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Central Haemodynamics during Hypoxia, Hyperoxia and Hypercapnoea in Severe Chronic Obstructive Lung Disease

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ABSTRACT

During inhalation of four different gas mixtures, with $F_{I_{O_2}}$ ~ 0.15 and ~0.11 and ~0.99 and with $F_{I_{CO_2}}$ ~ 0.055, the central haemodynamics of 25 patients with severe chronic obstructive lung disease and with a ventilatory capacity of ⩽35% of predicted normal values were studied. Fourteen patients (8 male, 6 female) had previously had periods of manifest respiratory insufficiency (R-group) and 11 patients (10 male, one female) had had no such severe respiratory symptoms (comparison group C).

The lowest tolerated $F_{I_{O_2}}$ level and the tolerated duration of the inhalation periods of different gas mixtures varied in relation to the severity of the disease. Hypoxia caused an increase in pulmonary arterial pressure and probably in vascular resistance. At the lowest attained hypoxaemic level the pulmonary arterial (PA) mean pressure was about 37 mmHg, although with large individual differences, in both groups. This PA pressure level was reached at significantly higher $F_{I_{O_2}}$, arterial saturation and oxygen tension levels in the R-group patients. During hyperoxia there was no significant difference between PA mean pressure in R- (25 mmHg) and C- (22 mmHg) group patients. The pressure reactions during hypoxia suggest that the vascular responsiveness might have been greater in R-group patients.

During induced hypercapnoea the increase in PA mean pressure (R-group 36 and C-group 33 mmHg) was mostly due to an elevation of PCV pressure, which occurred in relation to an increase in arterial blood pressure. The pulmonary vascular resistance probably did not increase during induced hypercapnoea. In a few patients latent failure of the left ventricle became manifest when the arterial blood pressure was raised due to the increased inspiratory CO_2.

INTRODUCTION

The clinical course in patients with severe ventilatory impairment from chronic obstructive lung disease is variable. Some patients have periods of manifest respiratory insufficiency while others have no severe acute exacerbations though the airways are equally obstructed in both types of patients, at least in between periods of manifest respiratory insufficiency. The mechanisms causing differences in the course of the disease are still unclear despite numerous investigations on the influence of oxygen and carbon dioxide tension and acidity on the pulmonary vessels and cardiac function. It therefore seemed of interest to study the central haemodynamics in two groups of patients in their habitual state: those with (R-group) and those without (C = comparison group) any periods of respiratory insufficiency in conditions simulating in some respects an acute exacerbation, such as hypoxaemia and hypercapnoea. Differences in toleration to hypoxia and hypercapnoea, in the pressure reactions of the systemic and pulmonary circulations and in the adaptation of the cardiac output to pressure changes might explain the differences between the two groups. The vascular reactivity of the most severely ill patients could not be studied by either induced hypoxia or hypercapnoea. It was hoped that conclusions might be drawn concerning the reversibility of the pulmonary hypertension by letting the patients breathe oxygen.

As the pressure reactions of the systemic and pulmonary circulation to oxygen are important in connection with therapeutic procedures the central haemodynamic studies were also considered of value from this point of view. Opinions are still divided in the literature concerning the use of oxygen as a therapeutic agent because of the fear that disappearance of the hypoxic ventilatory drive will outweigh its beneficial circulatory effects.

MATERIAL

The material consisted of 25 patients, selected among persons treated in 1968–1970 at the Department of Pulmonary Diseases, University Hospital, Uppsala, for chronic obstructive lung disease and with a maximal voluntary ventilation

(MVV_F) $\leqslant 35\%$ of predicted normal values. The principles for selection of the patients have been described and the material presented in detail by Brundin & Tammivaara-Hilty (6). Also some physiological findings have been given earlier (42, 43, 44).

The material was divided into two groups according to the clinical development of the disease: 1) a respiratory insufficiency (R) group of 14 patients (8 male, 6 female), who had had periods of manifest respiratory insufficiency on one or more occasions and 2) a comparison (C) group of 11 patients (10 male, one female), who had never had respiratory symptoms of the same degree of severity.

The average age, height and weight of the R-group male patients was 62 (50–69) years, 61 (52–82) kg and 174 (162–186) cm and of the female patients 64 (57–72) years, 53 (39–73) kg and 161 (158–165) cm. The corresponding values of the C-group male patients were 59 (39–70) years, 62 (53–83) kg and 172 (162–180) cm and of the one female patient 56 years, 46 kg and 158 cm.

METHODS

The principles of the catheterization procedure, pressure measurements, expiratory gas collection, analytical methods and calculations have been described elsewhere (7, 42, 43). Pressure changes inside ± 2 mmHg are referred to in the following as unchanged.

Hypoxia was induced after the Fick measurement during ambient air breathing at rest. It had to be omitted in patients R4 and R12 (who were already distressed during the Fick measurement on ambient air breathing), R16 (because of her poor general conditions, see "Results") and C9 (who was fatigued after a catheterization procedure which was prolonged for technical reasons). One or both of two hypoxic levels were used ($F_{I_{O_2}}$ 0.1395–0.1540 and 0.1036–0.1260). In cases where both levels were tolerated, these followed one another without interruption. The length of the hypoxic period was varied depending on the estimated risks and the patients' subjective symptoms.

Brachial arterial (BA) and either the pulmonary arterial (PA) or pulmonary capillary venous (PCV) pressure were measured every second minute during hypoxia. PCV pressure was measured, whenever possible, during the first 3–4 min if it was expected that only one hypoxic level would be tolerated. Otherwise the catheter tip was pushed to the PCV position during the last minutes of the first hypoxic "load" and withdrawn to the PA position after 3–4 min of the second hypoxic "load". BA and PA (or occasionally PCV) pressures were measured also 1, 4 and 10 min after hypoxia. In 5 R-group and 8 C-group patients the PCV pressure measurement was successful at least at one hypoxic level.

Expiratory gas was usually collected during the last 5 min of each hypoxic "load" of 10 min duration, for oxygen uptake ($\dot{V}_{O_2}$, ml/min) measurement. Blood was sampled in the middle of the gas collection period for measurement of the arterio-venous oxygen difference ($a\bar{v}_{O_2}$, ml/l) and arterial blood gases. If the test had to be terminated earlier, the sampling was performed, if possible, during the last minutes. The higher $F_{I_{O_2}}$ level was tolerated for 10 min by 6 R-group (R3, 5, 6, 8, 13 and 14) and all C-group patients, expect one (C8). All other patients and C8 managed the test for at least 5.5 min. The lower $F_{I_{O_2}}$ level was tolerated for 10 min by two R-group patients (R3 and 8), for 4.5 min by R6 and for 2 min by R14. The last mentioned patient was, however, included in the group "hypoxia terminated at 15% O_2 breathing" as no gas collection could be made during the 2 minutes at the lower $F_{I_{O_2}}$ level. In patient R5 this hypoxic level was omitted for reasons of caution, as on the day of catheterization the patient had right bundle branch block, which had not been observed in association with the exercise test on the previous day. In group C the lower $F_{I_{O_2}}$ level was tolerated for 10 min by two patients (C4 and 7), for 5–10 min by 4 patients (C1, 5, 10 and 11) and for 5 min by 2 patients (C2 and 3) The cardiac output ($\dot{Q}$, l/min) and pulmonary (PVR) and systemic (SVR) vascular resistance in (mmHg/l). min were calculated in the conventional way as described earlier (42).

