Acute Effect of Percutaneous Transvenous Mitral Commissurotomy on Ventilatory and Hemodynamic Responses to Exercise

Pathophysiological Basis for Early Symptomatic Improvement

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Background. Improvement of exertional dyspnea occurs immediately after percutaneous transvenous mitral commissurotomy (PTMC), but the pathophysiological basis for this early symptomatic improvement has not been elucidated.

Methods and Results. Exercise hemodynamic measurement and exercise ventilatory measurement with arterial blood gas analysis were performed in 21 patients aged 50.4±9.5 years (mean±SD) with symptomatic mitral stenosis before and a few days after PTMC. Exercise ventilatory measurement were also performed in 14 normal control subjects aged 48.9±4.9 years. After PTMC, mitral valve area increased (from 1.0±0.3 to 1.7±0.3 cm², P<.001), mean mitral gradient (from 12.2±5.2 to 5.2±2.2 mm Hg, P<.001), and mean left atrial pressure (from 18.7±6.1 to 12.1±4.0 mm Hg, P<.001) decreased. All patients experienced significant symptomatic improvement soon after PTMC. Comparison of hemodynamic parameters at the same ergometer work rate showed a significant decrease in pulmonary artery systolic pressure (from 77±18 to 67±14 mm Hg, P<.001) and diastolic pressure (from 36±10 to 28±7 mm Hg, P<.001) and a significant increase in cardiac output (from 6.4±1.4 to 8.1±1.9 L/min, P<.001). Despite the improvement in exercise hemodynamics and symptoms, exercise capacity determined by peak oxygen uptake (from 18.0±2.9 to 18.6±3.1 mL·kg⁻¹·min⁻¹) and anaerobic threshold (from 11.7±2.4 to 12.0±2.4 mL·kg⁻¹·min⁻¹) remained unchanged. Excessive exercise ventilation, as assessed by the slope of the regression line between expired minute ventilation and carbon dioxide output, decreased significantly from 37.2±6.7 to 33.9±5.8 (P<.001), but remained significantly higher than that in the normal subjects (27.9±3.6, P<.01). The ratio of total dead space to tidal volume and total dead space per breath during exercise decreased significantly after PTMC (P<.05). The change in excessive exercise ventilation after PTMC was correlated with the change in dead space to tidal volume ratio (r=.59).

Conclusions. Significant relief of exertional dyspnea immediately after PTMC is not accompanied by an improvement in exercise capacity. A decrease in excessive exercise ventilation due to a decrease in physiological dead space resulting from hemodynamic improvement partly contributes to the early relief of symptoms after PTMC. However, lung compliance, which was not measured in the present study, may have changed after PTMC. This change may also contribute to the symptomatic improvement. (Circulation. 1993;88[part 1]:1770-1778.)

Key Words • exercise • valves • dyspnea • heart failure

The principal symptom of mitral stenosis is exertional dyspnea.1 Several factors causing exertional dyspnea have been suggested, including early anaerobic metabolism due to low cardiac output,2 reduced lung compliance due to increased pulmonary capillary wedge pressures,3-5 increased use of anatomic dead space due to rapid shallow breathing, and increased physiological dead space due to ventilation-perfusion mismatch.6,7 An improvement of exertional dyspnea has been recognized to occur immediately after percutaneous transvenous mitral commissurotomy (PTMC),7,9 but the mechanism involved has not yet been elucidated.

Exercise ventilation is abnormally increased in patients with chronic heart failure, including those with mitral stenosis,10-16 and this excessive exercise ventilation is due mainly to an increase of physiological dead space.11-14 The magnitude of this abnormality, which may be an important factor in exertional dyspnea, appears to be related to the severity of exercise intolerance.13,14 However, whether the improvement in ex-

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TABLE 1. Clinical Characteristics of Patients and Results of PTMC

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Mean±SD  50.4±9.5  1.0±0.3  1.7±0.3  12.2±5.2  5.2±2.2  18.7±6.1  12.1±4.0  
P<.001   P<.001   P<.001

PTMC indicates percutaneous transvenous mitral commissurotomy; MVA, mitral valve area; mL A, mean left atrial pressure; mPG, mean mitral pressure gradient; MR, mitral regurgitation; NYHA, New York Heart Association; and pre and post, before and after PTMC. NYHA functional class II is subdivided into IIls (slight limitation of physical activity) and IIIm (moderate limitation of physical activity).

tnlventorial dyspnea after successful treatment of heart failure is directly related to a reduction in excessive exercise ventilation remains to be clarified.

