Subjects with obstructive pulmonary disease tend to be chronically vasodilated

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ABSTRACT

1. In 12 unselected outpatients with chronic obstructive pulmonary disease and six controls, arterial pH, PaO₂, PaCO₂ and oxygen saturation (SaO₂), forced expiratory volume in 1.0 s (FEV₁₀) and vital capacity were measured. Subjects were grouped into those with or without obstruction based on the Tiffenau index. The Baseline Dyspnoea Index was employed to objectify the severity of dyspnoea and the Borg index to evaluate the subjective sensation. Blood pressure was measured with a sphygmomanometer; calf arterial flow both at rest and during reactive hyperaemia with a plethysmograph. Basal and minimal resistance were calculated.

2. FEV₁₀ was 26% lower in patients with obstruction than in controls, and was also lower in patients with moderate-to-severe obstruction compared with those with mild or no obstruction. Arterial flow (75% greater in the patients with obstruction) progressively increased with increasing severity of obstruction, being 54% higher in those with mild obstruction than in those with no obstruction (P < 0.001), and 28% higher in moderate–severe than in mild obstruction (P < 0.005). In multiple regressions, F correlated inversely with FEV₁₀, PaO₂ and SaO₂, and directly with PaCO₂. Basal resistance correlated positively with FEV₁₀, SaO₂ and the Tiffenau index, and inversely with PaCO₂ (r = −0.52, P = 0.02). Minimal resistance was significantly lower in obstructed than in non-obstructed subjects. Both basal and minimal resistance progressively decreased, although insignificantly, with worsening bronchial obstruction. PaCO₂ did not correlate with any haemodynamic parameter. Borg index correlated indirectly with FEV₁₀ and basal resistance directly with arterial flow.

3. Patients with chronic obstructive pulmonary disease therefore tend to show chronic vasodilatation depending on hypoxia rather than PaCO₂. Other mechanisms could be involved in this phenomenon. The Borg index is a good indicator of oxygen desaturation and vasodilatation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global health problem with increasing rates of mortality. Two official Consensus Statements [1,2] clarified that COPD is a disease state characterized by airflow obstruction which does not change markedly over a period of several months. The forced expiratory volume in 1.0 s (FEV₁₀) and FEV₁₀/vital capacity (VC) ratio (the so-called Tiffenau index) are the most widely used indices for diagnosis and assessment of the severity of COPD, and are helpful in following its progress [3]. COPD is a major cause of cardiovascular mortality and morbidity [4–9] and also predicts in many cases the...

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Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁₀, forced expiratory volume in 1.0 s; VC, vital capacity.
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on the development of arterial hypertension [10]. On the other hand, as such evidence derives from epidemiological rather than clinical studies, information about the haemodynamic changes accompanying COPD is surprisingly sparse. Clinical features which are typical of COPD, such as hypoxia and hypercapnia, are known to influence peripheral haemodynamics [11–38], but the association between pulmonary and circulatory changes is practically limited to animal studies [27–38].

This work is aimed at evaluating whether COPD patients must be considered as chronically vasoconstricted subjects.

METHODS

General protocol

Twelve consecutive unselected outpatients with stable COPD [1] and six control subjects, whose general characteristics are summarized in Table 1, were studied. After a 48-h run-in period during which they read and approved the informed consent elaborated by the Committee of Bioethics of the University of Padova, and after any vasoactive and bronchodilator therapy had been stopped, the subjects underwent the manoeuvres described below.

Anthropometric measurements were taken in the morning after an overnight fast. Body mass index (kg/m$^2$) was then calculated from weight/height$^2$.

Arterial pH, oxygen partial pressure ($P_{aO_2}$, mmHg), carbon dioxide tension ($P_{aCO_2}$, mmHg) and oxygen saturation ($S_{aO_2}$, %) were measured with an ABL-330 (Radiometer, Copenhagen). According to the criteria of Table 1

