Arterial Oxygenation and Arterial Oxygen Transport in Chronic Myocardial Failure at Rest, During Exercise and After Hydralazine Treatment

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SUMMARY Arterial oxygen transport (cardiac output × arterial oxygen content) may be decreased in heart failure. We studied the determinants of arterial oxygen transport in 15 patients with chronic, severe myocardial failure at rest and during cycle ergometry. During control therapy at rest, arterial oxygen tension was normal (81 ± 8 mm Hg, mean ± SD) and increased slightly during exercise (90 ± 14 mm Hg). During hydralazine therapy at rest, arterial oxygen tension was slightly higher (87 ± 9 mm Hg) and also increased during exercise (92 ± 15 mm Hg). Hydralazine did not increase arterial oxygen tension (0.10 > p > 0.05), but exercise did (p < 0.02). Arterial oxygen saturation and content were normal and did not change under any condition or treatment. During control therapy at rest, arterial oxygen transport was low (313 ± 74 ml/min/m²) and remained abnormally low during exercise (434 ± 124 ml/min/m²). During hydralazine therapy, arterial oxygen transport was higher at rest (457 ± 100 ml/min/m²) and during exercise (577 ± 131 ml/min/m²). Hydralazine increased arterial oxygen transport (p < 0.01) because it increased stroke volume at rest and during exercise, but it did not change arterial oxygenation. Arterial oxygenation is normal in chronic heart failure patients at rest and during exercise. Hydralazine increases cardiac output and arterial oxygen transport without changing arterial oxygenation.

PATIENTS with chronic heart failure have, in addition to abnormally low cardiac output, the potential for defective arterial oxygenation. Defects of pulmonary ventilation, perfusion, diffusion and venous admixture have all been reported in heart failure. Therefore, arterial oxygen transport (QO₂, cardiac output × arterial oxygen content) may be abnormally low. Renewed interest in the drug treatment of heart failure has resulted in reports on the control of cardiac output and the effects of vasodilators. However, control of arterial oxygenation in these patients has not been studied during exercise or during treatment with the potent arterial vasodilator hydralazine. In this report, we summarize our findings on QO₂ at rest, during exercise and during hyalazaline therapy in patients with chronic myocardial failure.

Methods

Patients

We studied 15 patients who had severe left ventricular dysfunction on the basis of either ischemic heart disease (with previous myocardial infarction) or idiopathic cardiomyopathy. These patients were referred to our medical center because of intractable symptoms of heart failure. Some were studied as part of advanced diagnostic testing, while others were part of experimental drug protocols. Where appropriate, these protocols were approved by the Human Subjects Committee of this institution. Patients gave informed, written consent for all procedures. There were 11 men and four women, mean age 60 years (range 47–76 years). Each patient had marked limitation of exercise tolerance from dyspnea or generalized fatigue, but no patient was limited by angina. At the time of study, two patients were in New York Heart Association (NYHA) functional class II, seven patients were in class III and six patients were in class IV. We excluded patients who had had myocardial infarction or pulmonary edema within 1 month. Patients were hospitalized at least 48 hours before study entry and observed under constant conditions of bedrest, diet and medication (digoxin and furosemide). No patient had evidence of pulmonary disease by history, physical examination or chest roentgenogram.

Variables Measured and Calculated

We percutaneously inserted an indwelling radial artery line. Arterial blood gas samples were obtained by anaerobic technique, stored on ice, and rapidly analyzed on a blood gas analyzer (model 175, Corning Instruments) for arterial oxygen tension (Pao₂) and pH. Technical accuracy and reproducibility of Pao₂ were ± 1 mm Hg over the range of tensions in this report. Under stable clinical conditions, Pao₂ in patients varies little from day to day. We percutaneously inserted a triple-lumen Swan-Ganz balloon flotation catheter in the pulmonary artery to measure pulmonary artery pressure; mean pulmonary artery pressure was obtained by electronic damping. Pulmonary capillary pressure (PCP) was estimated as either the pulmonary occluded pressure or the pulmonary artery diastolic pressure, but the method remained constant in each patient. Cardiac output (CO) was measured in triplicate by the thermodilution technique using iced 5% dextrose in water and a thermodilution computer. Variation between the determinations of CO was less than 10%. Cardiac index (CI), stroke volume index and pulmonary vascular resistance (PVR) were calculated by standard formulas. Oxygen content of blood samples was calculated as Hgb × 1.34 × S, where Hgb is the hemoglobin concentration determined by the cyanmethemoglobin method in the hospital clinical laboratory, S is the saturation fraction (calculated from the oxygen tension, pH, base excess, and blood temperature) and
1.34 is the empirically observed oxygen carrying capacity of a gram of hemoglobin. Arterial oxygen transport (Qo2) was calculated as arterial oxygen content × CI. In six patients we collected expired gas and analyzed it for fractional oxygen and carbon dioxide concentrations on a medical mass spectrometer (model MGA-1100, Perkin Elmer). These values were used to calculate the respiratory exchange ratio and, along with PaO2, were used to calculate the oxygen tension of idealized alveolar gas and the alveolar-arterial oxygen difference (P[A-a]O2) according to the alveolar air equation. Oxygen saturation of arterial and mixed venous blood was directly measured by a quadruple-beam spectrophotometer (model IL 282, Instrumentation Laboratories). These were used to calculate venous admixture (Q/Qs). Expected normal values, adjusted for age, of PaO2, P(A-a)O2 and Q/Qs were calculated based on well-established normal values.

