

## THE PATHOGENESIS OF ACUTE PULMONARY EDEMA ASSOCIATED WITH HYPERTENSION

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### ABSTRACT

**Background** Patients with acute pulmonary edema often have marked hypertension but, after reduction of the blood pressure, have a normal left ventricular ejection fraction ( $\geq 0.50$ ). However, the pulmonary edema may not have resulted from isolated diastolic dysfunction but, instead, may be due to transient systolic dysfunction, acute mitral regurgitation, or both.

**Methods** We studied 38 patients (14 men and 24 women; mean [ $\pm$ SD] age,  $67 \pm 13$  years) with acute pulmonary edema and systolic blood pressure greater than 160 mm Hg. We evaluated the ejection fraction and regional function by two-dimensional Doppler echocardiography, both during the acute episode and one to three days after treatment.

**Results** The mean systolic blood pressure was  $200 \pm 26$  mm Hg during the initial echocardiographic examination and was reduced to  $139 \pm 17$  mm Hg ( $P < 0.05$ ) at the time of the follow-up examination. Despite the marked difference in blood pressure, the ejection fraction was similar during the acute episode ( $0.50 \pm 0.15$ ) and after treatment ( $0.50 \pm 0.13$ ). The left ventricular regional wall-motion index (the mean value for 16 segments) was also the same during the acute episode ( $1.6 \pm 0.6$ ) and after treatment ( $1.6 \pm 0.6$ ). No patient had severe mitral regurgitation during the acute episode. Eighteen patients had a normal ejection fraction (at least 0.50) after treatment. In 16 of these 18 patients, the ejection fraction was at least 0.50 during the acute episode.

**Conclusions** In patients with hypertensive pulmonary edema, a normal ejection fraction after treatment suggests that the edema was due to the exacerbation of diastolic dysfunction by hypertension — not to transient systolic dysfunction or mitral regurgitation. (N Engl J Med 2001;344:17-22.)

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IT is a clinical paradox that patients hospitalized with congestive heart failure may later be noted to have normal systolic function, as evidenced by a normal left ventricular ejection fraction ( $\geq 0.50$ ).<sup>1-5</sup> In this situation, the heart failure has been presumed to be due to isolated diastolic dysfunction.<sup>6</sup> For example, Vasan and Levy proposed that a normal left ventricular ejection fraction (of at least 0.50) within 72 hours after an episode of pulmonary congestion indicates that the patient had heart failure due to diastolic, rather than systolic, dysfunction.<sup>7</sup> Patients often have marked hypertension when they present with acute pulmonary edema.<sup>8</sup> However, the left ventricular ejection fraction is usually evaluated after the patient's clinical status has improved and the hy-

pertension has resolved. Thus, it is possible that the initial presentation was not the result of diastolic dysfunction but, instead, was due to transient systolic dysfunction or acute mitral regurgitation produced by hypertension, myocardial ischemia, or both.<sup>2,3</sup>

Accordingly, we hypothesized that many patients hospitalized with acute pulmonary edema in association with hypertension have transient left ventricular systolic dysfunction, which is no longer present when the left ventricular ejection fraction is subsequently evaluated after treatment. If this hypothesis is correct, then isolated diastolic dysfunction may be a less common cause of heart failure than has recently been believed. In addition, the evaluation of the left ventricular ejection fraction after treatment and the resolution of the acute pulmonary edema may not be adequate to identify those patients in whom heart failure is due to isolated diastolic dysfunction. To test this hypothesis, we evaluated the left ventricular ejection fraction, regional wall motion, and mitral regurgitation in patients with hypertensive pulmonary edema, both during the acute episode and 24 to 72 hours later, after treatment and the resolution of the hypertension and pulmonary congestion.

### METHODS

#### Selection of Patients

The study protocol was approved by the institutional review board of Wake Forest University Baptist Medical Center; the board issued a waiver regarding informed consent. Patients who presented to the medical center between February 1999 and March 2000 were initially screened by the house staff for inclusion in this study. Entry criteria included an acute onset of dyspnea within the preceding six hours, respiratory distress and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, and a systolic blood pressure greater than 160 mm Hg. Patients with clinical evidence of pneumonia, electrocardiographic evidence of myocardial infarction, or uremia were excluded. We were notified about 42 patients who were potentially eligible for this study. Two of these patients did not meet the entry criteria because they had uremia or pulmonary infection. In two other patients, the systolic blood pressure had dropped below 160 mm Hg before an echocardiogram could be obtained. Thus, the study population consisted of 38 consecutive patients who met the study criteria.