<table>
<thead>
<tr>
<th>General, respiratory and haemodynamic characteristics of the patients</th>
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<tbody>
<tr>
<td>Patients who have a Tiffenau index $\leq 88%$ in comparison to individual reference value. Between-group statistics: $^*$ $P &lt; 0.001$ compared with non-obstructed patients.</td>
</tr>
<tr>
<td>All subjects ($n = 18$)</td>
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<td>--------------------------</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Body mass index (kg/m$^2$)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td>Diastolic blood pressure (mmHg)</td>
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<td>Basal heart rate (beats/min)</td>
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<tr>
<td>FEV$_{1.0}$ (% theoretical)</td>
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<td>FEV$_{1.0}$/VC ratio (% theoretical)</td>
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<tr>
<td>$P_{aCO_2}$ (mmHg)</td>
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<td>$S_{aO_2}$ (%)</td>
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<tr>
<td>Arterial pH</td>
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<td>Arterial pH</td>
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<tr>
<td>Basal flow (ml·min$^{-1}$·dl$^{-1}$)</td>
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<td>Basal resistance (mmHg·dl$^{-1}$·min$^{-1}$)</td>
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<tr>
<td>Post-ischaemic flow (ml·min$^{-1}$·dl$^{-1}$)</td>
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<tr>
<td>Minimal resistance (mmHg·dl$^{-1}$·min$^{-1}$·ml$^{-1}$)</td>
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Kannen and Morris [39] hypercapnia was defined as a $P_{aCO_2}$ level $\geq$ 40 mmHg.

Pulmonary function

According to the 1995 Official Statement of the American Thoracic Society Board of Directors [2], diagnosis of chronic pulmonary disease was based on history, physical examination, chest radiography, spirometry and arterial blood gases.

Pulmonary function was studied with a dry spirometer (PFT-2130D, Sensormedics*, Yorba Linda, U.S.A.) according to the American Thoracic Society criteria [2]. FEV$_{1.0}$ and VC were measured twice with a 1-month interval (see Figure 1 for repeatability of measurements).
The second spirometry measurement was taken into consideration for calculation of FEV\textsubscript{1,0} and VC.

As FEV\textsubscript{1,0} is easily measurable and has less variability than other measurements of airway dynamics [3], the present study was mainly based on FEV\textsubscript{1,0}. The FEV\textsubscript{1,0}/VC ratio (Tiffenau index) was calculated. Individual theoretical reference values were calculated for each subject, and the parameters mentioned above were expressed as percentage ratio to theoretical value [40]. Subjects were grouped into those with an airway obstruction (Tiffenau index $< 88\%$ of the individual theoretical value) and those without obstruction. According to the Consensus Statement of the European Respiratory Society [1], the former were further separated into those having a mild (FEV\textsubscript{1,0} $\geq 70\%$ of theoretical) or moderate-to-severe obstruction (FEV\textsubscript{1,0} $< 70\%$ of theoretical).

**Measurement of dyspnoea**

The Baseline Dyspnoea Index of Mahler et al. [41] was employed to objectify the severity of dyspnoea. The Borg index [42] was also calculated to evaluate the subjective sensation of dyspnoea; this index is the most commonly employed to relate sensations during exercise to those experienced during daily activities [43]. For both indexes, effort was based on self-paced stair climbing using 126 steps with a slope of 32\%. It is accepted that such indexes closely reflect real lung function impairment [44,45].

**Haemodynamic measurements**

Blood pressure was measured in the supine position in triplicate with a sphygmomanometer, making sure that there was no terminal digit preference. The average of the last two measurements was considered for the analysis. Heart rate was measured by ECG.

Peripheral flow (ml·min\textsuperscript{-1}·dl\textsuperscript{-1} muscle) was measured in the calf with a strain-gauge plethysmograph (Angiomed®, Microlab, Padova, Italy), a method which has been widely validated [46]. In this technique, limb circumference variation is measured after occluding venous outflow for 15 s by means of a cuff inflated at a pressure over the venous and below the diastolic. In this situation, limb volume increase is proportional to arterial blood inflow. In the Angiomed automatic device, which has been used by our group for a number of years [47,48], the internal software performs a further check of abnormal values.

Basal peripheral resistance was calculated from mean blood pressure/flow and expressed as units of resistance (dl·min·mmHg·dl\textsuperscript{-1}) [49].

Mechanical ischaemia was then produced for 12 min with a thigh cuff to induce maximal calf vasodilatation. During the subsequent reactive hyperaemia, calf peak blood flow was recorded and minimal vascular resistance (reflecting vascular structure and diameter of arterioles) [49,50] was calculated from mean blood pressure/peak flow.