Protocol
Stable levels of CO and filling pressures were monitored for at least 12 hours before baseline measurements made at upright rest and during exercise. The patient was comfortably seated on the cycle ergometer for 10 minutes before resting hemodynamic measurements and blood and expired gas samples were taken. The patient then underwent incremental exercise beginning at zero load and increasing in increments of 25 W every 3 minutes. Patients performed symptom-limited maximal exercise (i.e., extreme dyspnea, generalized fatigue or leg fatigue). The median peak work load was 25 W (range 0–50 W) and the total cycling time averaged 7.1 minutes (range 5–11 minutes). Samples were repeated at peak exercise. Maximal oxygen uptake was 572 ± 157 ml/min. When indexed to body weight, 14 of 15 patients had a maximal oxygen uptake of less than 10 ml/min•kg.

Patients then received i.v. or oral hydralazine. Five patients received i.v. hydralazine, 20 mg, over 30 minutes and underwent repeat rest and exercise measurements 30–90 minutes after the infusion, when peak CO had apparently been achieved. Ten other patients received incremental oral doses of hydralazine over about 48 hours, beginning with 50 mg every 6 hours and increasing by 25 mg every fourth dose until resting CO increased at least 25% compared with the control value. Patients were restudied at rest and exercise 2 hours after an oral dose. The exercise study after hydralazine used work loads and exercise duration that were identical to those during control to ensure identical work intensity for comparison of oxygen transport, gas exchange, and hemodynamics.

Statistical Methods
Each variable was measured four times in each patient: at rest on control treatment, at rest during hydralazine, at peak exercise during control treatment, and at the exercise work load used during hydralazine treatment. We used a two-factor analysis of variance with repeated measurements on both factors. The presence or absence of drug therapy was treated as the first factor with two levels (control, hydralazine) and the rest-exercise conditions were treated as the second factor with two levels (rest, exercise). Using this technique, the following three null hypotheses were tested: (1) There was no difference between the presence and absence of drug therapy; (2) there was no difference between rest and exercise conditions; and (3) there was no interaction between drug therapy and exercise. The last null hypothesis was accepted based on a test of significance for each of the variables; therefore, because of this, individual tests of significance (e.g., control rest or exercise vs hydralazine rest or exercise) gave the same results as tests of significance for hypothesis 1. The other individual tests of significance (e.g., rest control or hydralazine vs exercise control or hydralazine) gave the same results as tests of significance for hypothesis 2.

Results
Blood Gases and Arterial Saturation and Content
During control therapy, mean pulmonary artery oxygen tension (Pao2) (fig. 1, table 1) was normal at rest (81 ± 8 mm Hg) and increased slightly during exercise. During hydralazine therapy, Pao2 was slightly higher at rest and during exercise. Four patients had mild arterial hypoxemia at rest (Pao2 < 75 mm Hg). In those patients, neither exercise nor hydralazine decreased Pao2. The two-way analysis of variance showed that differences in Pao2 between control and hydralazine therapy did not reach statistical significance (p = 0.08), while differences in Pao2 between rest and exercise were statistically significant (p < 0.02).

Arterial oxygen saturation fraction was normal at rest during control therapy (0.96 ± 0.01) and did not change by more than 0.01 under any other condition. Similarly, arterial oxygen content was normal at rest during control therapy (17.4 ± 1.1 ml/dl) and did not change by more than 0.2 ml/dl under any other condition. Arterial oxygen content was at the lower limit of normal in nine patients who had mild anemia, presumably due to chronic heart failure.

