Acute Changes in Cardiopulmonary Blood Volume During Upright Exercise Stress Testing in Patients with Coronary Heart Disease

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SUMMARY The effect of exercise-induced myocardial ischemia on cardiopulmonary blood volume was evaluated in patients with coronary artery disease during upright exercise stress testing. Regional pulmonary and cardiac blood volumes were measured with a multicrystal positron camera positioned over the chest during maximal exercise on a bicycle ergometer. Inhaled carbon monoxide (< 10 ppm) labeled with cyclopoton-produced carbon-11 (\(^{11}\)C) (half-life 20.3 minutes) was used to label the blood with \(^{11}\)C-carboxyhemoglobin. Regional \(^{11}\)C activity was measured over the heart and lungs during rest, exercise and recovery periods, and blood volume was calculated from regional \(^{11}\)C activity compared with the specific activity of a reference venous blood specimen. For patients developing angina pectoris and electrocardiographic ST-segment depression (ischemic group, \(n = 9\)), blood volume increased 18.7 ± 6.3% (SEM) \((p < 0.01)\) over the upper lung fields and 15.4 ± 6.8% \((p < 0.05)\) over the lower lung fields at peak exercise. Conversely, for patients without angina or ST-segment depression at peak exercise (nonischemic group, \(n = 7\)), the regional pulmonary blood volume was unchanged over both upper and lower lung fields. The cardiac blood volume rose 6.1 ± 2.6% \((p < 0.05)\) for the former group of patients and declined 10.6 ± 5.7% \((p < 0.05)\) for the latter group at peak exercise. Coronary arteriography revealed double- or triple-vessel coronary disease in all patients in the ischemic group and normal coronary arteries or single-vessel disease in the nonischemic group. These data indicate that an ischemic response to exercise stress testing is associated with a transient rise in pulmonary and cardiac blood volume, which may be due to ischemia-induced left ventricular dysfunction.

DECREASED MYOCARDIAL perfusion causes reduced contraction of the left ventricle within seconds after the onset of ischemia.\(^{1, 2}\) Exercise- and pacing-induced angina pectoris are associated with the prompt development of regional left ventricular asynchrony.\(^{3, 4}\) Reduced left ventricular ejection fraction,\(^{5}\) elevated left ventricular end-diastolic pressure,\(^{6-8}\) reduced left ventricular compliance\(^{9, 10}\) and a fall in cardiac output.\(^{11}\)

The sudden rise in left ventricular end-diastolic and pulmonary venous pressures is reflected as a rise in pulmonary capillary wedge pressure.\(^{12, 13}\) This elevation should result in a corresponding pressure increase in pulmonary blood volume. Previous attempts to determine the effect of angina pectoris on pulmonary blood volume have been limited by the lack of noninvasive techniques for continuously monitoring this parameter. The most widely applied technique for measuring pulmonary blood volume is the indicator-dilution method, which requires transseptal catheterization and is limited to intermittent measurements during supine exercise.\(^{14}\)

We have explored a noninvasive radionuclide approach for serial measurement of regional pulmonary blood volume in patients during upright exercise: Tracer quantities of \(^{11}\)C-carbon monoxide (\(^{11}\)CO) are administered by inhalation for labeling blood with \(^{11}\)C-carboxyhemoglobin (\(^{11}\)CO-Hb). The purpose of this investigation was to measure acute changes in pulmonary and cardiac blood volume during rest, exercise and recovery periods in patients with possible coronary heart disease and to correlate these changes with angiographic and electrocardiographic data. We anticipated that transient depression of left ventricular function during exercise-induced ischemia would result in a transient rise in pulmonary blood volume.

