Reduction of pulmonary capillary blood volume in patients with severe unexplained pulmonary hypertension

Colin Borland, Yolande Cox, Tim Higenbottam

Abstract

Background – Unexplained or primary pulmonary hypertension results in an obliteration and obstruction of resistance pulmonary arteries. In these patients gas exchange is impaired and the measurement of gas transfer for carbon monoxide is usually reduced. This has been thought to represent a reduction in pulmonary alveolar capillary blood volume (Vc). A single breath test, measuring simultaneously the uptake of both nitric oxide (NO) and carbon monoxide (CO), provides a simple and practical measurement of membrane diffusion (Dm) and Vc.

Methods – A standard single breath test for the measurement of gas transfer for carbon monoxide (TLCO) was adapted to include NO (40 ppm) in the inhaled gas mixture and a breathhold time at total lung capacity of 7.5 seconds was used. Twelve patients with primary pulmonary hypertension and 10 similar normal volunteers were studied while seated at rest.

Results – The patients had reduced values for TLCO and TLNO. The mean (SD) value of Dm in the patients was 36.7 (32.1) mmol/min.kPa compared with 52.8 (23.9) mmol/min.kPa in the normal subjects. Vc in the patients was 0.03 (0.03) l and 0.06 (0.01) l in the normal subjects.

Conclusions – The simultaneous measurement of NO and CO uptake is possible in healthy volunteers and patients with primary hypertension. In these patients capillary blood volume is reduced compared with normal subjects.

Keywords: pulmonary hypertension, pulmonary capillary blood volume, nitric oxide, carbon monoxide.

Severe unexplained pulmonary hypertension, where the histological pleuroparenchymal abnormalities or peripheral thrombotic lesions are associated with obstruction and obliteration of the pulmonary arteries, causes varying degrees of abnormal pulmonary gas exchange. A widened alveolar–arterial oxygen gradient (DA-ao2) occurs at rest and increases with exercise. This results from a low pulmonary arterial oxygen tension (Pao2). In addition, ventilation-perfusion imbalance occurs with an increased dead space and a right-to-left intrapulmonary shunt. The measurement of the carbon monoxide transfer factor (TLCO) is also usually reduced in unexplained pulmonary hypertension. This has been thought to result from a fall in alveolar capillary blood volume (Vc) as measured by the Roughton and Forster method from TLCO at two oxygen tensions.

We have recently described a method of measuring simultaneously the single breath uptake of carbon monoxide (TLCO) and nitric oxide (TLNO) which allows the membrane diffusion (Dm) for NO and CO to be calculated and Vc to be estimated from one single breath measure at only one oxygen tension. We have measured Dm and Vc in a group of patients with unexplained pulmonary hypertension since it is a unique example of a disease which affects the blood vessels rather than the air spaces. The age group affected by the disease allows ready comparison with a matched group of healthy volunteers.

Methods

The measurements were made using an adapted gas transfer apparatus (Transfer Test, PK Morgan, Chatham, UK). Patients and subjects were studied seated at rest. After exhaling to residual volume they inhaled to total lung capacity a gas mixture of 14% helium, 0.3% carbon monoxide (CO), nitric oxide (NO) at 40 parts per million (ppm), 25% oxygen balanced with nitrogen. The breath was held at total lung capacity for 7.5 seconds followed by a full exhalation. After discarding the first litre the remaining exhaled gas was collected for analysis. The inhaled and exhaled gas mixtures were analysed for helium with a katharometer, CO by an infrared analyser, NO with a chemiluminescent analyser (Model-42, Thermoelectron, Warrington, UK), and oxygen with a paramagnetic analyser. Each patient and volunteer completed three measurements. Immediately after the last measurement 6 ml of venous blood was obtained from an antecubital vein. The blood was analysed for concentrations of haemoglobin, methaemoglobin, and carboxyhaemoglobin using an automated spectrophotometer (IL282, Instrument Laboratories, Andover, Massachusetts, USA). The mean values for TLNO, TLCO, Dm, and Vc were calculated as previously described:

\[
(1) \ DmNO = \frac{(\text{ENO} - 2\text{ECO})}{(\text{ENO}/\text{TLNO} - \text{ECO}/\text{TLCO})}
\]

\[
(2) \ Vc = 1/C \left(\frac{\text{ECO}/\text{TLCO} - \text{EC}/\text{DmCO}}{\text{E}^2}\right)
\]