Hyperoxia ($F_{I_{O_2}} \sim 0.99$) was started more than 10 min after termination of the hypoxic test and was usually continued for 20 min except in R5 and 14 (about 18 min) and in R4 (25 min). BA and PA pressures were measured every 5 min during and 10 min after hyperoxia. The placement of the catheter tip in the pulmonary capillary venous (PCV) position without fluoroscopy during the last minutes of hyperoxia was successful in 4 R-group and 5 C-group patients. The cardiac output ($\dot{Q}$, l/min) during hyperoxia was calculated by assuming the oxygen uptake ($\dot{V}_{O_2}$) to be the same as during ambient air breathing at rest, and from the $a\bar{v}_{O_2}$ measured during the last 5 minutes of hyperoxia. Veno-arterial shunting ($\dot{Q}_{sh}/\dot{Q}$, %) was calculated as described elsewhere (7, 43) from the $a\bar{v}_{O_2}$ during hyperoxia. The hyperoxic test was performed in all 25 patients.

Hypercapnoea ($F_{I_{CO_2}} \sim 0.0542$–0.0604 in air) was induced in 22 patients out of 25. In R4 and R12 it was omitted because of inability of the patients to tolerate the test and in R8 for technical reasons. In patients R8 and R12 it was induced, however, in connection with the follow-up investigation $\frac{1}{2}$–1 year later after breathing exercises and circulatory training. It was induced more than 10 min after hyperoxia and before the work test in all patients except in 6 R-group (R1, 3, 5, 8, 12 and 14) and 3 C-group (C2, 3 and 7) patients, in whom it was induced more than 10 min after the work test.

BA and PA or PCV pressures were measured every second min. Usually the PCV pressure was measured during the first 3–4 minutes, but if the test had to be terminated earlier the catheter tip was withdrawn to PA before termination. During induced hypercapnoea the PCV pressure was measured successfully in 2 R-group (R6 and 11) and in all except 2 (C6 and 9) C-group patients.

Expiratory gas was collected during the last 5 min of a 10-min hypercapnoic "load" and blood was sampled in the

middle of the gas collection period for measurement of the $a\bar{v}_{O_2}$ and arterial blood gases. If, however, the patients became so distressed that the test had to be terminated earlier, sampling was performed during the last minutes before termination. The induced hypercapnoea could be continued for 10 min in 3 out of 11 R-group patients (R3, 14 and 15) and 7 out of 11 C-group patients (C3, 4, 6, 7, 9, 10 and 11). In 6 R-group and 2 C-group patients the test could be continued for more than 5 but less than 10 min. In 2 patients from both groups it was tolerated for less than 5 min (R7: 4.5 min, R16: 4 min, C1: 2 min and C8: 3 min). Because of sudden terminating of the test, the carbiac output could not be measured in patients R7 and C1. Also, measurement of the minute ventilation ($\dot{V}_E$) was unsuccessful in patient C8, who terminated the test abruptly.

During hypercapnoea the calculations of oxygen uptake ($\dot{V}_{O_2}$, ml/min), arterio-venous oxygen difference ($a\bar{v}_{O_2}$, ml/l), cardiac output ($\dot{Q}$, l/min), pulmonary vascular resistance, PVR (mmHg/l)·min, and systemic vascular resistance, SVR (mmHg/l)·min, were calculated in the conventional way, as described earlier (42). The carbon dioxide elimination ($\dot{V}_{CO_2}$, ml/min) was calculated according to the Fick principle: $\dot{V}_{CO_2} = \dot{V}_E \times F_{E_{CO_2}} - \dot{V}_I \times F_{I_{CO_2}}$.

RESULTS

1. *The central haemodynamic findings at rest during ambient air breathing* are presented in Table I. The patients are sub-grouped according to whether hypoxia was induced or not.

Hypoxia was induced in 11 out of 14 R-group and 10 C-group patients. The 3 patients (R4M, R12F and R16F) in whom hypoxia was not induced for medical contraindications have been excluded from the group mean values of patients in whom hypoxia was induced, and are presented separately. The central haemodynamic findings during ambient air breathing at rest are also given separately for those patients of groups R and C who terminated the induced hypoxia on breathing ~15% O_2 and for those who terminated it on breathing ~11% O_2.

In patients R4 and R12 there was no question of inducing hypoxia as the Fick measurement at rest had been terminated earlier in both patients for reasons described in detail by the author elsewhere (42) and which also can be observed in Table I. Both patients were hypoxaemic and hypercapnic and had severe pulmonary hypertension. The arterial blood pressure and the variables mentioned increased during the Fick measurement because of the ventilatory valve. Patient R4 might also have been orthopnoeic as he was less distressed, had higher $P_{a_{O_2}}$ and lower $P_{a_{CO_2}}$ and normalized pH in the same test situation in the sitting posture. Patient R12 had the severest hypoxaemia ($P_{a_{O_2}}$ 37 mmHg) of the whole material in this body posture at rest. In patient R16 inducement of hypoxia was considered contraindicated because of a combination of different pathological components in her disease. Her $P_{a_{O_2}}$ was 51 mmHg, $P_{a_{CO_2}}$ 57 mmHg and V_D/V_T ratio 0.58, but the pulmonary arterial pressure was only moderately increased during the Fick measurement at rest. This might have been a sign of heart failure, as RV pressure at the beginning of the heart catheterization had been on the same level as in patient R12. Also her blood volume, 2.4 l, might have contributed to the fact that the pressures at the time of the investigation were lower than might have been expected from her respiratory symptoms. Ten years earlier the patient had had a myocardial infarction over the anterior wall with atrio-ventricular block and thereafter delayed activation. The day after the catheterization the patient had atrial fibrillation with frequent ventricular extrasystolic beats. Among these 3 patients the arterial saturation was highest in the patient with the lowest cardiac output, and vice versa. In patient R12 one of the reasons for a low $S_{a_{O_2}}$ and high cardiac output was veno-arterial shunting, as described later. The PCV pressures were inside normal limits (< 13 mmHg) in these 3 patients, though on a higher level (11 mHg) in the male than in the female (6 mmHg) patients.