Methods

Patient Selection

Sixteen patients referred for coronary arteriography for evaluation of chest pain were studied during exercise stress testing. The subjects included 15 men and one woman, ages 37–63 years (mean 50 ± 1.8 years). Each patient had undergone diagnostic cardiac catheterization and coronary arteriography within 2 months previously. Patients with unstable angina, recent myocardial infarction, chronic pulmonary disease, or any physical disability impairing exercise were excluded from the study. Informed consent was obtained from each subject before study.
Exercise Testing

Each patient underwent maximal exercise testing on a bicycle ergometer after several hours of fasting. The patient’s medical regimen was not altered for the purposes of the study. Graded, continuous exercise was performed with the patient seated upright on a constant-load bicycle ergometer, calibrated in kiloponds. The work load was increased 150 kilopond-meters (kpm) /min every 3 minutes. The ECG was monitored continuously with a V5 chest lead, and the blood pressure and electrocardiographic leads II, III, aVF, and V6 were recorded each minute. With the appearance of angina pectoris, ST-segment depression > 2 mm, ventricular arrhythmia, or marked fatigue or dyspnea, the exercise load was reduced by abruptly reducing the work load on the bicycle ergometer. The patient was instructed to continue cycling at the same speed for approximately 1 minute before stopping.

Serial scintigraphic measurements of 13C activity over the patient’s lung fields were made with a multicrystal positron camera during rest, exercise and recovery (fig. 1). The patient was imaged between the two detector heads of the camera, each containing 127 NaI (TI) crystals over an area 27 x 30 cm, positioned over the chest. The detector heads were covered with 4-inch foam rubber cushioning and were compressed against the patient’s chest wall, effectively reducing chest motion during exercise.

13CO-Hb Blood Labeling

In recent experimental animal studies, 13CO (half-life 20.3 minutes) has been shown to be an effective radionuclide label for scintigraphic quantification of pulmonary blood volume in isolated, perfused lung preparations. Given by inhalation to patients, 13CO has been used for measuring blood volume and total hemoglobin and for placental imaging and cardiac blood pool imaging. The measured biological half-life of 13CO-Hb in human subjects is 161 minutes. The average fractional loss rate is 0.0039 ± 0.0011 min⁻¹, and the effective half-life is 18.03 minutes. The total body absorbed radiation dose after inhalation of 5 mCi of 13CO is 55 mrad, and the calculated radiation dose to the lungs is 196 mrad.

In the present study, 13CO was produced in a medical cyclotron by bombarding an isotopically enriched 10B target with a 7-meV, 50-mA deuteron beam. For patient use, the 13CO was diluted with room air, resulting in less than 10 ppm molecular carbon monoxide. Five mCi of this 13CO-air mixture contained in a 5-liter anesthesia bag was administered to the patient by inhalation through a mouthpiece. Each patient inhaled the 13CO mixture for approximately 1 minute until > 20,000 counts/second was recorded over the patient’s chest with the positron camera. Before positron imaging, 5-7 minutes were allowed for equilibration of 13C activity measured over the chest. Time-activity curves were measured over the thorax of a subject at rest for 20 minutes during and after inhalation of 5 mCi of 13CO (fig. 2). Five minutes after inhalation, steady count rates are achieved, demonstrating that equilibrium is reached and that 13CO-Hb remains a stable blood label. After exercise,
a 12-ml venous blood sample was obtained from each patient and counted between the detector heads of the positron camera to determine the specific activity of the $^{15}$CO-Hb in the blood.

Because elevated carboxyhemoglobin levels have a detrimental effect on left ventricular function in patients with coronary heart disease$^{23}$ and reduce exercise capacity of patients with angina pectoris,$^{24}$ we were careful to administer only trace quantities of molecular carbon monoxide to each patient. The molecular content of the $^{15}$CO was less than 10 ppm by gas chromatography, and the gas was inhaled for less than 1 minute. This concentration of carbon monoxide is less than the concentration inhaled during cigarette smoking$^{25}$ or exposure to heavy freeway traffic.$^{26}$

**Positron Scintigraphy**

Positron images were collected continuously for 20 minutes during $^{15}$CO inhalation (< 1 minute), during equilibrium (3-7 minutes), exercise (3-9 minutes), and recovery (3-5 minutes). Collection time for each image was 30 seconds, and chest images were constructed from coincident data with the positron camera, as previously described.$^{15, 27}$

Regional $^{15}$C activity was measured for each 30-second interval over regions of interest applied to the heart and upper and lower fields of each lung. The regional count rates were corrected for physical decay, biological clearance and chest wall attenuation. Radiation absorbed by the chest wall was corrected from the ratio of regional counts collected during transmission imaging for 300 seconds with a gallium-68 (half-life 68 minutes) plane source compared with regional counts collected during flood source imaging with the same positron source.