Accordingly, this study was undertaken to investigate the pathophysiological basis for the relief of exertional dyspnea immediately after PTMC. We examined the ventilatory and hemodynamic responses to exercise before and after PTMC and evaluated the changes in excessive exercise ventilation, dead space ventilation, breathing pattern, exercise capacity determined from the anaerobic threshold, and peak oxygen uptake (peak \( V_{O_2} \)) , pulmonary artery pressure, and cardiac output. Investigation of patients undergoing PTMC allowed us to assess the acute and direct effects of mitral commissurotomy on the ventilatory and hemodynamic responses to exercise without the influence of thoracotomy.

Methods

Study Population

Twenty-one patients (20 women and 1 man) with symptomatic mitral stenosis who underwent PTMC and 14 normal control subjects (13 women and 1 man) were studied. The mean age of the patients was 50.4±9.5 years (range, 32 to 69 years) and that of the controls was 48.9±4.9 years (range, 40 to 59 years). Five patients had previously undergone surgical commissurotomy. Eight patients were in normal sinus rhythm, and the remaining 13 were in atrial fibrillation. Twelve patients had trivial or mild aortic regurgitation, but no patient had severe aortic regurgitation or significant aortic stenosis. Informed consent for PTMC and/or exercise testing was obtained from all subjects.

Cardiac Catheterization and PTMC

All patients underwent diagnostic left and right heart catheterization and coronary arteriography before PTMC, and the coronary arteries were found to be normal or minimally sclerotic in all cases. PTMC was performed by the transseptal approach using an Inoue balloon.\(^{17,18}\) The mitral valve orifice area was calculated by the Gorlin formula before and immediately after PTMC. Left ventriculography was performed before and after PTMC to determine the severity of mitral regurgitation, and this was graded from 0 to 4+ by the Sellers classification.\(^{19}\)

Clinical status and symptoms were assessed by the New York Heart Association (NYHA) functional classification before and 1 week after PTMC.\(^{20}\) NYHA functional class II was subdivided into IIls (slight limitation of physical activity) and IIIm (moderate limitation of physical activity).
TABLE 2. Hemodynamic and Ventilatory Response to Exercise Before and After PTMC

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Mean±SD 77±18 67±14 36±10 28±7 6.4±1.4 8.1±1.9

PTMC indicates percutaneous transluminal mitral commissurotomy; AT, anaerobic threshold; CO, cardiac output; ND, not determined; PAd, pulmonary artery diastolic pressure; PAs, pulmonary artery systolic pressure; peak VO₂, peak oxygen uptake; VO₂/VT, ratio of total dead space to tidal volume; Ve–VCO₂, excessive exercise ventilation assessed by the slope of the regression line between expired minute ventilation and CO₂ output; and WR, work rate at the hemodynamic measurements.

Measurement of Exercise Hemodynamics

A 7F Swan-Ganz catheter was inserted into the pulmonary artery via an internal jugular vein on the day before PTMC. After baseline hemodynamics were measured, patients underwent symptom-limited supine ergometer exercise testing. The work rate was started at 20 W and increased in 20-W increments at 3-minute intervals. The ECG was continuously monitored, and the cuff blood pressure was measured at 1-minute intervals. Cardiac output determined by the thermodilution technique and pulmonary artery systolic and diastolic pressures were measured at the end of each work rate period. Each thermodilution curve was recorded and inspected for technical accuracy while the cardiac output was calculated by a thermodilution computer. Exercise hemodynamic measurements were repeated 1 day after PTMC, and the hemodynamic data obtained before and after PTMC were compared at the peak work rate level before PTMC.

