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EVALUATION WITH EQUILIBRIUM RADIONUCLIDE ANGIOGRAPHY OF LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION IN PULMONARY HYPERTENSION SECONDARY TO CHRONIC PULMONARY DISEASES

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INDEXING WORDS

pulmonary hypertension; left ventricular function; equilibrium radionuclide angiography

SYNOPSIS

To evaluate left ventricular systolic and diastolic function in patients with pulmonary hypertension secondary to chronic pulmonary diseases, 86 patients were studied using equilibrium radionuclide angiography with forward and reverse gating from the R wave. At rest left ventricular function, both in systolic and diastolic properties, in patients with pulmonary hypertension was significantly lower than in normal subjects (LVEF; $P < 0.05$, PER; $p < 0.05$, PFR; $P < 0.025$, FF; $P < 0.025$). During exercise left ventricular systolic function did not increase as much as in normals (LVEF; N.S., PER; N.S.). Left ventricular diastolic function during exercise was significantly lower than at rest (PFR; $P < 0.05$, FF; $P < 0.001$). The indices of left ventricular function obtained from radionuclide angiography had no close correlation with pulmonary hemodynamics or with blood gases.

These results demonstrated that left ventricular dysfunction in patients with pulmonary hypertension was observed both at rest

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and during exercise, and might play an important role in reduced exercise tolerance.

INTRODUCTION

Overt or latent biventricular failure is often seen in patients with chronic pulmonary disease, but the mechanism responsible for left ventricular dysfunction remains controversial. In those patients the severity of pulmonary hypertension and the development of cor pulmonale characterized with right ventricular hypertrophy may be closely related with mortality and reduced exercise tolerance. The major cause of heart failure in chronic pulmonary disease is a marked increase in the afterload to the right ventricle, but there are many other contributable factors. Recently attentions have been paid to the left ventricular function in patients with pulmonary hypertension and it has been studied by means of various methods.[15,17,19] Indeed, the left ventricular performance is closely associated with right ventricular function both clinically and experimentally, and that in isolated right ventricular failure, morphologic and biochemical changes were observed in left ventricle.[9,10] The purposes of this study are to evaluate the left ventricular dysfunction and to clarify its mechanism in patients with pulmonary hypertension sedondary to chronic pulmonary diseases. We used ^{99m}TC equilibrium radionuclide angiography with forward and reverse gating from the R wave which is a generally accepted method for the noninvasive estimation of the left ventricular ejection fraction and has the advantage of being less dependent on geometrical factors in comparison with methods based on the outlining of contours, e.g., angiography and echocardiography.[18,29] This study includes hemodynamic measurements at rest and during exercise with supine ergometer.

SUBJECTS AND METHODS

a) Patient population

Eighty-six patients with pulmonary hypertension (more than 20 mmHg in mean pulmonary artery pressure) secondary to chronic pulmonary diseases were studied. Fifty-two patients were male and

34 were female. The mean age was 59±11 years (44-74 years). Forty patients had chronic obstructive pulmonary disease and 46 had old pulmonary tuberculosis. All patients underwent ^{99m}Tc equilibrium radionuclide angiography with forward and reverse gating from the R wave, right cardiac catheterization and ^{201}Tl myocardial imaging. At the time of the study all patients were in a stable state and had no acute exacerbation within the previous two weeks. Patients were excluded who were known to have had systemic hypertension, valvular heart disease, congenital heart disease, coronary artery disease or primary myocardial disease. We also studied 50 normal subjects, aged 47 to 68 years (56± 11) to determine the normal values for the radionuclide angiography. In addition, nine-teen patients with pulmonary hypertension and 20 normal subjects underwent ergometer exercise testing using readionuclide angiography.