**Statistics**

The repeatability of the two baseline measurements of FEV\textsubscript{1,0} was evaluated with the Bland–Altman method [51]. Continuous values were averaged and expressed as means ± S.D. Grouped means were compared by analysis of variance and the Tukey’s post-hoc test [52].

All variables were initially tested for normal distribution with Shapiro and Wilk’s W statistics. Linear regressions of flow and resistance were then examined in all the subjects grouped together using the Pearson coefficient and then tested in separate multiple regression models, adjusting for confounders [age, body mass index, haemoglobin, heart rate, and (for flow only) systolic and diastolic blood pressures].

**RESULTS**

Both FEV\textsubscript{1,0} and the Tiffenau index were lower in the 12 obstructed patients than in the six controls (Table 1). They were also lower in patients with a moderate-to-severe obstruction than in those with a mild or no obstruction, progressively decreasing with the severity of bronchial obstruction (Table 2). VC was $99.3 \pm 1.1\%$ of the theoretical value in the subjects with COPD and $82.2 \pm 17.7\%$ in the controls ($P = 0.03$).

$P_{\text{CO}_2}$ was $32.2 \pm 2.8$ mmHg in the 13 normocapnic patients and $46.2 \pm 7.7$ mmHg in the 5 hypercapnic patients ($P = 0.002$). $P_{\text{CO}_2}$ and $\text{S}_\text{aO}_2$ were insignificantly lower and $P_{\text{CO}_2}$ insignificantly higher in obstructed patients compared with controls, and progressively worsened with the degree of obstruction (Figure 2).

Peripheral flow was significantly greater (+75\%, $P < 0.005$) and peak flow twice as great in the obstructed

**Table 2 Pulmonary and haemodynamic parameters according to severity of obstruction**

See text for definition of parameters. Statistical significance: * $P < 0.001$, ** $P < 0.0001$. 

<table>
<thead>
<tr>
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<th>Mild obstruction</th>
<th>Moderate-to-severe obstruction</th>
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<tbody>
<tr>
<td>FEV\textsubscript{1,0} (% theoretical)</td>
<td>78.9 ± 5.6</td>
<td>49.2 ± 17.6*</td>
</tr>
<tr>
<td>FEV\textsubscript{1,0}/VC ratio (% theoretical)</td>
<td>84.7 ± 6.1</td>
<td>50.9 ± 13.7**</td>
</tr>
<tr>
<td>$P_{\text{O}_2}$ (mmHg)</td>
<td>74.9 ± 10.2</td>
<td>78.6 ± 10.6</td>
</tr>
<tr>
<td>$P_{\text{O}_2}$ (mmHg)</td>
<td>38.4 ± 2.1</td>
<td>42.4 ± 9.2</td>
</tr>
<tr>
<td>$\text{S}_\text{aO}_2$ (%)</td>
<td>94.4 ± 1.6</td>
<td>92.0 ± 3.9</td>
</tr>
<tr>
<td>Basal flow (ml·min\textsuperscript{-1}·dl\textsuperscript{-1})</td>
<td>5.7 ± 2</td>
<td>7.3 ± 1.9</td>
</tr>
<tr>
<td>Basal resistance (mmHg·dl·min·dl\textsuperscript{-1})</td>
<td>23.1 ± 14.2</td>
<td>16.1 ± 5.7</td>
</tr>
<tr>
<td>Post-ischaemic flow (ml·min\textsuperscript{-1}·dl\textsuperscript{-1})</td>
<td>20.2 ± 12.7</td>
<td>16.8 ± 4.6</td>
</tr>
<tr>
<td>Minimal resistance (mmHg·dl·min·dl\textsuperscript{-1})</td>
<td>6.9 ± 3.1</td>
<td>6.6 ± 2.1</td>
</tr>
</tbody>
</table>
Figure 2  FEV$_{1.0}$, Pa$_{O2}$, peripheral arterial flow, basal and minimal resistance in subjects with no obstruction, mild obstruction and moderate-to-severe obstruction. $n = 6$ in each group. Statistical significance: *$P < 0.01$, **$P < 0.001$ compared with ‘Absent’.

patients compared with controls (Table 1), although statistical significance was not reached due to the high standard deviations which are typical of the plethysmographic measurement of maximal flow. Peripheral flow progressively increased with increasing severity of bronchial obstruction (Figure 2), being 54% higher in subjects with mild obstruction than in those with no obstruction, and 28% higher in moderate–severe than in mild obstruction. In separate multiple regressions, peripheral flow correlated inversely with FEV$_{1.0}$ and the Tiffenau index as well as with Pa$_{O2}$ and Sa$_{O2}$ (Figure 3). It also correlated directly with PaCO$_2$ ($r = 0.55$, $P = 0.04$).