Measurement of Exercise Ventilation

All subjects underwent a familiarization maximal exercise test with respiratory gas analysis 2 to 14 days before the study. Patients were given their usual cardiac medications, which were not changed during the study period. All patients underwent maximal symptom-limited exercise while seated on an electrically braked bicycle ergometer 2 to 4 days before and after PTMC. Exercise was done at least 2 hours postprandially and at almost the same time of day, usually at 3:00 pm. The normal control subjects also underwent maximal symptom-limited exercise to determine normal exercise ventilatory values. After a 3-minute rest period on the ergometer, exercise began with a 2- to 3-minute warm-up period at 10 W, followed by a continuous ramp protocol corresponding to increments of 10 to 20 W/min until the subject could no longer continue. The ECG was monitored throughout exercise, and a 12-lead ECG was recorded at 1-minute intervals. Cuff blood pressure was measured at 1-minute intervals. Respiratory gas analysis was performed on a breath-by-breath basis using an Aero Monitor AE-280 (Minato Medical Science, Osaka, Japan). This system consists of a hot-wire
TABLE 2. Continued

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<th>Peak VO₂</th>
<th>AT, mL · kg⁻¹ · min⁻¹</th>
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| NS       | NS        | P<.001   | P<.001   |

Spirometer, a zirconia cell oxygen analyzer, and an infrared absorption carbon dioxide (CO₂) analyzer, and it introduces only a small volume of dead space into the ventilatory circuit. The apparatus was calibrated before each study was performed. Data were processed using an on-line computer system, and the following parameters were calculated: expired minute ventilation (Ve), O₂ uptake (VO₂), CO₂ output (VCO₂), respiations, tidal volume, end-tidal Po₂ (ETO₂), end-tidal PCO₂ (ETCO₂), respiratory exchange ratio (RER; VCO₂/VO₂), ventilatory equivalent for O₂ (Ve/V0₂), and ventilatory equivalent for CO₂ (Ve/VCO₂). Before exercise, a cannula was introduced into the brachial artery. Arterial blood samples were drawn into heparinized syringes over a 20-second period at rest, during the warm-up period, and at 1-minute intervals throughout exercise. Blood samples were immediately placed in ice and analyzed within 30 minutes using a blood gas analyzer (Radiometer ABL-2, Copenhagen, Denmark). During exercise, Ve increases with VCO₂ so as to keep arterial PCO₂ relatively unchanged. Therefore, exercise ventilation was assessed by correlating Ve with VCO₂ from the start of ventilatory measurement to peak exercise using linear regression analysis. The correlation coefficient exceeded 0.97 in all subjects. The slope of the regression line between Ve and VCO₂ (Ve–VCO₂) was used to compare the level of excessive exercise ventilation. The ratio of total dead space to tidal volume (VD/VT) and total dead space per breath were derived from the modified alveolar gas equation:

\[ \dot{V_e} = 863 \cdot \frac{\dot{V}CO₂}{[P(a-ET)CO₂]} \]  

The total dead space comprises the mechanical dead space of the respiratory gas analysis system and the physiological dead space of the subject, which includes the anatomic dead space. VD/VT gradually decreases during exercise and reaches a plateau near peak exercise, so the minimal VD/VT during exercise was determined in each test. The arterial-end tidal PCO₂ difference [Pa–ETCO₂] was also calculated. Exercise capacity was assessed on the basis of peak VO₂ and anaerobic threshold values. Peak VO₂ was determined as the average of values obtained during the final 15 seconds of exercise. Anaerobic threshold was determined by two experienced reviewers using the V-slope method, as well as by the following conventional criteria: the point where Ve/VO₂ increases after being stable or decreasing while Ve/VCO₂ remains constant or decreasing, the point where an increase in ETO₂ occurs without a decrease in ETCO₂, and the point where a stable or slowly rising RER begins to rise more steeply.

Statistical Analysis

All data were expressed as mean±SD. Comparison of data obtained before and after PTMC was done using
the paired t test. Comparison of the ventilatory re-
sponse between patients after PTMC and the normal
subjects was performed with the unpaired t test. Two-
way ANOVA was used to assess the significance of
changes in the exercise ventilatory and arterial gas
responses before and after PTMC. Linear regression
analysis was used to assess the relationship between
changes in minimal VD/VT and changes in VE−VCO₂
and the relationship between minimal VD/VT and
NYHA functional class. A value of P<.05 was consid-
ered significant.