During control therapy, mixed venous oxygen tension (table 1) was abnormally low at rest (27 ± 4 mm Hg) and declined further during exercise. During hydralazine therapy, PVo2 was higher at rest and decreased during exercise. Differences in PVo2 between control and hydralazine treatment and between rest and exercise were significant (both p < 0.01).

Alveolar-Arterial Oxygen Difference and Venous Admixture
During control therapy, alveolar-arterial oxygen tension difference (P[A-a]O2) (table 1) was moderately elevated at rest in two of six patients and increased slightly during exercise in each patient. During hydralazine therapy, P(A-a)O2 decreased at rest and during exercise. Differences in P(A-a)O2 between control and
Cardiac Output, Stroke Volume and Oxygen Transport

During control therapy, CI (table 2) was abnormally low at rest (1.8 ± 0.5 l/min/m²) and increased slightly during exercise. During hydralazine therapy, CI was higher at rest and also higher at exercise. Differences in CI between control and hydralazine therapy were significant (p < 0.01). The increase in CI between control and hydralazine treatment during both rest and exercise was due to an increase in stroke volume.

During control therapy, arterial oxygen transport (QO₂, fig. 2, table 2) was abnormally low at rest (313 ± 74 ml/min/m²); it increased slightly but remained abnormally low during exercise. During hydralazine therapy, QO₂ was higher at rest and during exercise. Differences in QO₂ between control and hydralazine and between rest and exercise were significant (both p < 0.01).

Pulmonary Capillary Pressure and Pulmonary Vascular Resistance

During control therapy, PCP (table 2) was abnormally high at rest (20 ± 9 mm Hg) and increased abnormally during exercise. Four patients had a normal PCP in the upright position (≤ 12 mm Hg), but each had a marked elevation of PCP while supine, as well as clinical and radiographic evidence of left ventricular enlargement. During hydralazine therapy, PCP was slightly lower at rest as well as during exercise. Differences in PCP between control and hydralazine therapy and between rest and exercise were significant (p = 0.05, p < 0.02, respectively).

During control therapy, PVR (table 2) was high at rest (318 ± 156 dyn-sec-cm⁻²) and did not change during exercise. During hydralazine therapy, PVR was slightly lower at rest and during exercise. The differences in PVR between control and hydralazine treatment were significant (p < 0.01), but differences between rest and exercise were not significant (p > 0.10).

Discussion

All 15 patients had exercise intolerance, and 14 had severely impaired maximal oxygen uptake. A What abnormalities of arterial oxygen transport (QO₂) contributed to exercise intolerance in our patients?

QO₂ was reduced in patients with chronic heart failure at rest, primarily as a consequence of a reduced CO. Pulmonary artery oxygen tension (Pao₂) and arterial oxygen content were normal (or slightly reduced) and therefore did not contribute to the reduction in QO₂. During exercise, QO₂ increased slightly, but remained abnormally low. This small increase was due to a small increase in CO, while arterial oxygen content did not change. Hydralazine increased QO₂ at rest and during exercise by increasing stroke volume and thereby CO. Hydralazine had no effect on either Pao₂ or on arterial oxygen content. Despite normal arterial oxygenation on control therapy, the alveolar-arterial oxygen tension difference (P[A-a]O₂) was abnormally elevated at rest and increased slightly during exercise, while venous admixture (Q/C) was normal at rest and during exercise. Hydralazine did not have any substantive effect on either P[A-a]O₂ or Q/C.

The control of QO₂ is complex. CO is abnormally low in chronic left ventricular myocardial failure and does not increase normally during exercise, because of
a low stroke volume. Hydralazine increases stroke volume and thereby CO at rest and during exercise in patients who have chronic left ventricular myocardial failure. Despite a multitude of hemodynamic reports, there is little information concerning respiratory gas exchange or arterial oxygenation in these patients during exercise. Nor could we find a report that summarizes potential abnormalities in the control of arterial oxygenation in myocardial failure. Of the pulmonary factors that control arterial oxygenation, ventilation-perfusion relationships, diffusion, and Q/Qf require critical examination in patients with heart failure.