b) Hemodynamic measurements

Right heart catheterization was done in each patient with a baloon-tipped Swan-Ganz Catheter introduced from a subclavian vein or a femoral vein while breathing air, all drugs having been withheld for 12 hours prior to this study. Intravascular pressures were recorded through fluid-filled catheters with the transducer at the mid-axially level. Cardiac output was measured by the thermodilution method, using cardiac output computer (9520A Edwards). Arterial blood gas tension was measured using 178 blood gas analyzer (Corning). Then measurements of pulmonary capillary wedge pressure, pulmonary arterial, right ventricular, and right arterial pressures were sequentially made by averaging the values over at least three respiratory cycles. Systemic arterial pressure was measured by using cuff sphygmomanometer, and mean pressures were calculated by adding one-third of the pulse pressure to the diastolic pressure. Pulmonary vascular resistance (dynes/ sec /cm^5) was calculated as (PAP-PCWP) x 80/CO, where PAP is mean pulmonary artery, and PCWP is mean pulmonary capillary wedge pressure; and right ventricular stroke work index (gm.m/m^2BSA/beat) as SVI x (PAP - RAP) x 0.0136, where SVI is stroke volume index and RAP is mean right atrial pressure. Heart Rate was determined from an electrocardiogram record during the time of cardiac output measurement. Symptom-limited maximal supine bicycle ergometry with

25 Watt's per 3 minutes incremental method was performed in 19 patients from those with pulmonary hypertension, and before and during exercise observations were made with right cardiac catheterization and ^{99m}Tc equilibrium radionuclide angiography.

c) Equilibrium radionuclide angiography

All studies were performed with a portable scintillation camera (Gamma View F, Hitachi), with the gamma detector placed in the 45° left anterior oblique position with a 15° caudal tilt. A high-sensitivity, parallel-hole callimator was used in all studies, and energy selection was set 140 KeV with a 20% window. The cardiac image sequence spanning the average cardiac cycle was constructed from several hundred cardiac cycles by computerbased electrocardiographic gating, using list-mode data acquisition (framing rate up to 100 images/s). High temporal resolution LV time-activity curves were generated from the cardiac image sequence after background correction. Ectopic beats were excluded from the data, and the diastolic portion of the time-activity curve was constructed by combined forward and reverse gating from the R wave to evaluate left ventricular diastolic properties more accurately. The time-activity curve represents a measure of relative LV volume changes with time throughout the cardiac cycle. The following variables were analyzed (Fig. 1). LV ejection fraction was automatically determined by computer analyses of the time-activity curve. Peak ejection rate was computed from the time activity curve in counts per second, normalized for the number of counts at end-diastole, and expressed as enddiastolic volume per second (EDV/sec). Peak filling rate was also computed in counts per second, normalized for the number of counts at end-diastole, and expressed as end-diastolic volume per second (EDV/sec).

Filling fraction was obtained by dividing the time from end-systole to end-diastole into 3 equal intervals; the time for the first third of diastole could then be determined. Filling fraction was then defined as the difference between the counts at the end of the first third of diastole and at end-systole divided by the counts at the end of the first third of diastole and expressed as a percentage.

After images and time-activity curves were obtained at rest, imaging was repeated during supine ergometer in 19 patients with pulmonary hypertension and 20 normal subjects. Exercise loads were

increased in a stepwise fashion by 25 W at 3-minute intervals until the appearance of fatigue or dyspnea. Heart rate and blood pressure (by cuff sphygmomanometry) were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only the portion of the data series that occurred during maximal