**Quantitative Treatment of Data**

Corrected regional count rates were then converted to regional blood volumes from the specific activity of the $^{15}$CO-Hb in the blood as measured from the venous blood specimen. Regional pulmonary blood volume was expressed as milliliters of blood/cm$^2$ of chest wall area, by dividing the regional blood volume by the area of the region of interest. These regional values of blood volume/cm$^2$ of chest wall area were plotted for each subject during rest, exercise, and recovery, at 1-minute intervals. The pulmonary blood volume was not expressed in absolute volumes because of the undetermined quantity of blood in the chest wall and anatomic superimposition of the structures of the heart, lungs and great vessels. Finally, all regional pulmonary blood volume values were corrected for body surface area to permit comparison of values between subjects. Similar indices of regional blood volume measured over the cardiac region were also calculated for each patient. The reproducibility of the regional pulmonary blood volume measurements was determined from triplicate measurements obtained during the rest periods. The mean coefficients of variation calculated for each of the 16 patients

**FIGURE 2. Regional time-activity curves recorded over the left lung of a subject at rest after $^{15}$C-carbon monoxide ($^{15}$CO) inhalation. Within 5 minutes after $^{15}$CO inhalation, $^{15}$C-carboxyhemoglobin activity measured over the chest has reached equilibrium and remains constant, after correction for physical decay and biological clearance. cpm = counts/minute.**

- Left Lower Lung
- Left Middle Lung
- Left Upper Lung
- Left Apex
were: right upper lung, 4.5%; right lower lung, 3.3%; left upper lung, 3.1%; left lower lung, 3.0%; and cardiac blood pool, 2.5%.

The percentage change in regional pulmonary and cardiac blood volume during exercise was determined for each subject by comparison with rest volumes, and the percentage change for groups of patients was expressed as mean ± SEM. The significance of differences between patient groups was assessed by the t test for two means using a two-tailed distribution. The significance of differences between blood volume measurements obtained during rest, exercise, and recovery was assessed by the paired t test using a two-tailed distribution.

Results

Clinical and Angiographic Findings

The clinical diagnosis, coronary arteriographic findings, results of left ventriculography, and exercise response for each subject are listed in table 1. For analysis of the effect of maximal exercise on pulmonary and cardiac blood volume, the patients were separated into two groups. Group 1 consisted of nine patients with an ischemic response to exercise manifested by typical angina pectoris and horizontal or down-sloping ST-segment depression ≥ 1 mm. Group 2 consisted of seven patients who developed neither angina pectoris nor significant ST-segment depression during exercise. All nine patients in group 1 gave histories of typical stable angina pectoris. At coronary arteriography, five patients in this group had significant stenoses (> 70% intraluminal diameter reduction) of three major coronary arteries, and four had significant two-vessel coronary artery disease. All patients in group 2 gave histories of atypical chest pain syndromes characterized by chest pain unrelated to exertion. Five patients in this group had normal coronary arteriograms, and two had single-vessel coronary stenoses. Four of the patients in group 1 and two of the patients in group 2 had had a myocardial infarction. None of the patients in either group had congestive heart failure by physical examination or by chest radiograph.

The mean values for body surface area, resting heart rate, resting blood pressure, ejection fraction and left ventricular end-diastolic pressure did not differ significantly between the two groups. Thus, left ventricular function at rest did not differ for the two groups. Seven patients in group 1 and four patients in group 2 were receiving propranolol in doses ranging from 40–240 mg daily. Eight patients in group 1 and

<table>
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<th>Patient</th>
<th>Age (years)</th>
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<th>Exercise duration (sec)</th>
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Abbreviations: AMI = anterior myocardial infarction; IMI = inferior myocardial infarction; LAD = left anterior descending artery; RCA = right coronary artery; LCx = left circumflex artery; main LCA = main left coronary artery; Diag = diagonal branch; Inf = inferior wall; AL = anterolateral wall; SBP = systolic blood pressure (mm Hg); HR = heart rate (beats/min).
three patients in group 2 were receiving long-acting nitrates.

Exercise Capacity

The total duration of exercise and the maximum work load achieved were significantly reduced for patients in group 1 compared with those in group 2 (table 2). The maximal heart rate and the pressure-rate product at peak exercise were also significantly less for group 1 than for group 2. Exercise was discontinued for all patients in group 1 because of the onset of anginal chest pain accompanied by ≥ 1-mm horizontal or downsloping ST-segment depression. Exercise was discontinued for six of the seven patients in group 2 because of leg fatigue, and one patient discontinued exercise because of dyspnea.