Twelve patients with unexplained pulmonary hypertension diagnosed by right heart
Table 1  Mean (SD) data of patients and control subjects

<table>
<thead>
<tr>
<th>Patients (n = 12)</th>
<th>Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.6 (10.8)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 (0.06)</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/6</td>
</tr>
<tr>
<td>Haemoglobin concentration (g/dl)</td>
<td>15.7 (1.6)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>71 (25)</td>
</tr>
<tr>
<td>TLCO (mmol/min/kPa/l)</td>
<td>5.8 (1.2)</td>
</tr>
<tr>
<td>TLNO (mmol/min/kPa/l)</td>
<td>29.1 (7.5)</td>
</tr>
<tr>
<td>Dm (mmol/min/kPa)</td>
<td>37.6 (32.1)</td>
</tr>
<tr>
<td>Vc (%)</td>
<td>0.03 (0.03)</td>
</tr>
<tr>
<td>Mean Ppa (mm Hg)</td>
<td>65.9 (15.8)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (mmHg/1/min)</td>
<td>19.9 (6.7)</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in one second; TLCO, TLNO = carbon monoxide and nitric oxide lung transfer factors; Dm = membrane diffusion; Vc = alveolar capillary blood volume; Ppa = pulmonary artery pressure.

The lower Vc may reflect the reduction in cardiac output which is a characteristic finding in severe pulmonary hypertension. The reduction in cardiac output is a measure of severity of the disease and represents the haemodynamic result of the obstruction and obliteration of the pulmonary arteries. Over 80% of the resistance pulmonary arteries of 80–120 μm diameter are “lost” in these patients by the time they are diagnosed. An adaptation which allows survival is the development of collateral vessels which bypass the obstructed and narrowed resistance vessels. Although this will lower resistance, such vessels may not be accessible to inhaled oxygen, NO, or CO. However, the adaptation is unlikely to allow full recovery of normal capillary volume leaving Vc reduced in value. Whether this contributes to impaired gas exchange is unclear; TLCO is measured at total lung capacity during apnoea whereas gas exchange occurs during tidal breathing. If Vc is low in these patients while breathing tidally, it could contribute to hypoxia by shortening capillary transit time or by increasing the capillary resistance to oxygen transfer (1/Vc O2 Vc). In patients with unexplained severe pulmonary hypertension impaired gas exchange is not only due to imbalance of ventilation and perfusion but might also result from a reduction of alveolar capillary blood volume.

Results

The patients and volunteers had similar ages, heights (table 1), sex distribution, and haemoglobin. The patients with pulmonary hypertension had smaller dynamic volumes than the volunteers, indicated by the lower value for forced expiratory volume in one second (FEV1) (table 1). Their mean pulmonary pressure and pulmonary vascular resistance were raised compared with the volunteers, and TLCO and TLNO values were significantly reduced to 37.5% and 30.6%, respectively, below the values of the volunteers. Dm for the patients was not significantly less than for the volunteers but the Vc was lower in the patients (table 1).

Discussion

We have applied a new measurement of gas transfer factor, which uses simultaneous recording of the uptake of both NO and CO on inhalation, to patients with severe pulmonary hypertension. The patients had lower values for TLCO and TLNO than a group of volunteers with similar anthropometric characteristics. Significantly lower values of Vc were found in the patients. The value of Dm was also reduced but this did not reach statistical significance. No statistically significant differences emerged between the treatments but the numbers studied were small.

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