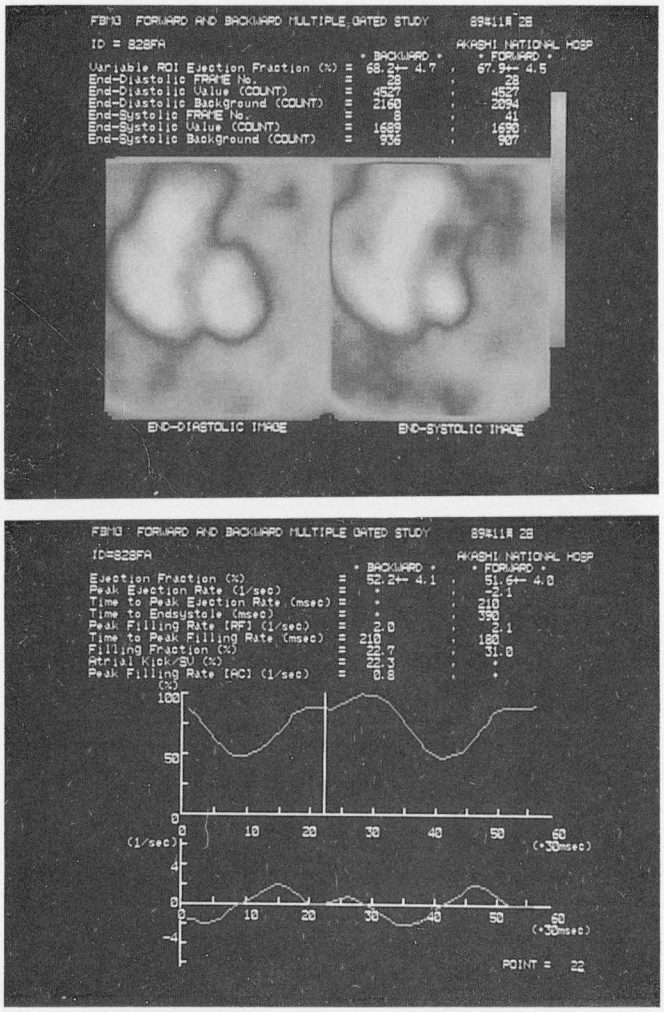


Fig. 1 Equilibrium radionuclide angiography.
End-diastolic and end-systolic image (top) and left ventricular volume curve (bottom).

exercise, encompassing the final 3 minutes of exercise, was used for analysis. After completion of imaging, left ventricular ejection fraction at rest and during exercise was determined by computer analysis of the time-activity curves as previously described.

Statistical analysis

All values were expressed as mean±SD. Differences in means were assessed by unpaired Student's t test. Probability (P) values of less than 0.05 were considered statistically significant. Regression analysis was performed by the least squares method.

RESULTS

1) Resting values

a) Hemodynamics

Baselne characteristics of all patients in hemocynamics are presented in Table I. Hemodynamic variables at baseline showed a moderate pulmonary hypertension (mean PAP 26.3±4.2 mmHg) and a

Table I Results of pulmonary hemodynamic data in patients with chronic pulmoanry diseases. (n=86)

PAP (systolic)	44.9±6.8
PAP (diastolic)	15.6±4.5
PAP (mean)	26.3±4.2
PCWP (mean)	9.2±5.0
C.I. l/min/m^2	2.80±0.30
PVR dynes/sec/cm^5	5.01±186
RAP (mean)	6.2±3.0
RVSWI gm・m/m^2 BSA/beat	12.4±3.3
PaO_2 mmHg	57.2±7.0
$PaCO_2$ mmHg	44.9±3.1

Data are mean±SD
Abbreviations : PAP=pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, C.I.=cardiac index, PVR=pulmonary vascular resistance, RAP=right atrial pressure, RVSWI=right ventricular stroke work index

moderate elevation of pulmonary vascular resistance (501±186 dynes/sec/cm^5). Mean pulmonary wedge pressure (9.2±5.0 mmHg) and cardiac index (2.80±0.30 l/min/m^2) were within the normal range. Mean right atrial pressure (6.2±3.0 mmHg) was slightly high, and right ventricular stroke work index (12.4±3.3 gm.m/m^2BSA/beat) was moderately high. Arterial oxygen tension (PaO_2) (57.2±7.0 mmHg) was low, but arterial carbon-dioxide tension ($PaCO_2$) PCO_2 (44.9±3.1 mmHg) was within the normal range.

b) Equilibrium radionuclide angiography

Table II summarizes the results of ejection fraction, peak ejection rate, peak filling rate and filling fraction in normal subjects and patients with pulmonary hypertension at rest. Of systolic function at rest, ejection fraction was statistically higher in normal subjects than in patients with pulmonary hypertension (63.2±5.8% vs 52.1±8.2%, P<0.05). Patients with pulmonary hypertension had lower peak ejection rate than did normal subjects (1.7±0.3 EDV/sec vs 2.4±0.3 EDV/sec, p<0.05). Of diastolic indices at rest, peak filling rate was lower in pulmonary hypertension than in normals (1.0±0.4 EDV/sec vs 1.9±0.4 EDV/sec, p<0.025) and filling fraction showed significantly lower in patients with pulmonary hypertension than in normals (15.4±8.9% vs 26.7±7.6%. p<0.025).

Table II Variables of left ventricular systolic function and diastolic filling at rest.