Disturbances of ventilation-perfusion relationships can occur as a result of pulmonary capillary hypertension. Increases in left atrial pressure increase pulmonary venous pressure, which in turn increases hydrostatic pressure in the pulmonary capillaries. Hydrostatic pressure will be greatest in the dependent lung zones, according to a gravity-dependent distribution. One consequence of this would be disturbances of pulmonary ventilation. The increased hydrostatic pressure can cause peribronchial edema and airway narrowing, particularly in the small airways. This may lead to premature airway closure, which can be demonstrated as an abnormally increased closing volume and could result in microatelectasis. Airway narrowing may also be caused by reflex bronchospasm. The effect of airway narrowing would be to cause airflow obstruction with reductions in forced expiratory flow rates. These abnormalities would reduce ventilation (V) with respect to perfusion (Q), resulting in low V/Q lung units, which contribute to hypoxemia.

Another consequence of pulmonary capillary hypertension would be disturbances of pulmonary perfusion. Increased hydrostatic pressure would produce interstitial pulmonary edema that could increase perivascular pressure and lead to both a redistribution and maldistribution of pulmonary blood flow. Radiographically, this appears as a redistribution of blood flow to apical lung segments and scintigraphically as bilateral nonsegmental perfusion defects in some patients with heart failure. Maldistribution of blood flow could also result from hypoxic vasoconstriction in regions of the lungs in which alveolar ventilation is reduced (low V/Q). Alternatively, reduced blood flow could reduce alveolar ventilation by causing pneumoconstriction of the alveolar ducts.

The overall effect of these maldistributions of ventilation and perfusion would be to create a wider dispersion of V/Q and contribute significantly to hypoxemia or, in milder form, increased P(A-a)O2. Tattersfield et al. reported mild hypoxemia (mean arterial Po2 70.5 mm Hg), an increased P(A-a)O2, and increased Q/Qf in patients with acute myocardial infarction and left ventricular failure. Our patients did not have hypoxemia, possibly because chronic heart failure allows sufficient time for improved matching of ventilation and perfusion in individual lung units (i.e., the physiologic locus of alveolar gas exchange with pulmonary capillary blood).

Disturbances of diffusion can occur as a result of pulmonary interstitial edema. This can cause hypoxemia by impairing diffusion of gas from the alveolus to the pulmonary capillary. Measurements of diffusing capacity (DLCO) in heart failure have been carried out.

### Table 1. Oxygen Tension, Oxygen Difference and Venous Admixture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Expected normal average</th>
<th>Control</th>
<th>Hydralazine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R vs E</td>
<td>C vs H</td>
<td></td>
</tr>
<tr>
<td>Pao2 (mm Hg) (n = 15)</td>
<td>88</td>
<td>90 ± 14</td>
<td>92 ± 15</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>81 ± 9</td>
<td>90 ± 14</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>27 ± 4</td>
<td>32 ± 5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>P(A-a)O2 (mm Hg) (n = 15)</td>
<td>15</td>
<td>25 ± 12</td>
<td>32 ± 12</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>25 ± 9</td>
<td>32 ± 12</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Q/Qf (%) (n = 6)</td>
<td>3.5</td>
<td>8</td>
<td>4.6 ± 1.8</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

### Table 2. Hemodynamics and Oxygen Transport

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Hydralazine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
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</tr>
<tr>
<td></td>
<td>R vs E</td>
<td>C vs H</td>
<td></td>
</tr>
<tr>
<td>Cl (l/min/m²) (n = 15)</td>
<td>1.8 ± 0.5</td>
<td>2.5 ± 0.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SVI (ml/m²) (n = 15)</td>
<td>22 ± 8</td>
<td>25 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>QO2 (ml/min/m²) (n = 15)</td>
<td>313 ± 74</td>
<td>434 ± 124</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PCP (mm Hg) (n = 15)</td>
<td>20 ± 9</td>
<td>29 ± 12</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>PVR (dyne-sec-cm⁻²) (n = 15)</td>
<td>318 ± 156</td>
<td>316 ± 172</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Abbreviations: Cl = cardiac index; SVI = stroke volume index; QO2 = arterial oxygen transport; PCP = pulmonary capillary pressure; PVR = pulmonary vascular resistance; R = rest; E = exercise; C = control; H = hydralazine.
in patients with mitral stenosis; DLCO may be normal, increased or decreased in these patients.\textsuperscript{16, 17} The behavior of these factors during exercise has not been systematically examined. Further, DLCO must be considerably reduced before oxygenation becomes impaired at sea level ambient pressure. Although DLCO was not measured in our patients, it is unlikely that this mechanism was responsible for the increased \( P(A-a)O_2 \).

