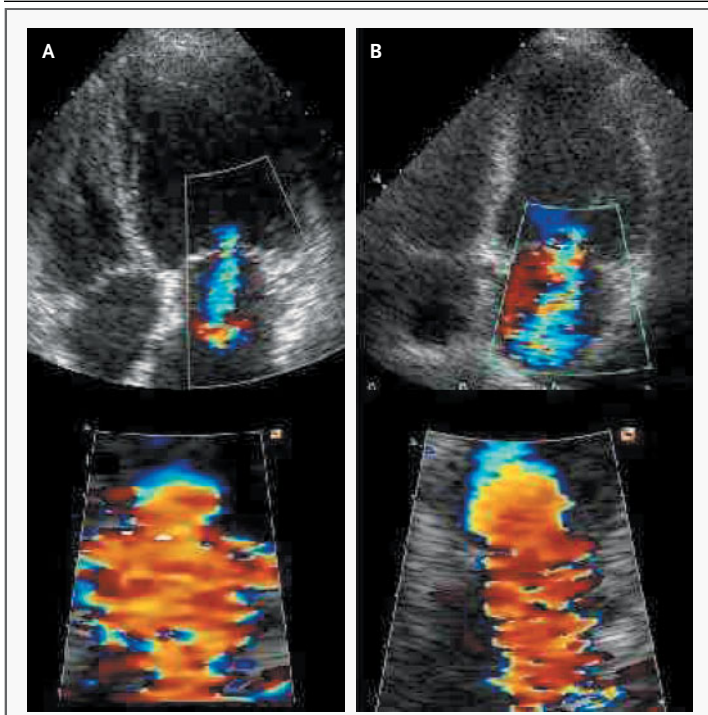


Figure 2. Mid-Systolic Apical Four-Chamber View Obtained at Rest and during Exercise in a Patient Who Presented with Acute Pulmonary Edema.

Panel A shows a color-flow Doppler echocardiogram and the flow convergence proximal to the effective regurgitant orifice while the patient is at rest (effective regurgitant orifice area, 24 mm²), and Panel B while the patient is exercising (effective regurgitant orifice area, 48 mm²). The patient presented with acute pulmonary edema four days before the exercise test. A large exercise-induced increase in mitral regurgitation was observed.

sively produces increased left atrial volume and compliance — an acute increase in regurgitant volume is handled without a large increase in left atrial pressure and pulmonary congestion. Compensatory mechanisms, such as higher lymphatic output and increased thickness of the alveolar–capillary barrier, further reduce the potential for the development of pulmonary extravascular fluid. In contrast, when a mild or moderate orifice area and regurgitant volume suddenly increase, the acute rise in left atrial pressure can be transmitted back to the pulmonary circulation, generating pulmonary edema. In addition to critical regurgitant volume and normal or reduced left atrial compliance, other hemodynamic factors can play a role, such as increased vascular resistance of venous pulmonary flow, reduced pulmonary vascular compliance, a reduced pulsatile component of pulmonary arterial circulation, decreased conductance across the alveolar–capillary barrier, and a variation of the right ventricular pulmonary arterial coupling to the detriment of mechanical efficiency.¹²

In our patients in the pulmonary-edema group, exercise-induced increases in the effective regurgitant orifice area and in the transtricuspid pressure gradient were independently associated with pulmonary edema. Several mechanisms such as arrhythmia, ischemia, hypertension, or exercise may increase the magnitude of mitral regurgitation. Patients admitted with arrhythmias or evidence of acute ischemia were prospectively excluded from our study. None of our patients had chest pain,

Table 2. Exercise-Induced Changes in Hemodynamic and Doppler Echocardiographic Variables.*

Variable	Pulmonary Edema (N=28)	No Pulmonary Edema (N=46)	P Value
Systolic arterial pressure (mm Hg)	+26±19	+27±18	0.65
Heart rate (beats/min)	+39±10	+37±17	0.15
Left ventricular end-diastolic volume (ml/m ²)	-0.25±20	-1.3±19	0.25
Left ventricular end-systolic volume (ml/m ²)	-6.8±16	-15±19	0.06
Left ventricular ejection fraction (%)	+5.4±4.3	+9.7±7.5	0.002
Left atrial area (cm ²)	+1.42±3.2	+0.96±3.7	0.57
Tenting area (cm ²)	+1.5±1.4	+0.14±1.3	0.001
Left ventricular wall-motion index	-0.25±0.20	-0.30±0.20	0.02
Regurgitant volume (ml)	+26±14	+5±14	<0.001
Effective regurgitant orifice area (mm ²)	+16±10	+2±9	<0.001
Transtricuspid pressure gradient (mm Hg)	+29±10	+13±11	<0.001

* Plus–minus values are means ±SD.

ST-segment changes, or echocardiographic evidence of ischemia during the exercise test, which suggests that the increase in mitral regurgitation was not related to myocardial ischemia.