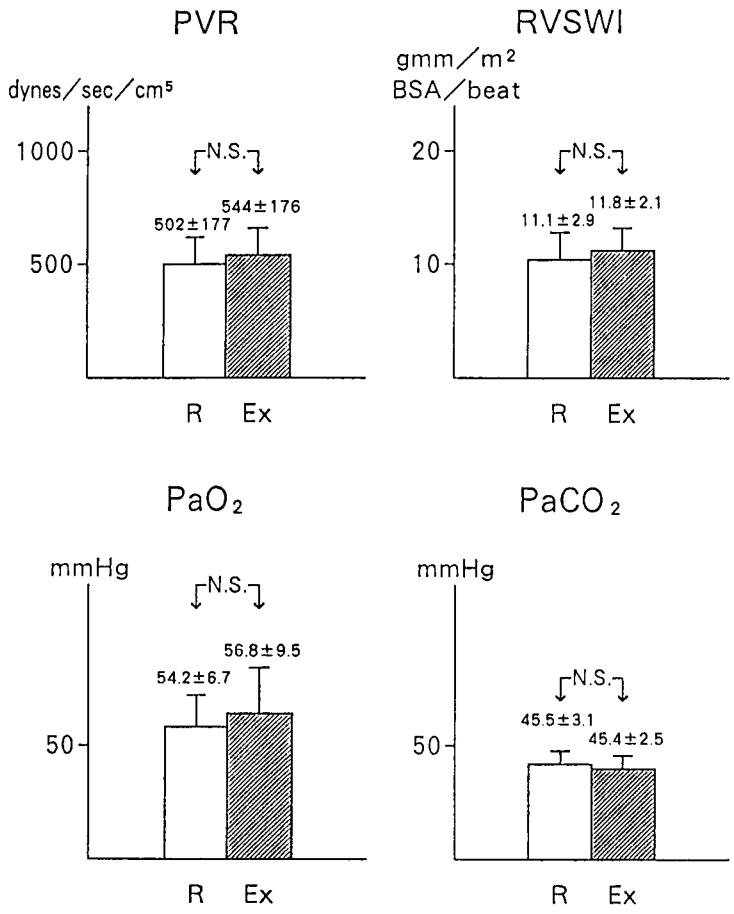
Group	Normal subjects (n=50)	Patients with chronic pulmonary diseases (n=86)
a) LV systolic function at rest		
Lv ejection fraction (%)	63.2±5.8	52.1±8.2*
Peak ejection rate (EDV/sec)	2.4±0.3	1.7±0.3*
b) LV diastolic filling at rest		
Peak filling rate (EDV/sec)	1.9±0.4	1.0±0.4**
Filling fraction (%)	26.7±7.6	15.4±8.9**
c) Heart Rate (beast/min)	69±12	75±13

Data are mean±SD
* P<0.05 vs normal subject, **P<0.025 vs normal subjects
Abbreviations : LV=left ventricular, EDV=end diastolic volume

II) Exercise values

a) Hemodynamics

Exercise on room air led to significant increase in mean pulmonary artery pressure (26.7± 3.9 to 38.8±3.8 mmHg, $p<0.001$), mean pulmonary capillary wedge pressure (8.9±2.1 to 14.1±5.7 mmHg, $p<0.05$), mean right atrial pressure (7.5±1.8 to 10.8±2.2 mmHg, $p<0.001$), and cardiac index (2.81 ±0.29 to 3.85±0.51 ml/min/m^2, $p<0.001$). But pulmonary vascular resistance (502± 177 to 544±176 dynes/sec/cm^5), right ventricular stroke work index (11.1±2.1 to 11.8±2.9 gm.m/m^2BSA/beat), PaO_2 (54.2± 6.7 to 56.8±9.5 mmHg) and $PaCO_2$ (45.5±3.1 to 45.4±2.5 mmHg) were unchanged (Fig. 2).