Basal peripheral resistance was positively correlated with FEV$_{1.0}$ ($r = 0.73$, $P = 0.003$), Sa$_{O2}$ ($r = 0.57$, $P = 0.03$) and the Tiffenau index ($r = 0.55$, $P = 0.02$) and inversely with PaCO$_2$ ($r = -0.52$, $P = 0.02$). Minimal resistance calculated from peak flow was significantly lower in obstructed than in non-obstructed patients (Table 1). Both basal and minimal resistance progressively decreased with worsening bronchial obstruction (Figure 2).

All these items were normally distributed, except for PaCO$_2$ which had a $W$ of 0.69 ($P = 0.0003$).

Peripheral flow was similar in normocapnic and hypercapnic patients (5.7 $\pm$ 2.0 versus 5.6 $\pm$ 3.0 ml min$^{-1}$ dl$^{-1}$ muscle). In univariate analysis arterial pH correlated directly with arterial flow, but no correlation was found in multivariate analysis including Pa$_{O2}$ and PaCO$_2$.

In the whole study group, as expected, peripheral flow

Figure 3  Correlations of peripheral arterial flow
$r$ is the multiple correlation coefficient after adjusting for confounders (age, body mass index, haemoglobin, heart rate, systolic and diastolic blood pressure). ○, obstructed (Tiffenau index < 88% theoretical value); ●, non-obstructed.
correlated directly \( r = 0.59, P = 0.004 \) and peripheral resistance indirectly \( r = -0.57, P = 0.01 \) with basal heart rate, which obviously is a determinant of systemic flows.

The Borg index correlated indirectly with \( \text{FEV}_{1.0} \) and directly with arterial flow (Figure 4). It also correlated inversely with resistance \( r = -0.57, P = 0.01 \) and with Tiffenau \( r = -0.52, P = 0.03 \).

**DISCUSSION**

Despite its clinical importance and its prognostic impact, the pathophysiology of COPD is still incompletely defined, particularly with regard to the changes in systemic haemodynamics.

It is generally taken for granted that hypobaric hypoxia (as it occurs for example in mountain resorts, air travel or hypobaric chamber) [11,12] raises heart rate [12–14], cardiac output [15–17], peripheral resistance [18,19], plasma catecholamines [20] and blood pressure [12,21,22], and reduces by 55% muscle blood flow to limbs [23]. These changes are similar to those observed during blood loss [24,25]. Oxygen administration, on the contrary, may reduce blood pressure [11,26]. The acute reduction of oxygen supply therefore would seem to stimulate the sympathetic nervous system [12,53] leading to systemic vasoconstriction [11,12].

Results of a limited number of experiments in patients with COPD, however, contradict this belief as an enhanced parasympathetic (not sympathetic) neural activity was observed [54,55], and many authors did not show in this class of patients any pressor effect of superimposed short-term hypoxia nor a heart rate reduction, cardiac output increase or total peripheral resistance fall after oxygen administration [11,56]. In other studies [57], cortisol and vasopressin were lower rather than higher in patients with COPD compared with control subjects, aldosterone and renin were not increased, and noradrenaline even correlated inversely (not directly) with \( \text{FEV}_{1.0} \).

So, although in short-term experiments it would seem that hypoxia causes vasoconstriction, the question of whether patients with COPD are vasoconstricted or else vasodilated is still open.

The data presented in this study indicate that patients with COPD are vasodilated. In fact, peripheral flow correlated inversely to \( \text{FEV}_{1.0} \), \( \text{PaO}_2 \) and \( \text{SaO}_2 \), being significantly higher in subjects with than in those without obstruction (Table 1) and progressively rising with increasing severity of COPD (Figure 2). The trend for peripheral resistance mirrored that of flow and directly correlated with \( \text{PaO}_2 \) and \( \text{SaO}_2 \), which were lower in the less oxygenated subjects. Even minimal resistance – which reflects arterial structural changes and arteriolar diameter rather than arterial tone [58] – showed the same behaviour. As Figure 3 clearly shows, subjects with the worst respiratory and blood gases parameters – both obstructed (●) and non-obstructed (○) – had the best haemodynamic pattern, with a peripheral flow which was consistently above 5 ml \( \text{min}^{-1} \cdot \text{dl}^{-1} \) muscle.