The ranges of values for the different central haemodynamic variables among R- and C-group patients in whom hypoxia was induced were large. Only $S_{a_{O_2}}$, $S\bar{v}_{O_2}$ and PVR in patient R12 and the stroke volume and respiratory quotient (R) in patient R4 lay outside the limits of corresponding findings in patients in whom hypoxia was induced. When, however, patients R1, R13 and C2, who tolerated induced hypoxia in spite of a high pulmonary arterial pressure—probably because of good myocardial performance and polycythemia (C2), were exluded, the pressures were found to be lower in the patients in whom hypoxia was induced. Patients R1 and C2 were the only patients with typical right ventricular hypertrophy on the ECG recording. Both patients had had a long-lasting pulmonary disease with bronchial asthma since childhood and both were among the youngest patients of this material (50 and 39 years, respectively). Patient R13 had an arterial blood pressure of 215/95, which caused an elevation of the PCV

Table I. *Central haemodynamic findings during ambient air breathing at rest in supine posture in patients of group R (respiratory insufficiency) and group C (comparison), sub-grouped according to whether hypoxia was induced or not, and to whether hypoxia was terminated during the higher $F_{I_{O_2}}$ level ($F_{I_{O_2}}$ 0.1395–0.1530) or the lower ($F_{I_{O_2}}$ 0.1035–0.1260)*

Mean values and S.E.M. and/or range are given. ^{z} = all PCV pressures not measured during Fick or calc. PCV pressures included in the calculation of the mean PCV pressure

	R-group						C-group			
	Male				Female		Male			Female
Induced hypoxia ...	–	+	terminated at ~15% O_2	terminated at ~11% O_2	–	+ and termin. at ~15% O_2	+	terminated at ~15% O_2	terminated at ~11% O_2	~11% O_2
	$n=1$	$n=7$	$n=4$	$n=3$	$n=2$	$n=4$	$n=10$	$n=2$	$n=7$	$n=1$
HR, beats/min	71	90±7 75–124	99±9 80–124	77±1 75–80	88 86–89	86±7 74–97	83±4 71–115	80 79–80	85±6 71–115	81
$\dot{V}_{O_2}$, ml STPD/min	204	230±10 201–262	233±12 207–262	226±18 207–262	203 201–204	204±9 184–225	234±8 202–266	243 223–263	232±10 206–266	200
R	0.72	0.79±0.02 0.74–0.92	0.76±0.00 0.74–0.78	0.83±0.04 0.79–0.92	0.75 0.74–0.75	0.74±0.00 0.74–0.75	0.75±0.02 0.61–0.86	0.74 0.73–0.74	0.77±0.02 0.70–0.86	0.76
Hb, g/l	129	124±4 107–136	125±7 107–136	124±4 117–130	115 112–117	126±6 112–140	135±6 104–169	150 131–169	130±7 104–169	125
$S_{a\bar{O}_2}$, %	87.5	88.6±2.5 78.2–95.8	84.4±2.9 78.2–91.5	94.2±0.8 93.3–95.8	74.6 64.3–84.9	87.5±3.0 79.1–92.8	90.1±1.5 80.9–95.7	86.7 80.9–92.5	91.7±1.5 83.4–95.7	92.6
$S_{\bar{v}O_2}$, %	58.4	59.1±3.2 47.9–70.5	54.5±3.8 47.9–62.9	65.1±3.5 58.7–70.5	48.0 39.7–56.2	62.3±2.0 58.2–65.8	61.8±1.7 52.7–71.4	59.0 58.9–59.0	62.6±2.4 52.7–71.4	61.0
$a_{\bar{v}O_2}$, ml/l	53.1	51.7±4.2 37.9–66.9	51.9±5.9 40.2–66.9	51.5±7.5 37.9–63.8	43.0 38.6–47.4	44.3±3.0 38.8–52.3	52.8±2.8 39.7–65.2	57.2 52.2–62.1	52.5±3.7 39.7–65.2	57.0
$\dot{Q}$, l/min	3.9	4.6±0.2 3.9–5.3	4.6±0.4 3.9–5.3	4.5±0.4 4.1–5.3	4.8 4.2–5.3	4.7±0.3 3.7–5.2	4.5±0.3 3.5–6.3	4.4 3.6–5.1	4.5±0.4 3.5–6.3	3.5
P_{PA_S}, mmHg	62	40±4 29–56	48±3 41–56	30±0 29–30	48 34–62	43±6 33–58	39±4 29–70	39 36–42	39±5 29–70	30
$\bar{P}_{PA}$, mmHg	41	29±3 21–42	35±3 30–42	23±1 21–24	33 25–40	30±4 22–40	26±2 18–42	28 25–30	26±3 18–42	24
P_{PA_d}, mmHg	29	25±3 15–39	29±3 24–39	19±2 15–23	24 20–28	23±3 17–29	21±2 13–31	23 18–28	21±3 13–31	16
$\bar{P}_{PCV}$, mmHg	11	^{z}10±1 7–13	^{z}10±1 7–13	10±2 7–13	6	10±2 6–15	^{z}11±2 5–23	12 8–15	12±2 5–23	11
PVR, (mmHg/l)·min	7.7	4.4±0.8 2.4–8.5	5.5±1.0 4.3–8.5	2.9±0.4 2.4–3.7	5.5 4.5–6.4	4.4±0.6 2.5–5.1	3.2±0.4 1.7–4.9	3.8 2.8–4.7	3.0±0.4 1.7–4.9	3.7
P_{BA_S}, mmHg	160	139±8 114–178	137±14 114–178	142±8 129–155	152 134–170	159±20 117–213	133±6 103–162	144 125–162	134±6 112–155	160
$\bar{P}_{BA}$, mmH	114	101±4 90–114	98±6 90–114	105±4 98–110	106 97–114	110±12 80–141	100±4 78–116	106 96–116	102±4 89–116	120
P_{BA_d}, mmHg	83	80±8 69–90	75±2 69–78	86±4 78–90	73 69–77	79±7 61–95	80±4 62–93	86 80–91	80±5 62–93	96
Stroke volume, ml	29	52±4 32–66	48±6 32–55	58±4 53–66	54 49–60	55±6 38–68	56±5 30–74	55 45–65	56±6 30–70	43
SVR, (mmHg/l)·min	29.2	22.3±1.1 17.0–25.9	21.5±1.5 17.0–23.4	23.5±1.5 20.7–25.9	22.7 18.3–27.1	24.0±2.9 17.0–29.2	22.8±1.7 15.9–32.2	25.5 18.8–32.2	23.0±1.6 18.6–28.6	34.3

pressure and therefore contributed to the pulmonary hypertension.

