THE EFFECT OF AMINOPHYLLINE ON THE RESPIRATION AND PULMONARY CIRCULATION

V. JEŽEK, A. OUŘEDNÍK, J. ŠTĚPÁNEK AND F. BOUDÍK

Second Medical Clinic, Charles University, Prague

(Received 8 December 1969)

SUMMARY

1. We have examined the effects of aminophylline on the respiration and pulmonary circulation of eleven patients with chronic bronchitis and six patients with peripheral bronchial carcinoma; the latter were free from bronchial obstruction at the time of study.

2. Aminophylline caused an increase in total and alveolar ventilation and a decrease in arterial carbon dioxide tension. Lung diffusing capacity was unaltered in subjects with marked respiratory insufficiency but increased slightly in an additional group of less severely affected patients, and in the control subjects.

3. Mean pulmonary arterial pressure decreased significantly in the patients with chronic bronchitis but not those with lung cancer. A positive correlation was observed between the level of pulmonary arterial pressure during the control period and the decrease after aminophylline.

4. For the group as a whole there was no significant change in cardiac output or arterial oxygen saturation or tension. However, in those subjects in whom the cardiac output was increased, the arterial blood oxygen was reduced despite an increase in alveolar ventilation. The data are interpreted as evidence for a disproportionate part of the increase in cardiac output being directed to poorly ventilated areas of the lung.

Aminophylline is commonly used in the treatment of chronic obstructive bronchitis and its effects on respiration are well documented. However, there is as yet no good explanation for the occurrence of hypoxaemia in some patients but not in others. With a view to elucidating the mechanism we have investigated the effects of aminophylline on the respiration and pulmonary circulation of patients with chronic obstructive broncho-pulmonary disease and in control subjects.

METHODS AND SUBJECTS

A total of seventeen subjects were examined in detail. Eleven of them suffered from chronic bronchitis with respiratory insufficiency. Additional subjects with bronchitis were used for
measurement of pulmonary diffusing capacity by a single breath method. The remaining six patients, who were considered as a control group, had a peripheral type of bronchial carcinoma but no history of chronic bronchitis and no spirographic signs of bronchial obstruction.

A right heart catheterization using a Cournand catheter was performed as a routine in all patients. The ventilation was measured using a mask and Metabograph (Fleisch). Then on reaching the steady state, the pressures were measured and the blood was withdrawn from the systemic and pulmonary arteries. The cardiac output was obtained by the direct Fick method in ten subjects and by the indicator dilution method using 1.5 ml of cardio-green in five subjects. After this aminophylline was injected in a dose of 240–360 mg in 10 ml of isotonic saline through the catheter placed in the pulmonary artery and the measurement procedure was repeated 10 min later.

Blood gases were analysed by the Astrup technique using Radiometer equipment. Blood pressures were measured by Hellige tensometers and registered on a Multiscriptor recorder; the reference level for pulmonary arterial pressure was 10 cm above the catheterization table.

Paired t-tests and the calculation of correlation coefficients were used for the statistical analysis. The symbols and abbreviations included in the text are listed in Table 1.

### Table 1. Symbols used in the text

- $\dot{V}_E$ = ventilation minute volume
- $\dot{V}_A$ = alveolar ventilation
- $\dot{V}_O_2$ = oxygen consumption
- $\dot{V}_C O_2$ = carbon dioxide output
- FEV₁ sec = forced expiratory volume
- VC = vital capacity
- RV = residual volume
- TLC = total lung capacity
- $P_a O_2$ = arterial oxygen tension
- $S_a O_2$ = arterial oxygen saturation
- $P_a C O_2$ = arterial carbon dioxide tension
- $(H^+)_o$ = ions concentration
- $Q$ = cardiac index
- $P_a$ = mean pulmonary arterial pressure
- $P_{a w}$ = mean pulmonary arterial wedge pressure
- TPR = total pulmonary resistance = $P_a : Q$
- PVR = pulmonary vascular resistance = $(P_a - P_{a w}) : Q$
- $D_{l, CO}$ = lung diffusing capacity for carbon monoxide

### RESULTS

**Respiration.** The total ventilation minute volume increased after aminophylline in both the chronic bronchitics and the control subjects (Table 2). Alveolar ventilation increased proportionally so there was no change in the ratio $\dot{V}_A / \dot{V}_E$. The increase in ventilation was effected by increases in respiratory rate and tidal volume and was accompanied by augmentation of oxygen consumption and carbon dioxide output. Alveolar oxygen tension increased slightly in both groups. Arterial oxygen saturation and tension varied over a wide range; there was a slight decrease on average but this change was not significant. The arterial carbon dioxide
Aminophylline and pulmonary circulation

Tension decreased slightly but significantly in both groups and the arterial pH shifted slightly to the alkaline side.