The inverse correlation between peripheral flow and \( \text{PaO}_2 \) as well as \( \text{SaO}_2 \) suggests that oxygen desaturation is involved in vasodilation in patients with COPD. In actual fact, the vasodilating properties of hypoxia have been demonstrated by the physiologists of Birmingham in a series of short-term studies in the rat [27–36], cat [37] and piglet [38], where a hindlimb vasodilation was
obtained after respiration of low partial oxygen pressure. Increase in heart rate [12–14] and cardiac output [15–17] as well as adenosine release [31–34,38], prostaglandin production [59], catecholamines [13], activation of β-adrenergic [60] or cholinergic fibres [61] and a direct action of hypoxia on the central nervous system [62] are possible explanations. In humans, where the ability to sense changes in oxygen tension has been demonstrated [63], a peripheral vasodilatation was occasionally found during acute hypoxia in normal men [61,62].

Unfortunately, the above-mentioned data derive from short-term experiments which are useless in exploring the effects of chronic hypoxia, and this topic has never been studied in patients with COPD. Furthermore, in the present study, the inverse relationship between peripheral flow and respiratory parameters (Figure 3) was not limited to hypoxic subjects but was also detectable in those in the normal $P_aO_2$ range. Finally, the small regression coefficient shown in Figure 3 is not able to explain more than one-third of the effect of $P_aO_2$ on peripheral flow, and the differences in $P_aO_2$ are actually too small to be responsible for the doubling in basal flow. Other mechanisms must therefore be involved in this phenomenon. One interesting possibility recently suggested is that vasodilatation is mediated by nitric oxide or S-nitrosohaemoglobin, released in tissues when the oxygen supply is failing [64,65]. It must also be emphasized that the plethysmographic method is unable to describe the microcirculatory changes which occur in small arterioles and capillaries, leading to different levels of oxygen tension in some regions of muscular and subcutaneous tissue [66,67].

Another question is whether or not hypercapnia plays a role in the circulatory changes in COPD. An excess of carbon dioxide in inspired air may in fact lead via a sympathtic stimulation [68] to an increase in arterial flow [68–70]. However, within the same experimental conditions, a vasodilatation and even a biphasic response was observed [71]. In our experience, peripheral haemodynamics did not correlate with $P_aCO_2$ as they were similar in normocapnic and hypercapnic subjects, indicating that $P_aCO_2$ is not a determinant of peripheral flow. Also, arterial blood pH was nothing more than a mere indicator of a less efficient pulmonary function.

Finally, it is worth noting that the Borg index [42], a subjective indicator of dyspnoea, inversely correlated with FEV$_{1.0}$. This parameter correlated directly with peripheral flow (Figure 4) and indirectly with peripheral resistance, thus qualifying the symptom dyspnoea as a reliable indicator of systemic hypoxia. The Baseline Dyspnoea Index, on the contrary, did not correlate with haemodynamic parameters.

In conclusion, patients with COPD tend to be vasoconstricted and thus not hypercapnic. A simple subjective index of dyspnoea such as that of Borg is a good indicator of oxygen desaturation and vasodilatation, comparable to measurement of FEV$_{1.0}$ or blood gases.

REFERENCES

5 Casiglia, E., Ginocchio, G., Spolaore, P., et al. (1993) Only uric acid and FEV$_1$ are predictors of mortality in very old subjects. Acta Cardiol. 48, 290–292
19 Wiler, F. (1975) Effects of hypoxia on distribution of cardiac output and organ blood flow in the rabbit. Cardiology 60, 163–172
of oxygen loss from arterioles is an order of magnitude higher than expected. Am. J. Physiol. 256, H921–924
69 Stepanek, J. (1979) Pathogenese einer akuten hyperkapnischen Hyperammoniämie. Respiration 37, 79–84

70 Carr, P., Graves, J. E. and Poston, L. (1993) Carbon dioxide induced vasorelaxation in rat mesenteric small arteries precontracted with noradrenaline is endothelium dependent and mediated by nitric oxide. Pflugers Arch. 423, 343–345

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