Changes in Regional Pulmonary Blood Volume

Figure 3 gives regional pulmonary blood volume measurements obtained over the left lung at 30-second intervals during rest, exercise and recovery in a patient with triple-vessel coronary artery disease. During exercise, the blood volume increases progressively over all regions of the lung. At peak exercise, after the patient experienced angina pectoris associated with ST-segment depression, the exercise workload was discontinued and regional blood volume fell to resting levels. With abrupt cessation of rapid cycling, a further prompt fall in blood volume was observed over the lung fields.

The regional pulmonary blood volume rose over both upper lung fields during exercise in all patients in group 1 (figs. 4 and 5). At peak exercise, the mean percentage increases in regional blood volume compared with resting values were 21.5 ± 6.9% (p < 0.01) and 16.0 ± 5.7% (p < 0.01) over the right and left upper lung fields, respectively. Similarly, pulmonary blood volume over the right and left lower lung fields rose

<table>
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<th>Table 2. Exercise Capacity and Circulatory Responses to Bicycle Ergometer Stress Testing</th>
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<td>Maximum workload (kpm/min)</td>
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<td>Heart rate (beats/min)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<td>Pressure-rate product (X 10^-5)</td>
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Data are expressed as mean ± SEM. Abbreviation: kpm = kilopond-meters.

Figure 3. Regional pulmonary blood volume measurements obtained over the left lung in a 51-year-old man with triple-vessel coronary artery disease. During exercise, the blood volume rises progressively over all regions of the lung. When the exercise work load is interrupted, the blood volume falls promptly to resting levels, and the blood volume drops further immediately after cessation of rapid cycling. The blood volume is largest in the lower and mid-lung fields.
17.6 ± 9.1 and 13.2 ± 4.5%, respectively, from rest values (p < 0.05) for patients in group 1 at peak exercise (figs. 6 and 7). The rise in 11CO-Hb activity over the lungs was evident on serial positron images in seven of the nine (78%) patients in group 1. Figure 8 shows representative positron images obtained at rest and during exercise in a patient (JG) with severe triple-vessel coronary artery disease. At peak exercise associated with angina pectoris and ST-segment depression, a progressive increase in 11CO-Hb activity is evident over both lung fields. For each patient in group 1, the rise in 11CO-Hb activity over the lung fields preceded the development of angina pectoris and ST depression by 1–2 minutes.

Conversely, for patients in group 2, the regional pulmonary blood volume remained unchanged over the right and left upper lung fields during exercise, and was not significantly different from resting values (figs. 4 and 5). Over the right and left lower lung fields, blood volumes were also unchanged from resting values (figs. 6 and 7). Serial positron images obtained during exercise did not show a visible rise in 11CO-Hb activity over the lung fields for any patient in group 2 (fig. 9). The changes in regional pulmonary blood volume from rest to peak exercise were significantly (p < 0.05) different for group 1 and group 2 for all pulmonary regions (figs. 4–7). The ratios of upper lobe to lower lobe pulmonary blood volume determined for each group of patients were constant during exercise and recovery, indicating that changes in the upper lobes paralleled changes in the lower lobes.

On discontinuation of the exercise work load, the pulmonary blood volume fell promptly over both upper and lower lung fields for both groups of patients (figs. 4–7). Within 1 minute, the values of pulmonary blood volume for patients in group 1 had fallen to resting levels (NS), and values for patients in group 2 had fallen an additional 7.2 ± 1.8% (p < 0.05) below resting levels. Representative positron images obtained from a patient in group 2 show a parallel decline in 11CO-Hb activity over upper and lower lung fields during recovery (fig. 9).

A further fall in pulmonary blood volume was observed over all pulmonary regions for both groups after the cessation of cycling. At 3 minutes after termination of the work load (2 minutes after cessation...
of cycling), the regional blood volume in the upper lobes had fallen to pre-exercise, resting levels for group 1 (NS) and to 18.4 ± 4.2% below resting levels for group 2 (p < 0.01) (figs. 4 and 5). The blood volume in the lower lung fields fell 10.9 ± 5.8% (p < 0.02) below resting levels for group 1 and 19.5 ± 4.6% (p < 0.001) for group 2 (figs. 6 and 7).