High systolic blood pressure at admission could have contributed to the exacerbation of mitral regurgitation through an increase in afterload. The distribution of the time of hospital admission indicates that in most patients pulmonary edema developed at night, owing to an increased preload in the prone position. Acute increases in afterload due to sleep apnea, dreams, or awakening could have been a precipitating factor.

We did not perform Doppler echocardiography in the emergency department at admission. Reliable quantitation of mitral regurgitation requires an experienced echocardiographer, and there is not always one immediately available. In addition, when patients with acute pulmonary edema arrive at the hospital, they usually have already received loop diuretics and nitrates during transport.¹³ Nitroglycerin substantially decreases mitral regurgitant volume and orifice area.¹⁴ Thus, even measurements obtained soon after admission would not necessarily correspond to the severity of mitral regurgitation and pulmonary arterial pressure present at the onset of the syndrome. The detection of a murmur at admission in only half the patients does not preclude the presence of clinically significant mitral regurgitation. Physical examination has been found to be insensitive in identifying patients with acute ischemic mitral regurgitation during myocardial infarction.¹⁵

Increased orifice area and regurgitant volume are associated with greater tethering at both the papillary muscle and annular ends of the leaflets.¹⁶ The increase in mitral regurgitation in the group with recent pulmonary edema was associated with a significant exercise-induced increase in systolic tenting area, an accurate descriptor of mitral deformation.^{10,17}

In patients with left ventricular dysfunction, the two main determinants of pulmonary hypertension are the severity of functional mitral regurgitation and diastolic dysfunction.¹⁸ The two groups in this study did not differ in diastolic function as assessed by pulsed-wave Doppler imaging of transmitral flow-velocity curves and by mitral deceleration time. A limitation of the proximal isovelocity surface area method was the measurement of the proximal isovelocity radius at only one velocity level and at one time point. However, we averaged the

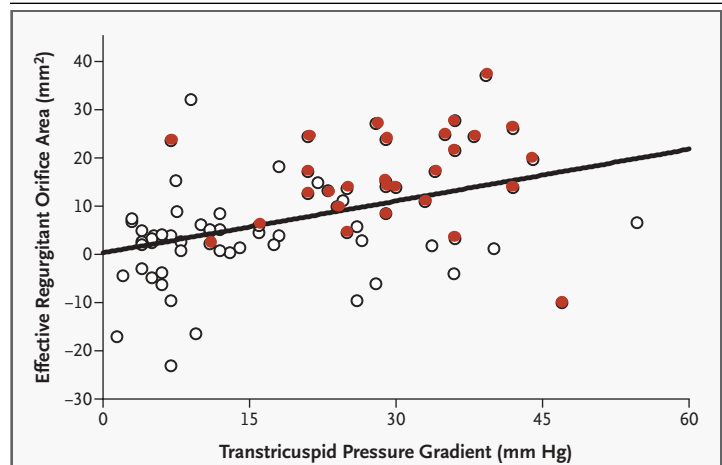


Figure 3. Correlation between Exercise-Induced Changes in the Effective Regurgitant Orifice Area and the Transtricuspid Pressure Gradient.

The correlation between the variables was significant ($r=0.4$, $P<0.001$). Red circles indicate patients who had pulmonary edema, and open circles patients in the comparison group, with no pulmonary edema. Some data points in the comparison group indicate values for more than one patient.

Table 3. Multivariate Predictors of Recent Pulmonary Edema.*

Variable*	Odds Ratio (95% CI)	P Value
Effective regurgitant orifice area	1.15 (1.05–1.25)	<0.001
Transtricuspid pressure gradient	1.13 (1.05–1.21)	0.001
Left ventricular ejection fraction	0.86 (0.77–0.96)	0.02

* The odds ratios indicate the association of recent pulmonary edema with exercise-induced changes in the variables shown. CI denotes confidence interval.

results of the proximal isovelocity surface area and the quantitative Doppler methods.

Our study may have clinical implications. Exercise testing coupled with quantitative Doppler echocardiography could be useful for patients with left ventricular systolic dysfunction in whom acute pulmonary edema develops without an obvious cause. A mild degree of mitral regurgitation at baseline can be associated with large dynamic changes, explaining the clinical spectrum from exertional dyspnea, as experienced by our patients during the exercise test, to the occurrence of flash pulmonary edema. High-dose nitrates would be particularly effective in this setting.¹³ If exercise largely increases both mitral regurgitation and pulmonary pressures, a specific therapy should be discussed in the light

of the respective contribution of adverse valve geometry and reduced closing force of the mitral valve.¹⁶

In conclusion, in patients with left ventricular systolic dysfunction, we found a large increase in mitral regurgitation and systolic pulmonary-artery pressure during exercise a few days after acute pulmonary edema. These changes were markedly different from those measured in a comparison group of patients with similar characteristics but without

a history of pulmonary congestion. This suggests that an acute increase in pulmonary vascular pressure can be produced by the dynamic nature of chronic ischemic mitral regurgitation.

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