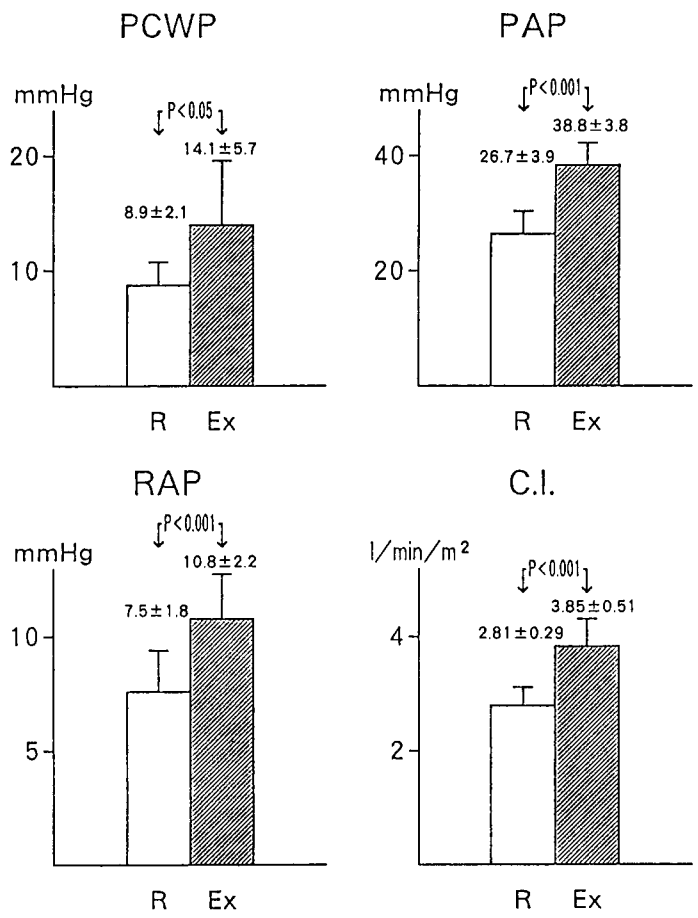


Fig. 2 Effect of exercise on mean pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), right ventricular stroke work index (RVSWI), right atrial pressure (RAP), cardiac index (C.I.), PaO_2 and $PaCO_2$ in patietns with pulmonary hypertention secondary to chronic pulmonary diseases. (R: rest, Ex: exercise)

b) Equilibrium radionuclide angiography

During exercise in normal subjects, ejection fraction (64.5 ±4.2 to 78.2±6.9%, P<0.001), peak ejection rate (2.3±0.3 to 3.4 ±0.4 EDV/sec, p<0.001), peak filling rate (2.1±0.2 to 3.1±0.4 EDV/sec, P<0.001), and filling fraction (28.5±5.1 to 32.3±6.3%, p<0.05) were significantly higher than at rest (Fig. 3).

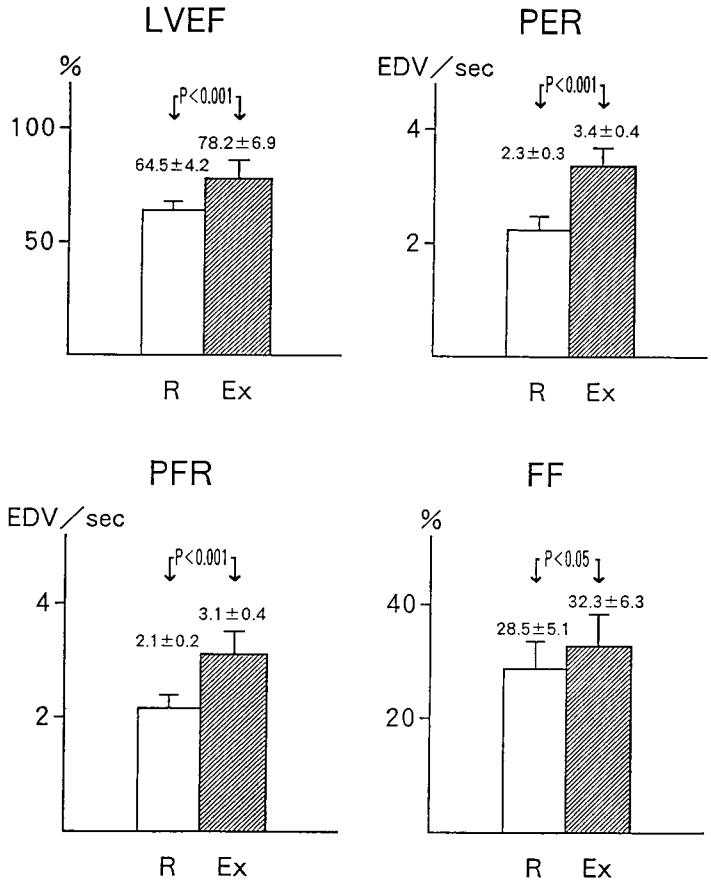


Fig. 3 Left ventricular ejection fraction (LVEF), peak ejection rate (PER), peak filling rate (PFR) and filling fraction (FF) at rest and during exercise in 20 normal subjects. Values are indicated as mean±S.E.