**Results**

**Results of PTMC**

After PTMC, mitral valve area increased from
1.0±0.3 to 1.7±0.3 cm² (P<.001). Mean mitral gradient
decreased from 12.2±5.2 to 5.2±2.2 mm Hg (P<.001),
and mean left atrial pressure decreased from 18.7±6.1
to 12.1±4.0 mm Hg (P<.001). Before PTMC, 10 pa-
tients had no mitral regurgitation, 8 patients had 1+
mitral regurgitation, and 3 patients had 2+ mitral
regurgitation. Immediately after PTMC, 17 patients
had no change in the grade of mitral regurgitation, 3
patients had a 1+ increase (2 patients from 0 to 1+ and
1 patient from 1+ to 2+), and 1 patient had a 2+ increase
(from 0 to 2+). All patients experienced symptomatic
improvement almost immediately after PTMC, and the
mean NYHA functional class improved significantly
from 2.6±0.3 to 1.7±0.5 (P<.001) (Table 1).

**Hemodynamic Response to Exercise**

Supine ergometer exercise testing after PTMC re-
vealed a significant decrease in pulmonary artery sys-
tolic pressure from 77±18 to 67±14 mm Hg (P<.001)
and in pulmonary artery diastolic pressure from 36±10
to 28±7 mm Hg (P<.001), as well as a significant in-
crease in cardiac output from 6.4±1.4 to 8.1±1.9
L/min (P<.001) after PTMC (Table 2).

**Ventilatory Response to Exercise**

Peak VO₂ did not improve after PTMC (from 18.0±2.9
to 18.6±3.1 mL·kg⁻¹·min⁻¹) (Table 2). Peak VO₂ in
the normal control subjects (27.1±4.1 mL·kg⁻¹·min⁻¹) was
significantly higher than that in the patients (P<.01).
Anaerobic threshold could be determined in 20 of the 21
patients and in all of the control subjects. In 12 patients
and all 14 controls, anaerobic threshold was determined
by the V-slope method. In the other 8 patients, anaerobic
threshold was determined by the conventional method
because anaerobic threshold occurred within the first
1 minute after starting incremental exercise. As with peak
VO₂, anaerobic threshold did not improve after PTMC
(from 11.7±2.4 to 12.0±2.4 mL·kg⁻¹·min⁻¹), and anaer-
obic threshold of the control subjects (16.5±2.4
mL·kg⁻¹·min⁻¹) was significantly higher than that of the
patients (P<.01). RER at rest was 0.88±0.06 before
PTMC and 0.86±0.08 after PTMC. RER at peak exercise
was 1.17±0.07 before PTMC and 1.20±0.08 after PTMC,
indicating that near maximal exertion was achieved in
both exercise tests. Excessive exercise ventilation, as
assessed by VE−VCO₂, decreased significantly from
37.2±6.7 to 33.9±5.8 (P<.001) after PTMC but remained
significantly higher than in the normal controls (27.9±3.6;
range, 21.0 to 34.0; P<.01) (Fig 1). Respirations during

![Fig 1. Plot of excessive exercise ventilation assessed by the slope of the regression line between expired minute ventilation and carbon dioxide output (VE−VCO₂). Shaded area represents the mean±SD of the 14 normal subjects. PTMC indicates percutaneous transvenous mitral commissurotomography.](http://circ.ahajournals.org/content/88/4/1774/F1)

exercise tended to decrease after PTMC but not to a
statistically significant extent (Fig 2). Tidal volume during
the exercise test was nearly identical at a comparable work
rate before and after PTMC (Fig 2). VD/VT decreased
significantly after PTMC (P<.05) and total dead space per
breath also decreased significantly (P<.05) (Fig 3). Min-
imal VD/VT decreased significantly from 0.38±0.08 to 0.34±0.08 (P<.001) but remained larger than that of the
control subjects (0.25±0.06; range, 0.15 to 0.33; P<.01).
The relationship between NYHA functional class and
minimal VD/VT is shown in Fig 4. Minimal VD/VT was
significantly correlated with NYHA functional class
(r=.55, P<.001). There was a tendency for minimal
VD/VT to decrease after PTMC as NYHA functional
class improved. Minimal VD/VT was above the normal
range in all patients in NYHA functional class III before
PTMC, and minimal VD/VT was within the mean±SD of
the normal subjects in all 6 patients who improved to
NYHA functional class I after PTMC. The change in
VE−VCO₂ was significantly correlated with the change
in minimal VD/VT (r=.59, P<.005) (Fig 5). Arterial Po₂
and PCO₂ were nearly identical throughout the exercise period
before and after PTMC (Fig 6). P(a−ET)CO₂, which was
positive before exercise and became increasingly negative
with exercise, decreased significantly after PTMC (P<.05)
(Fig 7). These results indicate that the decrease in exces-
sive exercise ventilation after PTMC was mainly due to a
reduction in physiological dead space during exercise.