#### Protocol

Two-dimensional transthoracic echocardiography with color Doppler imaging was performed in each patient as therapy was being initiated. The patient's blood pressure was measured while echocardiography was being performed. A second echocardiogram

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was obtained one to three days after presentation and after clinical stabilization had occurred, so that the patient was normotensive and no longer had symptomatic pulmonary congestion.

### Echocardiography

Seventy-six echocardiograms were obtained (38 at the time of presentation during the acute episode and 38 during follow-up). The same experienced observer analyzed each echocardiogram three times to measure the left ventricular volume and the velocity of the blood flow through the mitral valve, as detected by the Doppler studies. The echocardiograms were presented in random order, with the reader unaware of the name of the patient and when the echocardiogram was obtained. The left ventricular volumes were measured in the apical four-chamber view, with the use of the area-length method.<sup>9</sup> The median value of the three separate measurements is reported.

The echocardiograms were also reviewed in a similar randomized, blinded fashion by a second observer to detect any segmental wall-motion abnormalities and to assess the presence and the severity of any mitral regurgitation, as revealed by the color Doppler studies. The regional systolic function was evaluated according to the 16-segment model of wall motion, as recommended by the American Society of Echocardiography.<sup>9</sup> A wall-motion score was assigned to each segment, which was classified as follows: 1, normal; 2, hypokinetic; 3, akinetic; 4, dyskinetic; or 5, aneurysmal. The wall-motion index was calculated as the mean score for all visualized segments.

The thickness of the septal and posterior walls of the left ventricle and its internal dimensions were measured at the level of the tips of the mitral-valve leaflets. The transmitral flow velocity was measured with the use of pulsed-wave Doppler imaging, with the sample volume positioned between the tips of the mitral leaflets during diastole.<sup>10</sup> The peak velocities of the E wave and the A wave, the ratio of these velocities, the E-wave deceleration time, and the isovolumetric relaxation time were measured. Data on transmitral flow velocity were not obtained for one patient who presented in atrial fibrillation and for a second patient with fused E and A waves.