The central haemodynamic findings that *during ambient air breathing* were different in the R-group patients who terminated the induced hypoxia on breathing ~15% O_2 and ~11% O_2 were as follows: S_{aO_2} was lower ($p < 0.05$) and the pulmonary arterial mean pressure higher ($p = 0.05$) in the patients who terminated the test at the higher F_{IO_2} level. There was also a tendency to a higher heart rate and PVR in these patients ($p < 0.10$). Their respiratory quotient, perhaps because of more severe airway obstruction, was also lower ($p < 0.01$). No such differences existed between the corresponding C-group patients, as the two patients who terminated the induced hypoxia on breathing ~15% O_2 (C6 and C8) differed from each other in most variables studied. The most important differences between these two patients were found in Hb concentration, S_{aO_2}, cardiac output, PVR, PCV pressure and SVR.

2. *The central haemodynamic findings during induced hypoxia* are presented in Table II for groups corresponding to those in Table I. Values obtained during breathing of ~15% O_2 are given separately for those patients who terminated the test at this F_{IO_2} level (in the R-group, 4 male and 4 female, and in the C-group, 2 male patients) and for those who continued further at the lower F_{IO_2} level; values obtained at the lower F_{IO_2} level are also presented.

2.1. *Breathing ~15% O_2.* Among the *R-group* patients the main differences *during breathing of ~15% O_2* between those who did and did not terminate the induced hypoxia at the higher F_{IO_2} level were that the former showed lower saturation and higher cardiac output, pulmonary arterial pressure and pulmonary vascular resistance. Differences between R-group male and female patients who terminated at ~15% O_2 consisted in a higher output in relation to body size and a tendency to higher systemic vascular resistance and to higher arterial blood pressure in the female patients ($p < 0.20$). Out of 4 R-group male patients the PCV pressure could be measured in 2; it was unchanged in patient R7 who had had a normal PCV pressure and decreased in R5 who had had an increased PCV pressure (and also RBBB) during ambient air breathing. Out of 4 R-group female patients this pressure was unchanged (11 mmHg) in the only patient, R11, in whom it could be measured.

Among the *C-group* male patients the only differences between the patients who terminated the induced hypoxia at the higher F_{IO_2} level and those who continued at the lower were a higher PVR ($p < 0.05$) and a tendency to lower $\dot{V}_{O_2}$ ($p < 0.10$) and higher R ($p < 0.10$) and SVR ($p < 0.20$) in the former group. The ranges of values for different central haemodynamic variables were large among both groups of patients, as was also found during ambient air breathing. As an example may be mentioned patients C2 and C6, who in spite of one common characteristic—secondary polycythemia—behaved differently during induced hypoxia. Patient C6, who had an increased PCV pressure during ambient air breathing, decreased his cardiac output simultaneously with an increase of the PA pressure and terminated the induced hypoxia on breathing ~15% O_2 (10 min). Patient C2, with normal PCV pressure during both ambient air breathing and hypoxia, increased his cardiac output while his orginally high PA mean pressure did not increase simultaneously at the higher F_{IO_2} level, and he was able to continue for a further 5 min at the lower F_{IO_2} level.

2.2. *Breathing ~11% O_2.* Of the *R-group* patients, 3 men (R3, 6 and 8) and one woman (R14) continued the test further with *breathing 11% O_2*. Only the male patients are included under the title "induced hypoxia terminated at 11% O_2" in the Table, however, as the female patient discontinued this breathing after only 2 min and there was no time for cardiac output or pulmonary gas exchange measurements. In the 3 R-group male patients the average PA pressure increased by 4 mmHg from ambient air breathing with S_{aO_2} 94% to this lower F_{IO_2} level with S_{aO_2} 70%. PVR and SVR showed greater increases as the cardiac output decreased in all these patients. In patient R3 the cardiac output decreased to 1.4 l/min and the arterial mean pressure to 52 mmHg without an increase of the heart rate. In this patient these measurements were exceptionally performed from 9–11 min breathing on the lower F_{IO_2} level. The pressure reaction was reproduced the next day. Decreased sensitivity of the sympatho-adrenal system towards hypoxia was suspected in this patient. The cardiac output decreased also in patients R6 and R8. In patient R6 the arterial blood pressure increased and the PCV pressure, which was normal, remained unchanged at this load. In patient R8 the arterial blood pressure

Table II. *Central haemodynamic findings at rest in supine posture during hypoxia in groups corresponding to those in Table I*

Mean values and S.E.M. and/or range at the higher $F_{I_{O_2}}$ level are given both for patients who terminated the hypoxic test at this level ($F_{I_{O_2}}$ in 4 R-group male patients 0.1496±0.0033, in 4 R-group female and 2 C-group male patients 0.1395) and for those who continued at the lower $F_{I_{O_2}}$ level ($F_{I_{O_2}}$ in 3 R-group male patients 0.1514±0.0014 and 0.1179±0.0041, in 7 C-group male patients 0.1465±0.0024 and 0.1073±0.0017, and in the C-group female patient 0.1395 and 0.1038). ^{z} = calc. PCV pressure or calc. PCV pressures included in calculations of the mean PCV pressure