**Discussion**

The present study suggested that the significant relief of
exertional dyspnea immediately after PTMC may be asso-
ciated with a decrease in excessive exercise ventilation
resulting from improved exercise hemodynamics rather
than being related to exercise capacity, which showed little
change in the early period following PTMC. Exces-
sive exercise ventilation and rapid shallow breathing
during exercise are common in patients with severe
mitral stenosis, and studies have shown that
these abnormalities are improved after surgical commissurotomy.29,30 However, these studies were performed in the late phase following thoracotomy, and exercise capacity had also increased by this time. Therefore, the acute effect of commissurotomy on the exercise ventilatory response has not been shown previously. Since the clinical application of PTMC for the treatment of mitral stenosis,17,31 most patients experience the relief of exertional dyspnea immediately after PTMC.7-9 McKay et al8 noted that the NYHA functional class improved within 1 to 2 weeks after PTMC and showed no further change at 3 months in most cases. They showed that exercise capacity as assessed by treadmill exercise time was significantly increased 3 months after PTMC, but they did not measure it in the early post-PTMC phase.8 The significant increase in cardiac output and significant decrease in pulmonary artery pressure that were noted at rest and during exercise after PTMC have been regarded as the physiological explanation of the improvement in symptoms.7,8 However, acute hemodynamic improvements are not generally accompanied by an immediate increase in exercise capacity.32-34 In patients with chronic heart failure, acute administration of vasodilators or inotropic agents does not increase exer-

**FIG 3.** Plot of effect of percutaneous transvenous mitral commissurotomy (PTMC) on ratio of total dead space to tidal volume and total dead space per breath at rest and during exercise.

**FIG 2.** *Plot of effect of percutaneous transvenous mitral commissurotomy (PTMC) on respiratory rate and tidal volume at rest and during exercise.*

**FIG 4.** Scatterplot shows correlation between NYHA functional class and minimal VD/VT. Shaded area represents the mean ± SD of the minimal VD/VT in the 14 normal subjects. Minimal VD/VT was significantly correlated with NYHA functional class (r = .55, P < .001). There was a tendency for minimal VD/VT to decrease after PTMC as NYHA functional class improved. NYHA indicates New York Heart Association; PTMC, percutaneous transvenous mitral commissurotomy; and VD/VT, ratio of total dead space to tidal volume.
cise capacity, despite causing a marked increase in cardiac output and a decrease in filling pressure during exercise. On the other hand, chronic vasodilator therapy improves the exercise tolerance and clinical state after a period of weeks to months.

Skeletal muscle hypoperfusion is the major cause of poor exercise tolerance in patients with chronic heart failure, but reduced skeletal muscle aerobic enzyme activity and impaired peripheral vasodilatory function also play an important role in limiting exercise. Amelioration of these abnormalities may produce a gradual and variable increase in exercise tolerance after central hemodynamic improvement. Our study also showed that exercise capacity as assessed by anaerobic threshold and peak Vo2 was not improved soon after PTMC, despite an increase in exercise cardiac output during exercise. Thus, neither hemodynamic improvement per se nor a delay in the onset of anaerobic metabolism was the cause of the reduction in exertional dyspnea in the early period following PTMC.