Changes in Cardiac Blood Pool Volume

The effect of exercise on total cardiac blood volume was determined by serially measuring \(^{14} \text{CO-Hb}\) activity over the cardiac blood pool during rest, exercise and recovery. In group 1 at peak exercise, the cardiac blood volume rose 6.1 ± 2.6% (p < 0.05) above pre-exercise rest levels, and declined 10.6 ± 5.7% (p < 0.05) below resting levels in group 2 (fig. 10). This difference in percentage change between the two groups was statistically significant (p < 0.01). Representative enlargement of the cardiac blood pool during exercise-induced angina pectoris is illustrated for a patient in group 1 in figure 8. For both groups of patients, the cardiac blood volume promptly declined after discontinuation of the exercise work load, with a further decline after discontinuation of cycling (fig. 10).

Discussion

The results of the present study indicate that an acute rise in pulmonary blood volume accompanies exercise-induced myocardial ischemia in patients during upright exercise stress testing. This transient pulmonary engorgement was not observed in a control group of patients who did not develop ischemia during exercise stress testing. These results are consistent with the hypothesis that acute left ventricular dysfunction that occurs during exercise-induced ischemia and impairs left ventricular emptying, results in acute pulmonary engorgement. This acute rise in pulmonary blood volume disappeared promptly after recovery from myocardial ischemia. The observation that pulmonary blood volume rises before the onset of angina pectoris and ST-segment depression suggests that pulmonary engorgement may be an early manifestation of myocardial ischemia.

The transient rise in pulmonary blood volume observed in this study may explain the sensation of dyspnea that patients sometimes experience during angina pectoris.\(^{28}\) Pepine and Wiener\(^ {29}\) showed that pacing-induced angina pectoris causes a transient increase in airway resistance and a reduction in pulmonary compliance, associated with increased pulmonary capillary pressure in patients with coronary heart disease. These acute alterations in pulmonary function may be related to the transient pulmonary engorgement observed in the present study.

The rise in \(^{14} \text{C}\) activity over the cardiac blood pool...
angiographic and radionuclide studies that have documented acute left ventricular enlargement during acute ischemia. The increase in total cardiac volume found in the present study, however, was less than the increase reported for left ventricular volume in other studies. This discrepancy suggests that right ventricular volume does not usually increase during exercise-induced ischemia. In the present study, the cardiac blood volume decreased during exercise in subjects without ischemia during exercise, which is consistent with previous radiographic, angiographic, and radionuclide studies.

A pronounced fall in pulmonary blood volume was observed immediately after cessation of exercise in both groups of patients in the present study. This rapid shift in pulmonary blood volume may be explained by several physiologic mechanisms. First, left ventricular function improves promptly after cessation of transient myocardial ischemia. Improved emptying of the ventricle lowers left ventricular end-diastolic pressure and would be expected to reduce pulmonary blood volume. Second, systemic venous return to the right heart is facilitated by muscular contraction during rhythmic muscular exercise, and sudden cessation of exercise would be expected to abruptly reduce heart filling, resulting in decreased flow to the lungs. Third, blood flow to the calf muscles is markedly augmented during heavy and rhythmic exercise in the upright position. This increased flow persists for several minutes after exercise, and causes pooling of blood in the legs, which further reduces systemic venous return to the right heart.

Previous studies of the effect of exercise on cardiopulmonary blood volume in normal subjects have observed among patients with ischemia in the present study suggests that exercise-induced myocardial ischemia may lead to transient cardiac dilatation. This observation is consistent with recently reported

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Change in blood volume measured over the left lower lung field for group 1 (solid circles) and group 2 (open circles) during exercise testing. The regional blood volume rose for group 1 and was unchanged for group 2 at peak exercise. The blood volume fell for both groups upon termination of exercise. Details as in figure 4.