	R-group				C-group				
	Male			Female	Male			Female	
Induced hypoxia terminated at ...	~15% O_2	~11% O_2		~15% O_2	~15% O_2	~11% O_2		~11% O_2	
	$n=4$	$n=3$		$n=4$	$n=2$	$n=7$		$n=1$	
		~15% O_2	~11% O_2			~15% O_2	~11% O_2	~15% O_2	~11% O_2
HR, beats/min	108±11	81±2	85±5	97±3	87	93±6	105±7	88	96
	84–135	78–84	76–92	90–104		78–124	84–138		
$\dot{V}_{O_2}$, ml STPD/min	222±13	203±4	153±38	176±10	177	223±12	221±15	188	186
	195–259	197–212	82–213	149–192	168–186	196–282	169–291		
R	0.98±0.05	0.97±0.01	1.72±0.54	1.06±0.03	1.17	0.95±0.02	1.15±0.05	0.99	1.16
	0.89–1.11	0.95–1.00	1.07–2.80	1.02–1.14	0.97–1.36	0.86–1.02	1.01–1.42		
Hb, g/l	126±6	123±2	124±2	127±5	152	131±7	134±7	127	127
	110–136	119–126	120–127	116–141	132–172	103–157	105–161		
$S_{a_{O_2}}$, %	66.3±5.7	86.8±1.7	69.9±2.8	67.2±2.7	72.6	78.4±2.8	54.8±3.7	81.6	66.5
	54.7–81.9	85.0–90.1	64.3–73.3	59.3–70.3	68.0–77.1	63.6–85.3	38.7–71.0		
$S_{\bar{v}O_2}$, %	40.9±6.4	55.7±2.3	42.5±6.5	46.4±1.6	48.1	52.2±2.3	32.3±3.3	52.4	39.3
	25.2–55.6	51.4–59.3	29.6–49.9	42.2–49.3	46.2–50.1	43.3–61.2	22.6–47.1		
$a\bar{v}_{O_2}$, ml/l	44.4±3.9	54.0±3.1	47.8±6.7	37.1±1.6	50.0	46.9±3.6	40.6±2.9	52.6	49.2
	37.4–51.8	48.1–58.8	37.6–60.5	33.7–40.8	43.1–56.8	29.3–59.3	32.2–55.3		
$\dot{Q}$, l/min	5.0±0.3	3.8±0.2	3.5±1.0	4.8±0.3	3.7	5.0±0.6	5.6±0.6	3.6	3.8
	4.3–5.7	3.6–4.1	1.4–4.7	4.2–5.7	3.0–4.3	3.4–8.4	3.8–9.0		
P_{PA_S}, mmHg	62±11	32±3	38±4	54±10	45	41±4	58±7	37	43
	48–95	27–36	32–44	39–84	42–48	34–65	36–93		
$\bar{P}_{PA}$, mmHg	45±8	24±2	27±1	39±7	31	28±3	40±5	25	31
	35–69	20–28	25–30	26–57	28–34	23–43	27–60		
P_{PA_d}, mmHg	37±8	19±3	21±1	28±4	27	22±2	30±4	22	24
	28–60	16–24	20–23	21–40	22–31	18–29	19–43		
$\bar{P}_{PCV}$, mmHg	^{z}9±0	^{z}8±1	^{z}8±1	^{z}10±2	^{z}10	9±2	^{z}10±2	11	11
	^{z}8–9^z	6–9	6–10	^{z}5–13^z	^{z}7–13^z	0–16	4–19		
PVR, (mmHg/l)·min	7.2±1.6	4.2±0.8	7.9±3.9	6.3±1.4	6.0	4.0±0.3	5.4±0.5	3.9	5.3
	4.9–12.0	3.0–5.6	3.2–15.6	3.2–9.6	4.9–7.0	3.0–5.0	3.8–7.1		
P_{BA_S}, mmHg	131±9	140±14	123±31	165±22	148	135±6	131±5	163	161
	120–157	126–167	71–177	127–227	122–173	121–164	120–153		
$\bar{P}_{BA}$, mmHg	94±6	106±10	94±23	116±13	110	100±4	98±5	119	115
	88–111	94–124	52–132	88–152	95–126	90–122	82–117		
P_{BA_d}, mmHg	71±1	84±7	74±17	85±7	86	80±4	75±4	94	96
	67–73	75–98	45–102	70–104	75–96	67–96	61–87		
Stroke volume, ml	48±4	47±1	40±11	49±3	42	55±7	55±6	41	40
	37–55	45–49	18–51	44–55	35–49	27–91	36–80		
SVR, (mmHg/l)·min	18.9±1.4	27.5±1.4	29.5±4.8	24.6±3.0	32.1	22.2±2.1	18.2±1.5	33.1	33.0
	15.6–21.8	26.1–30.2	20.6–37.1	19.6–33.0	22.1–42.0	14.5–30.9	13.0±25.5		

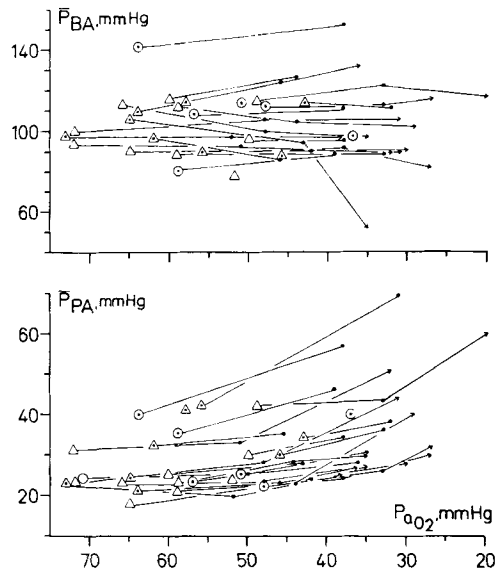

Fig 1. Brachial artery ($\bar{P}_{BA}$) and pulmonary ($\bar{P}_{PA}$) arterial mean pressure in mmHg in relation to arterial oxygen tension (P_{aO_2}, mmHg) during ambient air breathing in respiratory insufficiency (R) group (△ male, ⊙ female) and comparison (C) group (△ male, ○ female) patients and during hypoxia at a higher (·0.1395–0.1530) and a lower (→0.1035–0.1260) F_{IO_2} level.

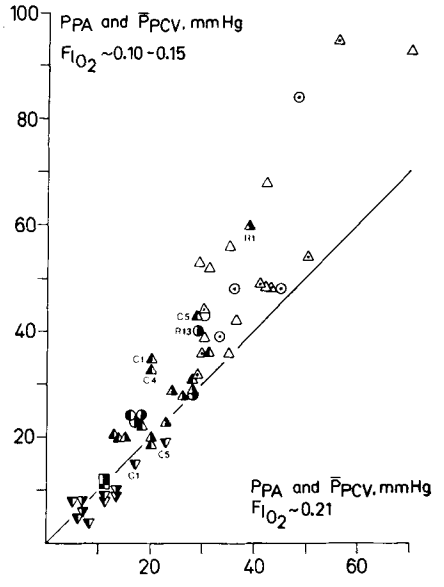

Fig 2. The relationship between pulmonary arterial (P_{PA}, mmHg) systolic (R-group male △ and female ⊙; C-group male △ and female ○) and diastolic (R-group male ◭ and female ◑, C-group male ◭ and female ◐) and pulmonary capillary venous ($\bar{P}_{PCV}$, mmHg) pressure (R-group male ▽ and female ◨, C-group male ▼ and female ◧) at the lowest F_{IO_2} level (0.1530–0.1036) attained and at ambient air breathing (F_{IO_2} ~ 0.21).

remained unchanged and the PCV pressure, which was 13 mmHg at rest during ambient air breathing, decreased to 10 mmHg.