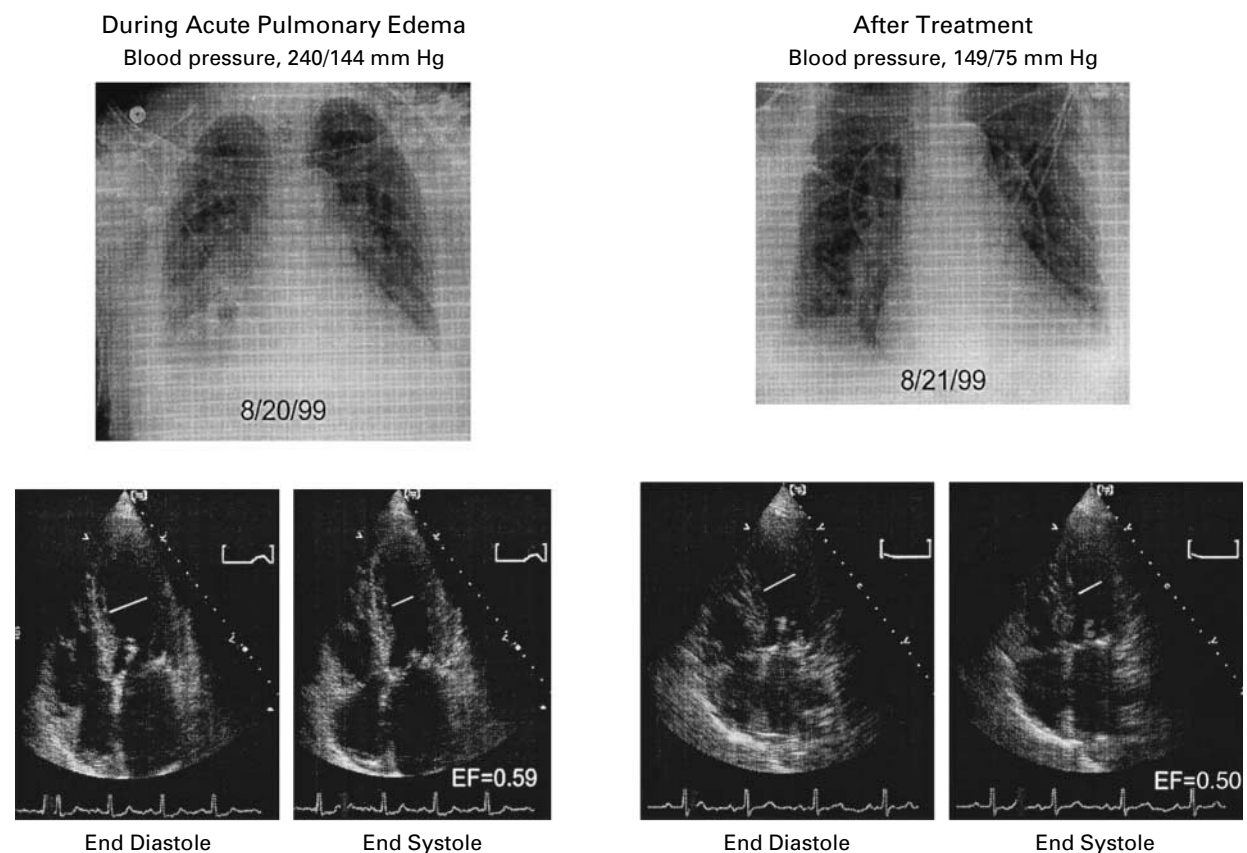
The presence and the severity of mitral regurgitation in 36 of the patients were evaluated on the basis of the mitral-regurgitation jet discernible on the color Doppler images in the parasternal long-axis view and the apical four-chamber view.<sup>11</sup> On the basis of the size and characteristics of the jet (central vs. eccentric), the degree of mitral regurgitation was graded as none, mild, moderate, or severe.

### Statistical Analysis

Data are expressed as means  $\pm$ SD. Comparisons were made with the use of paired t-tests and linear regression analysis. A P value of less than 0.05 was considered to indicate statistical significance.

### RESULTS

Chest radiographs and echocardiograms from a representative patient are shown in Figure 1. There



**Figure 1.** Chest Radiographs and End-Diastolic and End-Systolic Apical Four-Chamber Echocardiograms from a Representative Patient, Obtained on Presentation with Acute Pulmonary Edema and Again after Treatment. EF denotes ejection fraction.

were 14 men and 24 women whose mean age was  $67 \pm 13$  years. All the patients had pulmonary rales on presentation (one of the criteria for entry into the study). The mean systolic blood pressure was  $200 \pm 26$  mm Hg during the initial echocardiographic examination and was  $139 \pm 17$  mm Hg during the follow-up examination ( $P < 0.05$ ) (Table 1). The mean heart rate was higher initially than at follow-up.

Acute pulmonary edema was treated with furosemide (in all patients) and nitroglycerin (in 34 of 38 patients). One patient received nitroprusside, which was discontinued before the follow-up echocardiogram was obtained. At the time of the follow-up study, 22 patients (58 percent) were receiving beta-adrenergic blockers, 29 (76 percent) were receiving angiotensin-converting-enzyme inhibitors, and 11 (29 percent) were receiving calcium-channel blockers. Ten patients (26 percent) were receiving beta-blockers before admission.

None of the patients had mitral stenosis, aortic regurgitation, or aortic stenosis. The mean ratio of the peak transmitral flow velocity of the E wave to the peak velocity of the A wave was higher after treatment, because there was a decrease in the mean peak velocity at the A wave (Table 1). The deceleration time of the mitral E wave was longer after treatment, a finding consistent with an improvement in left ventricular diastolic stiffness.<sup>12</sup> The thickness of the left ventricular posterior wall was more than 12 mm in 18 patients (47 percent) at the time of the follow-up examination and was not significantly different during the acute episode of pulmonary edema.