![Figure 8](http://circ.ahajournals.org/)

**Figure 8.** Serial positron images of the chest obtained during rest, exercise, and angina in a 62-year-old man with severe triple-vessel coronary artery disease. During exercise, the $^{13}$C-carboxyhemoglobin blood label increases over the lung fields, indicating an acute increase in pulmonary blood volume. The cardiac blood pool increased concomitantly, indicating acute left ventricular dilatation. The transmission image was obtained with a gallium-68 plane source for correction of chest wall attenuation and for positioning of the patient's chest. Abbreviations: RL = right lung; LL = left lung; LV = left ventricle.
been performed with the indicator-dilution technique of Stewart and Hamilton,\textsuperscript{35} which necessitates transseptal cardiac catheterization and requires that the patient be exercised in the supine position with multiple catheters in place. This technique is relatively inaccurate for measuring small changes in pulmonary blood volume and is limited by the number of indocyanine green injections possible.\textsuperscript{36} The results of studies using this technique conflict; some investigators have reported an elevation in cardiopulmonary blood volume,\textsuperscript{36, 37} and others have reported no significant change in this parameter in normal subjects during supine muscular exercise.\textsuperscript{38}

Using the indicator-dilution technique for measuring pulmonary blood volume, Yu and his colleagues showed that pulmonary blood volume increases in patients with ischemic heart disease during supine exercise.\textsuperscript{39} Studies of the effect of exercise on cardiopulmonary blood volume during supine exercise, however, are not directly comparable to the present study of the effect of upright exercise. Supine exercise significantly alters the hemodynamic response of patients with coronary artery disease\textsuperscript{13} and reduces exercise tolerance.\textsuperscript{40} In addition, blood is shifted out of the thorax when the upright position is assumed,\textsuperscript{41} and changes in body position markedly influence the distribution of blood in the lungs.\textsuperscript{42}

Few studies on the effect of upright exercise on pulmonary blood volume in normal subjects have been reported, and the results have conflicted.\textsuperscript{43} In the present study, pulmonary blood volume did not change significantly during exercise in the group of patients without exercise-induced myocardial ischemia. An increase in pulmonary blood volume might be anticipated due to distension and recruitment of pulmonary capillaries resulting from the large increase in total pulmonary flow that occurs during vigorous exercise. However, Glazier et al.\textsuperscript{44, 45} showed that pulmonary capillary distension and recruitment result primarily from elevation of pulmonary arterial
and pulmonary venous pressures. 46 Since neither pulmonary artery pressure nor pulmonary venous pressure rise significantly in normal subjects during exercise, 47, 48 the total pulmonary blood volume would be unchanged. Conversely, coronary patients may experience elevation of both pulmonary arterial pressure and pulmonary venous pressure during exercise-induced myocardial ischemia, 13 which may account for the acute rise in pulmonary blood volume observed in the present study during myocardial ischemia.

The radionuclide technique developed in the present investigation provides several advantages for noninvasive measurement of changes in cardiopulmonary blood volume. 11CO effectively labels the blood pool with 11CO-Hb and is conveniently administered by inhalation. Positron imaging with a multicrystal camera permits uniform detection of 11C activity over a large field with a relatively high sensitivity, and allows quantitation of regional activity in comparison to an external reference source, since coincident detection of positron annihilation emission between two opposing detectors is independent of spatial geometry. 19 In addition, correction of regional attenuation of radiation by the chest wall may be corrected by transmission imaging with a positron plane source. Finally, serial positron imaging can be performed sequentially at short intervals for evaluation of acute changes in pulmonary blood volume resulting from hemodynamic alterations.

In summary, this investigation shows that exercise-induced myocardial ischemia is associated with transient elevation of pulmonary blood volume and cardiac blood pool volume, which decline promptly to resting levels during the recovery after exercise. In a group of patients without evidence of ischemia during exercise, pulmonary blood volume was unchanged during vigorous muscular exercise and cardiac blood pool volumes diminished. The acute rise in cardiopulmonary blood volume observed in this study is probably due to ischemia-induced left ventricular dysfunction and may be an early manifestation of myocardial ischemia.

Acknowledgments

The authors gratefully acknowledge statistical assistance provided by Marcia B. Leavitt and John B. Newell of the IHd-SCOR Management Project and technical assistance provided by Steven B. Weise and William M. Bucelewicz.

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Acute changes in cardiopulmonary blood volume during upright exercise stress testing in patients with coronary heart disease.
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Circulation. 1979;60:520-530
doi: 10.1161/01.CIR.60.3.520

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