Lung diffusing capacity for carbon monoxide was on average unchanged after aminophylline in ten subjects with respiratory insufficiency but was increased in the control subjects and in bronchitic subjects without material respiratory insufficiency (Table 3).

TABLE 2. Respiratory values at rest and after aminophylline

<table>
<thead>
<tr>
<th>Value</th>
<th>Chronic bronchitis (eleven subjects)</th>
<th>Lung cancer (six subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Aminophylline</td>
</tr>
<tr>
<td>$V_E$ (l min$^{-1}$)</td>
<td>$7.7 \pm 2.2$</td>
<td>$8.9 \pm 2.3$</td>
</tr>
<tr>
<td>$V_A$ (l min$^{-1}$)</td>
<td>$4.9 \pm 1.2$</td>
<td>$5.6 \pm 0.9$</td>
</tr>
<tr>
<td>$V_A/V_E$ (%)</td>
<td>$65 \pm 6$</td>
<td>$64 \pm 8$</td>
</tr>
<tr>
<td>$V_O_2$ (ml min$^{-1}$)</td>
<td>$289 \pm 40$</td>
<td>$316 \pm 24$</td>
</tr>
<tr>
<td>$V_CO_2$ (ml min$^{-1}$)</td>
<td>$255 \pm 39$</td>
<td>$277 \pm 28$</td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>$1536 \pm 565$</td>
<td>—</td>
</tr>
<tr>
<td>FEV$_1$/VC (%)</td>
<td>$59 \pm 16$</td>
<td>—</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>$51 \pm 12$</td>
<td>—</td>
</tr>
<tr>
<td>$P_aO_2$ (mmHg)</td>
<td>$51.8 \pm 10.3$</td>
<td>$49.5 \pm 14.0$</td>
</tr>
<tr>
<td>$S_aO_2$ (%)</td>
<td>$80.6 \pm 9.5$</td>
<td>$78.4 \pm 14.0$</td>
</tr>
<tr>
<td>$P_aCO_2$ (mmHg)</td>
<td>$44.5 \pm 9.4$</td>
<td>$41.6 \pm 8.5$</td>
</tr>
<tr>
<td>(H$^+$) (nmol l$^{-1}$)</td>
<td>$43.1 \pm 3.6$</td>
<td>$41.3 \pm 4.8$</td>
</tr>
</tbody>
</table>

All values are given as a mean ± SD. * = Values of three patients only.

TABLE 3. $D_{L,CO}$ values before and after aminophylline

<table>
<thead>
<tr>
<th>Group</th>
<th>$D_{L,CO}$ (ml min$^{-1}$mmHg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>Chronic bronchitis in respiratory insufficiency (ten subjects)</td>
<td>$5.4 \pm 2.1$</td>
</tr>
<tr>
<td>Bronchitis without respiratory insufficiency and healthy controls (fourteen subjects)</td>
<td>$12.3 \pm 5.3$</td>
</tr>
</tbody>
</table>

Four patients from the Tables 2 and 4 are included in the first and three in the second group in this table.

Pulmonary haemodynamics. After aminophylline the cardiac output varied over a wide range (Table 4). There was a tendency for it to increase particularly in the control group but this difference was not significant. The mean pulmonary arterial pressure did not change significantly in the control group but decreased significantly in the patients with chronic bronchitis. A slight decrease was also observed in pulmonary arterial wedge pressure. The pulmonary resistance expressed as $P_a/Q$ and as $(P_a - P_{awp})/Q$ both decreased, but the latter change was not significant.

Interrelations between the observed changes. A relation between the values at rest and their change after aminophylline was demonstrable only for the mean pulmonary arterial pressure.
the higher this pressure at rest the greater was the decrease after aminophylline. The fall in pulmonary arterial pressure showed no relation to the respiratory changes after aminophylline.

The changes of $P_{aO_2}$ or $S_{aO_2}$ were not related to the changes of alveolar ventilation but in some patients both values were observed to decrease whilst the alveolar ventilation rose significantly. The change was not related to the lung diffusing capacity; however, the arterial blood oxygen was significantly reduced in those subjects in whom the cardiac output increased after aminophylline, whereas in the remainder there was no change (Table 5).