Despite the marked difference in blood pressure, the left ventricular ejection fraction during the acute episode ( $0.50 \pm 0.15$ ) was similar to that measured after treatment ( $0.50 \pm 0.13$ ) (Table 1). The ejection fraction after treatment correlated directly with the ejection fraction during the acute episode ( $r = 0.83$ ,  $y = 0.84x + 0.08$ ;  $P < 0.01$ ) (Fig. 2). Eighteen patients had a normal ejection fraction (0.50 or greater) after treatment (Table 2). In all these patients, the ejection fraction was also 0.43 or greater during the acute episode; in 16 of the 18 patients, the ejection fraction was 0.50 or greater during the acute episode (Fig. 2). In 29 of the patients, the ejection fraction at the time of the follow-up examination was 0.40 or greater. In all these patients, the ejection fraction during the acute episode was 0.35 or greater, and in 25 of the 29 it was 0.40 or greater.

In 19 patients (50 percent), the ejection fraction during the acute episode was 0.50 or greater. In 16 of these patients, the ejection fraction at follow-up was also 0.50 or greater. In all of these patients, the ejection fraction at follow-up was greater than 0.45. In the 20 patients who had an ejection fraction of less than 0.50 at follow-up, the ejection fraction during the acute episode ( $0.41 \pm 0.09$ ) was also similar to the ejection fraction at follow-up ( $0.40 \pm 0.06$ ,  $P = 0.53$ ).

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

VARIABLE	DURING ACUTE PULMONARY EDEMA	AFTER TREATMENT
	mean $\pm$ SD	
Blood pressure (mm Hg)		
Systolic	200 $\pm$ 26	139 $\pm$ 17*
Diastolic	100 $\pm$ 25	64 $\pm$ 15*
Heart rate (beats/min)	83 $\pm$ 14	72 $\pm$ 12*
Mitral flow velocity (cm/sec)		
E wave	98 $\pm$ 33	98 $\pm$ 28
A wave	88 $\pm$ 33	78 $\pm$ 26*
E wave:A wave	1.31 $\pm$ 0.80	1.51 $\pm$ 0.97*
E-wave deceleration time (msec)	174 $\pm$ 62	194 $\pm$ 62*
Isovolumic relaxation time (msec)	78 $\pm$ 19	75 $\pm$ 25
Left ventricular volume (ml)		
End diastolic	109 $\pm$ 43	117 $\pm$ 50
End systolic	58 $\pm$ 32	61 $\pm$ 37
Left ventricular ejection fraction	0.50 $\pm$ 0.15	0.50 $\pm$ 0.13
Left ventricular wall thickness (mm)		
Posterior	12.8 $\pm$ 2.9	12.8 $\pm$ 3.1
Septal	12.5 $\pm$ 3.7	12.9 $\pm$ 3.6
Left ventricular dimension (mm)		
End diastolic	49.7 $\pm$ 9.5	49.4 $\pm$ 9.8
End systolic	38.3 $\pm$ 10.1	38.3 $\pm$ 10.7

\* $P < 0.05$  for the comparison with the value during the acute episode.

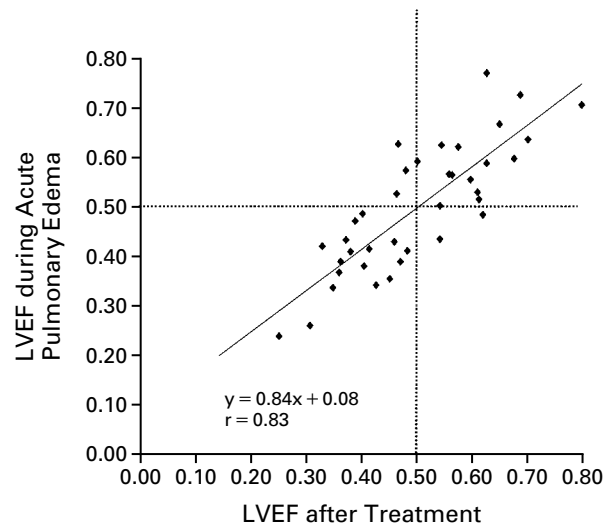


Figure 2. Left Ventricular Ejection Fraction (LVEF) during Acute Pulmonary Edema and One to Three Days Later, after Treatment.

The solid line is the regression line. The dotted lines indicate normal values for the ejection fraction.