Of the *C-group* patients, 7 men and one woman, continued the test further with breathing ~11 % O_2. The mean increase in mean PA pressure was 14 mmHg, corresponding to a reduction of the arterial saturation from 92 to 54%. A possible reason that the arterial saturation decreased more in the C-group male patients than in the R-group male patients or in the one C-group female patient, might be that they increased their cardiac output, which shortens the time of oxygenation in the lung capillaries. This explanation is supported by the finding that in patient R3 the arterial saturation did not decrease further than to 64.3%, although the cardiac output decreased to extremely low values. The C-group patient C2, who was hypoxaemic even at rest during ambient air breathing, had secondary polycythemia; he showed no change in mean PA pressure at the higher F_{IO_2} level when P_{aO_2} was 33 mmHg, but the mean PA pressure increased abruptly from 43 to 60 mmHg while the P_{aO_2} level decreased to 20 mmHg at the same time as the cardiac output increased further from 8.4 to 9.0 l/min. In the C-group patients PCV pressures remained unchanged or at a decreased level during hypoxia. In patient C5 with the highest PCV pressure of the whole material and ECG signs of previous myocardial infarction the PCV pressure decreased at the higher F_{IO_2} level, but started to rise again on breathing at the lower F_{IO_2} level. This rise was interpreted as a sign of left ventricular failure at the lower F_{IO_2} level.

The individual changes in brachial and pulmonary arterial mean pressure are presented in relation to P_{aO_2} during ambient air breathing and during breathing at one or two hypoxic levels in Fig. 1. There is no consistent change in the brachial arterial pressure. The mean PA pressure shows a tendency to increase, but there are large individual differences. The mean pressures are influenced by both vasoconstriction and flow changes.

The individual changes in pulmonary arterial systolic and diastolic and mean PCV pressure from ambient air breathing to the lowest F_{IO_2} level that the patient could tolerate are presented in Fig. 2. As, according to Harvey et al. (18), PA diastolic nor

Table III. *Central haemodynamic findings at rest in supine posture during hyperxia ($F_{IO_2} \sim 0.99$, for at least 15 and at most 25 min) in R- and C-group patients*

Mean values and S.E.M. and/or range are given. ^{z} = as in Table II

	R-group			C-group		
	Male $n=8$	Female $n=6$	All $n=14$	Male $n=10$	Female $n=1$	All $n=11$
HR, beats/min	87±5 69–118	83±6 58–99	85±4 58–118	84±6 64–123	78	83±5 64–123
Hb, g/l	123±3 105–135	122±5 112–142	122±3 105–142	135±6 102–168	123	134±6 102–168
$S\bar{v}_{O_2}$, %	76.0±2.1 64.7–82.0	81.8±1.7 74.1–86.1	78.5±1.6 64.7–86.1	77.8±2.0 64.3–84.9	72.0	77.2±1.9 64.3–84.9
$a\bar{v}_{O_2}$, ml/l	56.1±4.1 43.8–77.7	44.1±4.0 29.6–59.7	50.9±3.3 29.6–77.7	56.2±2.7 42.8–70.5	67.7	57.2±2.6 42.8–70.5
$\dot{Q}$, l/min	4.3±0.3 3.2–5.5	4.8±0.5 3.2–6.9		4.3±0.3 3.1–5.5	3.0	
P_{PA_S}, mmHg	36±5 25–47	36±5 21–53	36±3 21–53	31±2 25–41	28	31±2 25–41
$\bar{P}_{PA}$, mmHg	26±2 18–37	25±2 18–33	25±2 18–37	22±1 16–29	19	22±1 16–29
P_{PA_d}, mmHg	22±2 15–31	19±2 13–24	21±1 13–31	17±1 10–24	15	17±1 10–24
$\bar{P}_{PCV}$, mmHg	^{z}10±1 ^{z}7–14^z	^{z}9±2 ^{z}6–16^z	^{z}10±1 ^{z}6–16^z	^{z}12±2 1–24^z	11	^{z}11±2 ^{z}1–24^z
PVR, (mmHg/l)·min	3.7±0.8 1.8–8.2	3.3±0.3 2.3–4.1	3.5±0.4 1.8–8.2	2.3±0.3 0.4–3.6	2.7	2.3±0.3 0.4–3.6
P_{BA_S}, mmHg	146±8 116–186	159±16 117–228	151±8 116–228	134±5 119–168	165	137±5 119–168
$\bar{P}_{BA}$, mmHg	109±4 92–126	112±9 84–150	110±4 84–150	102±4 88–119	118	103±4 88–119
P_{BA_d}, mmHg	84±2 77–95	81±6 62–103	82±3 62–103	82±3 70–98	92	83±3 70–98
SVR, (mmHg/l)·min	25.2±1.6 16.7–31.9	24.2±2.6 15.2–31.6	24.8±1.4 15.2–31.9	24.6±1.8 15.7–33.2	39.3	25.9±2.1 15.7–39.3
$\dot{Q}_{sh}/\dot{Q}$, %	5.7±1.3 1.7–11.2	10.1±2.6 6.4–23.0	7.6±1.4 1.7–11.2	5.1±0.6 2.6–8.6	6.1	5.2±0.6 2.6–8.6

PCV pressure should be influenced by flow changes, conclusions on pulmonary vasoconstriction can be drawn from PA diastolic pressure changes. As the pH was normal or alkalotic during hypoxia in these patients the increase in PA pressure should be due to $P_{a_{O_2}}$. A decreased pH might in a few patients (R4 7.32, R14 7.35, C2 7.35 and C6 7.34) have contributed to the increased PA diastolic pressure during ambient air breathing.

3. *The central haemodynamic findings during hyperoxia* (F_{IO_2} ~0.99, usually for 15 to 25 min) in all 25 patients are presented in Table III. The PA mean pressure was 5.5±0.1 mmHg lower ($p < 0.001$) in

the R-group and 3.9 ± 0 mmHg lower ($p < 0.05$) in the C-group during oxygen breathing than during ambient air breathing. There was no consistent change in PCV pressure, which however, was not measured successfully in all patients. Assuming that the oxygen uptake was the same during oxygen breathing as during ambient air breathing PVR was 1.04 ± 0.02 (mmHg/l)·min lower in the R-group and 0.95 ± 0.02 (mmHg/l)·min lower ($p < 0.001$) in the C-group during oxygen than ambient air breathing. The arterial blood pressure also was lower in the R-group patients during hyperoxia ($\bar{d} \pm$S.E.M. = -3.6 ± 0.1 mmHg, $p < 0.05$). Out of 6 R-group female patients, 5 had, however, higher arterial blood pressure during hyperoxia (all except R15).

The individual changes in PA systolic and diastolic pressures from ambient air breathing to breathing of pure oxygen are presented in Fig. 3. The decrease is greatest in the patients with the highest pressures during ambient air breathing.

Veno-arterial shunting, found during pure oxygen breathing to be around 5–6% in both male groups and in the C-group female patient and around 10% in the R-group female patients, is one of the reasons for the higher cardiac output in relation to body size in these patients. The low P_{aO_2} in patient R12 during ambient air breathing was due largely to venoarterial shunting, which was found to be 23% of the cardiac output during hyperoxia.