Disturbances of \( Q/Q_T \) (physiologic right-to-left shunt) could occur with airway collapse due to the previously mentioned mechanisms, resulting in lung units where pulmonary capillary blood does not come in contact with alveolar gas. Because our patients had normal \( Q/Q_T \), breathing room air, a significant right-to-left shunt could not have been present. Similarly, when mixed venous blood has a low oxygen content, it can contribute to \( Q/Q_T \), especially by perfusing low \( V/Q \) lung units.\textsuperscript{18} Our chronic heart failure patients had low oxygen content of mixed venous blood at rest and especially during exercise and yet had normal \( Q/Q_T \). It is unlikely that their low mixed venous oxygen tension (\( P(\text{VO}_2) \)) had significant effects on arterial oxygenation.

Vasodilator drugs could act either to the detriment or to the benefit of arterial oxygenation. Hydralazine lowered PVR in our patients, which might be expected to induce hypoxemia by increasing perfusion and creating more low \( V/Q \) lung units. However, hydralazine had no effect on \( P(a-a)O_2 \), \( P(\text{A-a})O_2 \), or \( Q/Q_T \). The increases in CO and \( P(\text{VO}_2) \) caused by hydralazine probably offset the potentially detrimental effects of pulmonary vasodilation, and prevented \( Q/Q_T \) from increasing. Although a decrease in PCP could improve oxygenation by reducing interstitial and peribronchial edema, hydralazine did not substantially change PCP in our patients. Other investigators have reported on the increases in \( Q/Q_T \) caused by nitroprusside\textsuperscript{19, 20} and nitroglycerin.\textsuperscript{21} Nitrates may cause hypoxemia, especially if another defect in gas exchange is present.\textsuperscript{21}

Nitrites are believed to override local hypoxic vasoconstriction in the lung, and cause an increase in abnormalities of \( V/Q \) or \( Q/Q_T \).\textsuperscript{22, 23} We infer that hydralazine does not alter local factors that control hypoxic vasoconstriction. The net effect of a vasodilator on pulmonary gas exchange appears to depend on its effect on CO, \( P(\text{VO}_2) \), PVR and PCP.

From the standpoint of arterial oxygenation, the pulmonary venous hypertension and low CO of patients with mitral stenosis should be similar to those of patients with left ventricular myocardial failure. We found three studies involving 41 patients with heart failure due to pure mitral stenosis who were studied at rest and during exercise.\textsuperscript{24-26} At rest, \( P(a-a)O_2 \) was 86 ± 12 mm Hg and \( P(\text{A-a})O_2 \) was 15 ± 9 mm Hg. These normal resting values were also normal during exercise. PCP, measured in 21 of these patients, was 22 ± 5 mm Hg at rest and 37 ± 10 mm Hg during exercise. Nonetheless, some patients with mitral stenosis had mild hypoxemia, especially those who had severe symptoms.\textsuperscript{27} In two studies, the effects of mitral valve commissurotomy on \( P(a-a)O_2 \), at rest in 13 patients with pure mitral stenosis were reported.\textsuperscript{28, 29} \( P(a-a)O_2 \) increased and \( P(\text{A-a})O_2 \) decreased postoperatively. Hemodynamically, mitral commissurotomy lowered PCP but did not increase CO. Beneficial effects on arterial oxygenation probably occurred because of decreased interstitial and peribronchial edema.

The position of the patient during exercise and the relationship of positional changes to pulmonary capillary pressure do not appear to have a substantial bearing on \( P(\text{a-a})O_2 \). We reported, in preliminary form, the effects of supine exercise on \( P(a-a)O_2 \) in patients with heart failure\textsuperscript{30} who were similar to those in this report. Except for the position of the patients during exercise, the methods were identical. In those nine patients, \( P(a-a)O_2 \) was 75 ± 14 mm Hg at rest and 85 ± 12 mm Hg during exercise; PCP was 24 ± 6 mm Hg at rest and 37 ± 7 mm Hg during exercise. Thus, arterial oxygenation...
lation was normal at rest and exercise, even though PCP increased to a very abnormal level.

We conclude that abnormally low $Q_0_2$ in patients with chronic myocardial failure is principally due to abnormally low CO rather than to low $Pao_2$. Even though there are potential disturbances of $V/Q$, DLCO and $Q/O_2$, they are not severe enough to produce ab-

normal arterial oxygenation either at rest or during exercise. However, in the presence of coexisting lung disease (such as chronic obstructive pulmonary disease or pneumonia), mild gas exchange abnormalities of myocardial failure could be additive and could further impair arterial oxygenation. Hydralazine does not im-

pair arterial oxygenation, but increases CO at rest and during exercise and thereby increases $Q_0_2$.

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