The left ventricular regional wall-motion index at presentation ( $1.6 \pm 0.6$ ) was the same as that at follow-up ( $1.6 \pm 0.6$ ). The wall-motion index at follow-up correlated directly with the index at presentation ( $y = 0.97x - 0.06$ ,  $r = 0.98$ ;  $P < 0.01$ ) (Fig. 3). In 31 of the 38 patients, the wall-motion index during the

**TABLE 2.** CHARACTERISTICS OF THE 18 PATIENTS WITH A LEFT VENTRICULAR EJECTION FRACTION OF AT LEAST 0.50 AT FOLLOW-UP.

VARIABLE	DURING ACUTE PULMONARY EDEMA	AFTER TREATMENT
	mean ±SD	
Blood pressure (mm Hg)		
Systolic	209±28	142±15*
Diastolic	96±20	60±15*
Heart rate (beats/min)	79±12	66±11*
Flow velocity (cm/sec)		
E wave	98±36	104±29
A wave	94±27	86±19
E wave:A wave	1.04±0.37	1.25±0.38*
E-wave deceleration time (msec)	186±60	212±57
Isovolumic relaxation time (msec)	77±15	74±23
Left ventricular volume (ml)		
End diastolic	85±31	94±32
End systolic	36±19	37±16
Left ventricular ejection fraction	0.59±0.09	0.61±0.07
Wall-motion index	1.28±0.96	1.25±0.96
Left ventricular wall thickness (mm)		
Posterior	13.2±3.2	13.5±2.9
Septal	13.5±3.3	13.8±3.3
Left ventricular dimension (mm)		
End diastolic	45.0±6.4	43.9±5.7
End systolic	34.4±5.7	32.3±6.1

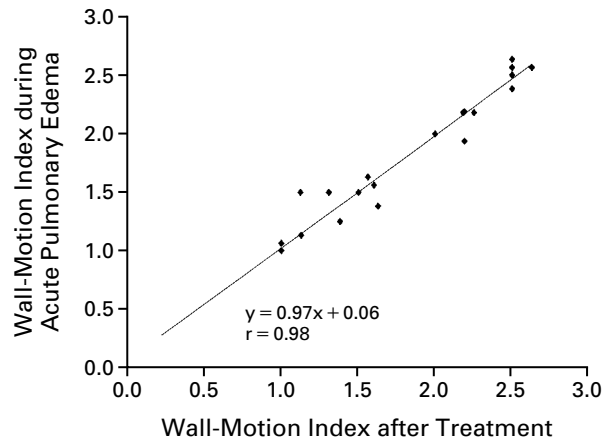
\*P<0.05 for the comparison with the value during the acute episode.

acute episode was identical to or lower than the index in the follow-up study. In two patients, the wall-motion index was at least 0.25 higher in the study performed during the acute episode than in the follow-up study. In all other patients, the wall-motion index was no more than 0.13 higher during the episode of acute pulmonary edema than in the follow-up study. Fourteen patients had a completely normal wall-motion index (1.0) at follow-up. All these patients also had an index at presentation of 1.06 or lower. Some mitral regurgitation could be detected in 32 patients during the initial echocardiographic examination. It was minimal in 26 patients and moderate in 6 patients. No patient had severe mitral regurgitation.

### DISCUSSION

We undertook this study to test the hypothesis that acute pulmonary edema in association with hypertension is frequently due to transient systolic dysfunction. Contrary to our supposition, we found that the left ventricular ejection fraction and the extent of regional wall motion measured during the acute episode of hypertensive pulmonary edema were similar to those measured after the resolution of the congestion, when the blood pressure was controlled.

Half the patients in this study who presented with acute pulmonary edema and hypertension were subsequently found to have a normal left ventricular ejection



**Figure 3.** Left Ventricular Regional Wall-Motion Index during Acute Pulmonary Edema and One to Three Days Later, after Treatment.

Some data points indicate values for more than one patient.

fraction (0.50 or greater). This finding is consistent with previous observations suggesting that in 40 percent or more of such patients, particularly elderly patients, heart failure is due to isolated diastolic (not systolic) dysfunction.<sup>1,3,4</sup> Since, in previous studies, the left ventricular ejection fraction was measured only after the treatment of the patient and stabilization of his or her condition, it was not known whether the acute episode of pulmonary congestion resulted from transient systolic dysfunction due to hypertension, from myocardial ischemia, or both.<sup>3</sup> Possible causes of pulmonary edema other than diastolic dysfunction include pulmonary disease and transient, severe mitral regurgitation. We addressed these possibilities in this study.