Excessive exercise ventilation in patients with chronic heart failure is caused mainly by an increase in physiological dead space, and the magnitude of this ventilatory abnormality appears to be related to the severity of exercise intolerance and exertional dyspnea. During exercise, VE increases with VCO2 so as to keep arterial Pco2 relatively constant. Therefore, the slope of the regression line between VE and VCO2 (VE-VCO2) has been used to assess the excessive ventilatory response to exercise. However, few studies have shown that the relief of exertional dyspnea is directly related to a reduction in excessive exercise ventilation. The present study demonstrated that excessive exercise ventilation assessed by VE-VCO2 improved significantly within a few days after PTMC, in close relation to the symptomatic improvement. In contrast to our results, Marzo et al reported in a preliminary report that not only exercise capacity but also excessive ventilation remained unchanged 48 hours after PTMC. The inconsistent results may be due to the marked difference in the functional state of the subjects, because exercise capacity in their subjects (peak VO2, 10.2±4.7 mL·kg⁻¹·min⁻¹) was much lower than that in our subjects (peak VO2, 18.0±2.9 mL·kg⁻¹·min⁻¹). Organic lung change, which is liable to occur in more severe mitral stenosis, may be a factor. We showed that the change in VE-VCO2 was significantly correlated with the change in minimal VD/VT. Total dead space per breath during exercise significantly decreased, which primarily reflects the decrease in physiological dead space, but breathing pattern did not change significantly after PTMC. Therefore, the decrease in excessive exercise ventilation was mainly caused by the reduction in physiological dead space rather than by the decreased use of anatomic dead space. The increases in VE-VCO2 and physiological dead space that occur in severe heart failure imply a greater ventilation-perfusion mismatch. Attenuated pulmonary perfusion plays an important role in causing excessive exercise ventila-
tion and increased physiological dead space by producing adequately ventilated or even overventilated alveoli that receive little pulmonary blood flow. Pulmonary parenchymal abnormalities secondary to long-standing pulmonary venous hypertension may also contribute to increasing the physiological dead space.10,11 The present study showed that cardiac output increased significantly and pulmonary artery systolic and diastolic pressures decreased significantly both at rest and during exercise soon after PTMC. A chronic increase in cardiac output would reduce alveolar hypoperfusion, and a chronic reduction in pulmonary pressure would improve parenchymal abnormalities by decreasing interstitial fluid accumulation, thus providing a physiological basis for the reduction in excessive exercise ventilation and physiological dead space. The decrease in P(\(a\)-ET)\(CO_2\) during exercise also suggests that the number of ventilated alveoli with adequate perfusion increased after PTMC, ie, the ventilation-perfusion mismatch was improved.25

Some limitations must be considered when interpreting our results. The present study suggested that the decrease in excessive exercise ventilation due to a reduction in physiological dead space immediately after PTMC may contribute to early symptomatic improvement. However, the decrease in dead space was only modest, and a few patients did not show any reduction in excessive exercise ventilation or physiological dead space despite the symptomatic improvement. Therefore, the significant relief of exertional dyspnea cannot be attributed solely to the decrease in excessive exercise ventilation. Dyspnea is a subjective sensation of discomfort experienced during the act of breathing, and it is closely related to the work of breathing.3,4,22-44 The work of breathing depends on both the total ventilation and the mechanical properties of the lungs.42,43 If the total ventilation is greater than normal, and if the respiratory muscles must exert an abnormal amount of force to achieve a given ventilation, the work of breathing increases and the sensation of dyspnea consequently increases. Patients with severe mitral stenosis have been shown to suffer from a striking decline in lung compliance and an increase in respiratory work concomitant with rising pulmonary pressures.3,5,45 These abnormalities return toward normal when pulmonary congestion is relieved after surgical commissurotomy.46 We did not measure lung compliance and respiratory work in the present study. However, it is possible that not only the decrease in excessive exercise ventilation shown in the present study but also an improvement in the mechanical properties of the lung such as lung compliance resulting from reductions in pulmonary pressures may contribute to the amelioration of exertional dyspnea through reducing the work of breathing.

In conclusion, exercise capacity, as assessed by anaerobic threshold and peak \(VO_2\), was not improved despite significant symptomatic improvement in the early period after PTMC. A decrease in excessive exercise ventilation due to a reduction in physiological dead space resulting from improvements in exercise hemodynamics appeared to contribute to the early relief of symptoms. However, the decrease in excessive exercise ventilation was not particularly large, so other factors that influence the work of breathing such as lung compliance may also need to be considered to explain all of the significant amelioration of exertional dyspnea.

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