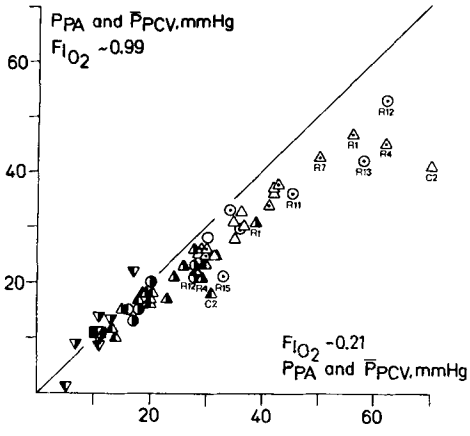

Fig 3. The relationship between pulmonary arterial (P_{PA}, mmHg) systolic and diastolic, and pulmonary capillary venous mean ($\bar{P}_{PCV}$, mmHg) pressure during hyperoxia ($F_{IO_2} \sim 0.99$) and ambient air breathing ($F_{IO_2} \sim 0.21$). The symbols for different patient groups and pressures are the same as in Fig. 2.

4. *The central haemodynamic findings during induced hypercapnoea* (F_{aCO_2} 0.0542–0.0604) are presented in Table IV.

No hypercapnoea was induced in patient R4. In R12 it was postponed until a later time point because of disability and in R8 for technical reasons. During induced hypercapnoea the arterial oxygen saturation increased to normal values except in patients R1, R2 and R7 and C2, C4 and C6 in whom it increased to levels slightly below normal. There was a slight increase in cardiac output due to increased oxygen uptake. Also the heart rate and arterial blood pressure were consistently higher. The heart rate increased least in patients who during ambient air breathing had the lowest arterial oxygen saturation (R2, C2 and C6). The brachial (BA) and pulmonary (PA) arterial pressures also increased. PVR, however, remained unchanged. There were very few patients in whom the PA diastolic pressure increased without an increase in PCV pressure. Both the PA systolic and diastolic pressure increased by > 2 mmHg in 7 R-group (4 male and 3 female) and 6 C-group (5 male and one female) patients. A decrease of the PA diastolic pressure by > 2 mmHg was seen in one R-group (R14) and three C-group (C2, C3 and C6) patients. The PA systolic pressure decreased to about the same extent except in C6, in whom it was unchanged. A correlation was found between increase in arterial diastolic blood pressure and increase in PA and PCV pressure (Fig. 4). The PCV pressure measurements during hypercapnoea were, however, successful in only a limited number of patients. Diastolic pressures were chosen for this comparison as, like PCV pressure, they should be dependent as mentioned earlier (17, 18) to only a limited extent on flow changes. There are however also contradictory results in regard to influence of flow on left atrial pressure (29). The greatest increase in PCV pressure was seen in patients C5 (14 mmHg), C1 (11 mmHg), R6 (10 mmHg) and C8 (9 mmHg). In patients C5 and C1 the PCV pressure was pathologically increased already at rest. The reason for the earlier termination of the induced hypercapnoea in these patients after 9, 2, 6.5 and 3 min, respectively, might have been acute left ventricular failure, as there was a breathing reserve left at the time of the gas collection. In C8, $\dot{V}_E$ could not be measured as the test was terminated abruptly. In the above mentioned patients P_{aCO_2} was normal during ambient air breathing, which

Table IV. *Central haemodynamic findings during induced hypercapnoea (F_{ICO_2} 0.0542–0.0604) at rest in the supine posture in R- and C-group patients*

F_{ICO_2} given in the R-group male patients was 0.0581±0.0080, in the C-group male patients 0.0562±0.0080 and in all female patients 0.0542. Mean values and S.E.M. and/or range are given. ^{z} = 1, and ^{zz} = 2 patients fewer than indicated, or ^{z} = as in Table II in regard to PCV pressures

	R-group			C-group		
	Male $n=6$	Female $n=5$	All $n=11$	Male $n=10$	Female $n=1$	All $n=11$
HR, beats/min	102±7 84–133	97±4 88–112	100±4 84–133	95±4 83–128	95	95±4 83–128
$\dot{V}_{O_2}$, ml STPD/min	^{z}274±9 257–307	216±10 194–247		^{z}270±10 217–295	234	
R	^{z}0.51±0.05 0.41–0.72	0.55±0.04 0.45–0.68	^{z}0.53±0.03 0.41–0.72	^{z}0.52±0.05 0.21–0.73	0.60	^{z}0.53±0.04 0.21–0.73
Hb, g/l	124±4 107–140	125±5 116–143	124±3 107–143	^{z}136±7 102–170	126	^{z}135±6 102–170
S_{aO_2}, %	94.0±1.3 90.3±–97.7	94.3±0.4 93.0–95.4	94.1±0.7 90.3–97.7	^{z}94.7±0.8 90.0–97.2	96.1	^{z}94.8±0.7 90.0–97.2
$S\bar{v}_{O_2}$, %	62.7±2.9 51.6–69.2	67.9±1.1 65.3–71.2	65.1±1.8 51.6–71.2	^{zz}67.1±2.5 52.3–75.0	65.7	^{zz}66.9±2.2 52.3–75.0
$a\bar{v}_{O_2}$, ml/l	55.1±3.4 46.9–69.2	47.2±1.8 43.3–52.8	51.5±2.3 43.3–69.2	^{zz}51.4±3.2 42.3–68.3	56.8	^{zz}52.0±2.9 42.3–68.3
$\dot{Q}$, l/min	^{z}4.9±0.4 4.0–5.9	4.6±0.3 4.2–5.6		^{zz}5.3±0.3 4.1–6.8	4.1	
P_{PA_S}, mmHg	53±6 31–73	50±10 30–86	52±5 30–86	45±4 30–71	44	44±4 30–71
$\bar{P}_{PA}$, mmHg	37±4 24–52	35±7 21–58	36±4 21–58	33±3 21–55	31	33±3 21–55
P_{PA_d}, mmHg	32±3 21–41	27±6 15–46	30±3 15–46	^{z}25±3 16–45	28	^{z}25±3 16–45
$\bar{P}_{PCV}$, mmHg	^{z}16±1 ^{z}11–20^{z}	^{z}14±3 ^{z}9–23^{z}	^{z}15±1 ^{z}9–23^{z}	^{z}16±3 6–37	15	^{z}16±3 6–37
PVR, (mmHg/l)·min	^{z}4.6±1.3 2.2–9.5	4.9±1.1 1.3–7.8	^{z}4.7±0.8 1.3–9.5	^{zz}3.3±0.4 1.7–4.8	3.9	^{zz}3.3±0.4 1.7–4.8
P_{BA_S}, mmHg	177±17 128–235	186±17 156–249	181±12 128–249	153±8 125–222	181	155±8 125–222
$\bar{P}_{BA}$, mmHg	129±12 95–173	131±10 111–168	130±7 95–173	116±6 92–160	140	118±6 92–160
P_{BA_d}, mmHg	99±6 82–122	93±7 81–119	96±4 81–122	92±5 73–126	105	93±5 73–126
SVR, (mmHg/l)·min	^{z}25.8±2.3 17.8–30.4	28.0±2.0 22.5–34.3	^{z}26.9±1.5 17.8–34.3	^{zz}22.1±1.0 13.5–26.8	34.1	^{zz}23.4±1.6 13.5–34.1