On admission, our patients had clinical and radiographic evidence of pulmonary edema that subsequently resolved with diuresis and control of hypertension; these observations ruled out unrecognized pulmonary disease as the cause of the acute problem. Furthermore, none of the patients had severe mitral regurgitation.

The left ventricular ejection fraction measured during the acute episode was similar to the ejection fraction measured one to three days later, after treatment. Eighty-nine percent of the patients who had a normal ejection fraction after treatment also had an ejection fraction of 0.50 or greater during the acute episode, and all these patients had an ejection fraction of at least 0.43 during the acute episode. Thus, the ejection fraction as measured one to three days after the episode of acute hypertensive pulmonary edema accurately identified patients with a normal ejection fraction at presentation whose acute heart failure was due to isolated diastolic dysfunction.

Even in the patients with systolic dysfunction (i.e., a follow-up ejection fraction of less than 0.50), the left ventricular ejection fraction measured during the acute episode was similar to that measured after therapy. This similarity suggests that diastolic dysfunction may also be an important contributor to acute hypertensive pulmonary edema in patients with baseline systolic dysfunction.

Acute pulmonary edema can be due to transient ischemic dysfunction of the left ventricle. More than half our patients had segmental wall-motion abnormalities that were detectable on the echocardiogram obtained after treatment, suggesting the presence of ischemic heart disease. However, in our patients, the ejection fraction was not lower during the acute episode, and only two patients had recognizable regional wall-motion abnormalities at presentation that were not present after therapy. Thus, acute left ventricular systolic dysfunction related to ischemia was not the cause of acute heart failure in our patients. However, ischemia may have contributed to diastolic dysfunction without causing a measurable reduction in the ejection fraction or in the extent of regional wall motion.<sup>2</sup> It is possible that many patients with pulmonary edema due to ischemic left ventricular systolic dysfunction or acute mitral regurgitation are not able to generate high systolic pressures and, thus, were not included in our study.<sup>13</sup> Also, we cannot be certain that transient systolic dysfunction was not present in our patients before the first echocardiogram was obtained.

Since the pulmonary congestion in our patients cleared when their blood pressure was lowered, hypertension may have contributed to the diastolic dysfunction.<sup>14</sup> Normally, the left ventricle compensates for an increase in systolic load by using preload reserve (i.e., an increase in the end-diastolic volume). In a patient with diastolic dysfunction, this small increase in left ventricular end-diastolic volume may be associated with a marked elevation in diastolic pressure, because of the reduced distensibility of the left ventricle. However, we did not observe a consistent increase in end-diastolic volume during the episode of acute pulmonary edema. Acute hypertension might also decrease left ventricular distensibility by increasing coronary turgor.<sup>15</sup> Although this mechanism may have contributed to the development of pulmonary edema, the increase in intramyocardial blood volume was not large enough to produce a detectable increase in the thickness of the left ventricular wall.

Markers of the performance of the left ventricle, such as the ejection fraction, are dependent on the afterload.<sup>16,17</sup> Thus, one expects the ejection fraction to decline as the systolic blood pressure increases if the contractile state of the left ventricle remains constant. In contrast, we found that the left ventricular ejection fraction was the same during an episode of acute hypertensive pulmonary edema as it was when

the blood pressure was controlled. It is possible that the inotropic stimulation produced by increased beta-adrenergic tone during acute pulmonary edema offsets the effects of increased afterload on systolic performance. Although a higher heart rate during pulmonary edema is consistent with this possibility, it is also the case that more of the patients were receiving beta-blockers during the follow-up examination.

In conclusion, we found that the left ventricular ejection fraction during an episode of acute hypertensive pulmonary edema is similar to that measured after treatment, when the blood pressure has been controlled. Thus, a normal left ventricular ejection fraction after the treatment of a patient with hypertensive pulmonary edema indicates a high probability that the pulmonary congestion was due to isolated, transient diastolic dysfunction, since transient systolic dysfunction and severe acute mitral regurgitation are infrequent during acute episodes in these patients.

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