In patients with pulmonary hypertension secondary to chronic pulmonary diseases, ejection fraction (51.9±8.5 to 52.9±11.5%) and peak ejection rate (1.94±0.52 to 2.01±0.60 EDV/sec) were unchanged. Peak filling rate was significantly lowered (1.25±0.38 to 1.18±0.42 EDV/sec, $p<0.05$) and filling fraction significantly fell (13.1±3.6 to 7.9±1.9%, $p<0.001$) (Fig. 4).

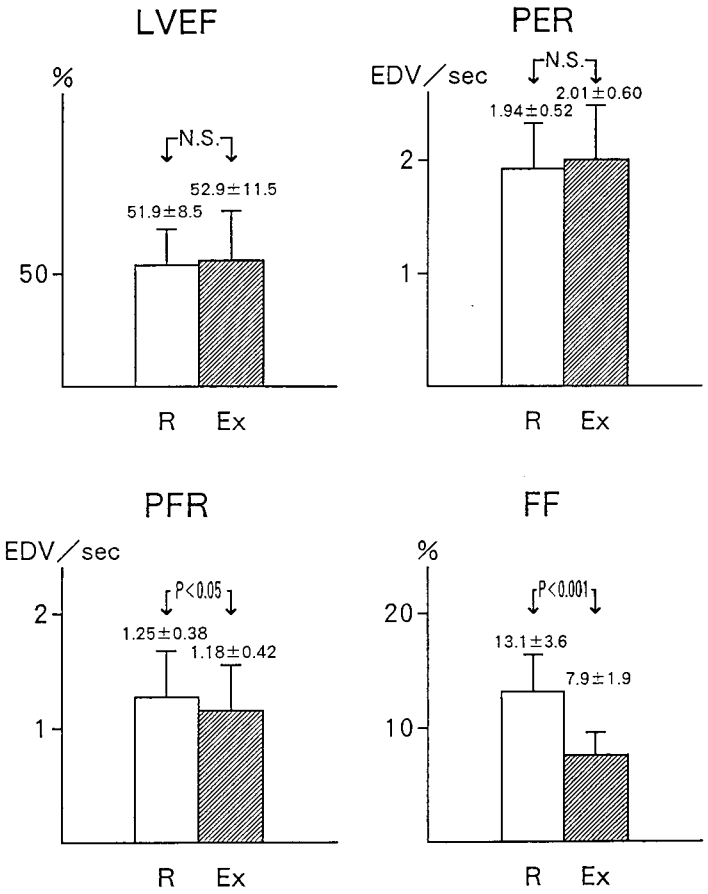


Fig. 4 Effect of exercise on left ventricular ejection fraction (LVEF), peak ejection rate (PER), peak filling rate (PFR) and filling fraction (FF) in patients with pulmonary hypertension secondary to chronic pulmonary diseases.

However, these parameters of left ventricular function had no close correlation with pulmonary artery pressure, right atrial pressure, cardiac index, pulmonary vascular resistance, right ventricular stroke work index, or blood gases.

Resting thallium-201 scintigraphy performed in all patients with pulmonary hypertension revealed increased uptake of the right ventricle, but showed no abnormal findings of the left ventricle in any patients.

The symptoms at the end-point of exercise were dyspnea in 16 and fatigue in 13 patients. No complications occurred in this study.