### DISCUSSION

Our data are in agreement with previous studies describing vasodilatory effects of aminophylline both in man (Harris & Heath, 1962; Parker, Kelkar & West, 1966; Parker et al., 1967; Rees et al., 1969; Storstein, Helle & Rokseth, 1958; Zimmerman, 1951) and animals (Aviado, 1965; Barer & Gunning, 1959; Borst, Berglund & McGregor, 1957). However, other authors consider the fall of pulmonary arterial pressure to be due to a concomitant reduction in cardiac output (Harasawa & Rodbard, 1961).

The changes reported for cardiac output are very variable. A fall of cardiac output in healthy subjects has been described by Rees et al. (1969); small and insignificant changes in different patients were observed by Dulfano et al. (1956), Parker et al. (1966), Helander et al. (1967) and Rees et al. (1969); an increase was observed by James, Turner & Merrill (1948), Howarth, McMichael & Sharpey-Schafer (1947), Parker et al. (1967) and Werkö & Lagerlöf (1950). The different doses of aminophylline injected and the different diagnoses of subjects examined cannot explain this variability because it also exists between subjects within the individual studies.

A similar situation obtains for the arterial oxygen saturation. All authors, except Helander et al. (1967) who found a significant increase of $S_{aO_2}$, describe an insignificant change on average with a decrease of saturation in a proportion of patients and an improvement in others (Halmagyi & Cotes, 1959; Christensen et al., 1958; Daly & Howard, 1965; Parker et al., 1966, 1967; Rees et al., 1967). The cause of decreased saturation in some patients is not clear and...
cannot be explained by a reduction in alveolar ventilation since this rises in all cases. Our data indicate that the decrease of saturation is not due to a reduction in lung diffusing capacity. Thus when a decrease occurs it is probably due to increased venous admixture. This may happen in two ways. Firstly, vasoconstriction due to hypoxaemia in poorly ventilated lung areas may be reversed by aminophylline. This change will lead to increased 'shunting' of venous blood. Secondly, the vascular bed serving the well-ventilated areas of the lung may be restricted so it cannot accommodate the additional blood flow. On this account if cardiac output rises an increased proportion is directed through poorly ventilated areas.

If this latter supposition is correct we can expect a positive correlation between an increase in blood flow and a decrease in oxygen saturation. For our data this correlation is not significant \((r=0.260)\). However, if we increase the number of subjects by combining our data with those of Parker et al. (1966, 1967), a significant correlation is obtained \((r=0.416, P<0.05)\). As a means of illustrating this observation we have divided the patients from our study into two groups regardless of diagnosis, according to whether or not the cardiac output increased after aminophylline (Table 5). \(Sao_2\) and \(Pao_2\) both decreased significantly in the patients in whom the blood flow increased, but they did not change in the patients with an unchanged or decreased blood flow. It is of interest that the patients in whom \(Sao_2\) decreased after aminophylline also had low values for \(Sao_2\) during the control period. This is consistent with the presence of hypoxaemic pulmonary vasoconstriction in these patients.

We did not find any substantial difference in the changes of saturation between the patients with chronic bronchitis and with lung cancer; \(Sao_2\) fell in five out of eleven bronchitics and in two out of six patients with cancer. Cardiac output rose in four out of nine patients from the former group and in three out of six patients from the latter. With the exception of the mean pulmonary arterial pressure which was unchanged in lung cancer, a similar situation obtained for the other respiratory and haemodynamic values. It is probable that the vasodilator action of aminophylline on the pulmonary circulation is demonstrable only in subjects with pulmonary hypertension due to increased vascular resistance.

Table 5. Changes of oxygen saturation and tension after aminophylline related to the changes of blood flow

<table>
<thead>
<tr>
<th>Patients</th>
<th>(Sao_2) (%)</th>
<th>(Pao_2) (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Aminophylline</td>
</tr>
<tr>
<td>Cardiac index augmented (seven subjects)</td>
<td>80.0 ± 12.4</td>
<td>74.3 ± 14.5</td>
</tr>
<tr>
<td>Cardiac index unchanged or diminished (eight subjects)</td>
<td>87.0 ± 4.8</td>
<td>87.4 ± 10.5</td>
</tr>
</tbody>
</table>

Cardiac index was augmented in four subjects out of nine with chronic bronchitis and in three subjects out of six with bronchogenic cancer (by more than 20% of resting value).
REFERENCES