DISCUSSION

Some reports have documented negative implications of pulmonary hypertension for the prognosis of chronic pulmonary disease,[34] but few detailed studies of the role of left ventricular performance, in particular during exercise, in those patients have been performed. It has been controversial whether in patients with pulmonary hypertension left ventricular performance is impaired or not. Matthy et al.[20] reported that in 30 patients with chronic obstructive pulmonary disease, abnormal left ventricular performance was infrequent using first pass quantitative radionuclide angiography. Olvery et al.[21] also found normal left ventricular ejection fraction at rest in those 18 patients by means of first pass radionuclide method, but they did not observe pulmonary hemodynamics. Thus, it is hard to assess left ventricular performance in pulmonary hypertension. Slutsky et al.[29] observed that certain indeces of early systolic left ventricular ejection were abnormal in many patients with chronic obstructive pulmonary disease. Baum et al.[1] reported that in 15 patients with chronic obstructive lung disease, biventricular cardiac catheterization showed elevated left ventricular end-diastolic pressure in seven and abnormal left ventricular curves in 14 patients. Macnee et al.[19] also found in patients with chronic bronchitis and emphysema who had clinical evidence of cor pulmonale at the time of the study significantly lower values of left ventricular ejection fraction than patients with no previous cor pulmonale or those who had had cor pulmonale in the past. First pass radionuclide angiography had been often utilized in previous

reports on left ventricular function in pulmonary hypertension, but it requires careful positioning of the scintillation probe as even small errors in placement can result in marked differences in left ventricular ejection fraction. So in our study, we used equilibrium radionuclide angiography which is a reliable non-invase method based on the fact that the heart is a periodically contracting organ, and the amount of radioactivity in the heart is proportional to the amount of blood in its cavity, provided there is homogenous distribution in the blood pool.[5,30] Our results that left ventricular systolic function at rest was statistically lower in patients with pulmonary hypertension though some cases had normal left ventricular systolic function. In addition, less cases had normal left ventricular diastolic properties at rest. During exercise, left ventricular systolic function did not increase significantly as compared with one at rest. Moreover left ventricular diastolic function was significantly lower during exercise than at rest.

Left ventricular diastolic dysfunction is often observed in patients with coronary artery disease,[2,3,22,23,26,33] and those with ventricular hypertrophy.[4] Not only intrinsic factors of ventricular muscle, such as elastic and viscous properties but also extrinsic ones which include heart rate, arterial pressure, pericardium and ventricular interaction may affect left ventricular diastolic dysfunction.[12,13,16,24,31] In patients with pulmonary hypertension secondary to chronic pulmonary diseases, the following causes are considered to influence the left ventricular performance. In those patients, wide swing in intrathoracic pressure can elevate pulmonary artery pressure, right ventricular afterload, and venous return to the right side of the heart.

These changes lead to right ventricular dilatation that can distort the geometry of the left ventricle and reduce its function. Brinker et al.[7] reported that Muller maneuver induced increased right ventricular loading and acute leftward displacement of the intraventricular septum in end diastolic phase by means of echocardiography in normal subjects. Transmural pressure of the left ventricle can be elevated by inspiratory drops in pleural pressure observed in patients with chronic pulmonary disease, which increases the afterload of the chambers and reduces the ejection fraction. This condition may be provoked by a left ventricular distortion with bellow-like motion which is associated

with hypertrophy and dilatation of right ventricle.

In addition, hypoxia is considered to have a direct action on smooth muscle constraction and in particular on the transmembranary flux of calcium.[14]

In our study, hemodynamic parameters derived from cardiac catheterization and arterial blood gases had no correlation with left ventricular indices obtained from equilibrium radionuclide angiography at rest and during exercise. Therefore left ventricular dysfunction observed in patients with pulmonary hypertension is not considered to be governed by single factor, but multiple factors may affect this impairment complicatedly.

Recently it is known that vasodilator therapy can often improve right ventricular failure observed in pulmonary hypertension.[6,11,25,27,32] However, these agents necessarily affect not only right sided heart, but also left sided heart. So we cannot neglect the influence of vasodilators on left ventricular function when we evaluate the effectiveness of those drugs on patients with pulmonary hypertension.

In conclusion, this study demonstrated that left ventricular function at rest was often impaired in patients with pulmonary hypertension secondary to chronic pulmonary diseases, and in particular left ventricular diastolic function was significantly lowered than systolic function.

In addition, left ventricular systolic function during exercise did not increase as much as in normals, and that left ventricular dysfunction during exercise was more remarkable than at rest. Left ventricular diastolic impairment may be an early indicator of left ventricular dysfunction caused by pulmonary hypertension, and the lack of increase in left ventricular function during exercise in patients with pulmonary hypertension may play an important role in reduced exercise tolerance.

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