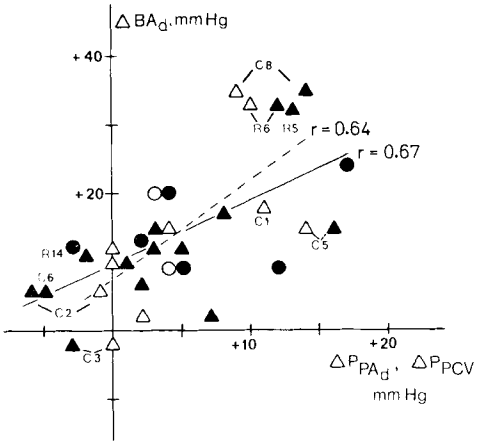

Fig 4. The cange in diastolic brachial arterial pressure (△ BA_d, mmHg) from ambient air breathing to CO_2-breathing ($F_{I_{CO_2}}$ 0.0542–0.0604) related to change in diastolic pulmonary arterial (△ P_{PAd}, mmHg) pressure (▲ male and ● female) and in mean pulmonary capillary venous (△ PCV, mmHg) pressure (△ male and ○ female). —, relationship between BA and PA; – – – –, relationship between BA and PCV, r = correlation coefficient.

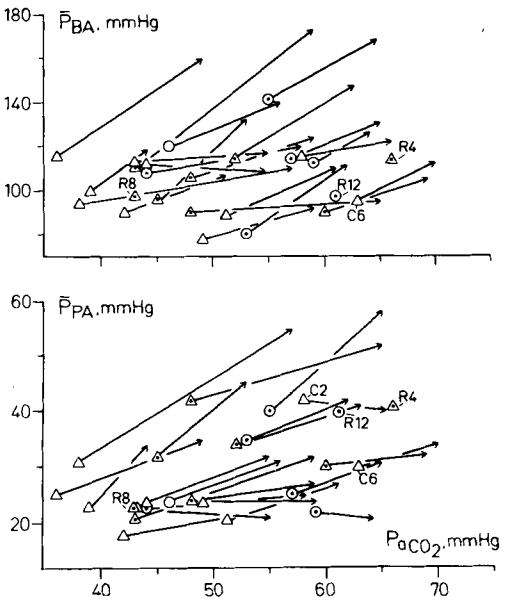

Fig 5. Brachial ($\bar{P}_{BA}$) and pulmonary ($\bar{P}_{PA}$) arterial mean pressure in mmHg in relation to arterial carbon dioxide tension ($P_{a_{CO_2}}$, mmHg) during ambient air breathing in R-group (△ male and ⊙ female) and C-group (△ male and ○ female) patients and during induced hypercapnoea (→) with $F_{I_{CO_2}}$ 0.0542–0.0604.

may have been the reason for the intensity of the arterial blood pressure increase.

When patients with a diastolic arterial blood pressure increase of < 15 mmHg and ≥ 15 mmHg during induced hypercapnoea were compared, also the pulse amplitude was found to be higher ($p < 0.05$) in the latter group. The differences in arterial blood gases, acid–base balance, Hb and cardiac output were not statistically significantly different in these two groups of patients either during ambient air breathing or during hypercapnoea. $P_{a_{CO_2}}$ during ambient air breathing was 51 ± 2 and 46 ± 2 mmHg ($p < 0.20$) and during induced hypercapnoea 61 ± 2 and 57 ± 2 mmHg ($p < 0.20$) in the respective groups. $P_{a_{O_2}}$ during ambient air breathing was 57 ± 2 and 62 ± 3 mmHg ($p < 0.20$) and during induced hypercapnoea about 83–85 mmHg in both groups. pH during ambient air breathing was 7.40 ± 0.01 and 7.41 ± 0.01 ($p < 0.20$) and during induced hypercapnoea 7.33 ± 0.00 and 7.34 ± 0.01 (N.S.), respectively. Hb was 134 ± 4 and 122 ± 4 g/l ($p < 0.10$). Therefore, the acid–base status may be involved in stimulation of the sympatho-adrenal system in these patients. As both the pulse amplitude and the diastolic arterial blood pressure increased, both the inotropic effect of adrenalin and the vasoconstrictive effect of noradrenalin should be involved in the arterial blood pressure increase.

The increase in brachial arterial and pulmonary arterial mean pressure in relation to $P_{a_{CO_2}}$ during ambient air breathing and induced hypercapnoea is presented in Fig. 5. Patients with the highest Hb values (C2 and C6) were among those with only a slight or moderate increase in BA mean pressure (Fig. 4). There were, however, a few other patients who also showed only slight changes in arterial and pulmonary arterial (R3, R14, R15, C3, C4 and C9) or PCV (C3; in the others PCV pressure measurement unsuccessful) pressure.

The individual changes in PA systolic and diastolic and *PCV mean pressure* from ambient air breathing to conditions during induced hypercapnoea are presented in Fig. 6.

DISCUSSION

Owing to the severity of the pulmonary disease in this material standardisation of the conditions for the heamodynamic studies was not always possible. The cardiac output measurements with the direct Fick method were not performed in all patients under steady state conditions either during induced

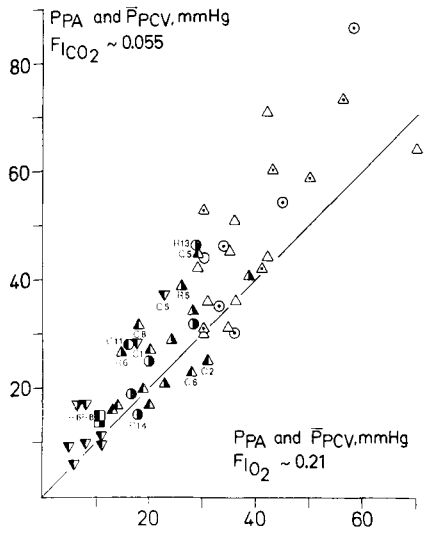

Fig 6. The relationship between pulmonary arterial (P_{PA}, mmHg) systolic and diastolic, and pulmonary capillary venous mean ($\bar{P}_{PCV}$, mmHg) pressure during induced hypercapnoea ($F_{I_{CO_2}}$ 0.0542–0.0604) and ambient air breathing at rest. The symbols for different patient groups and pressures are the same as in Fig. 2.

hypoxia or hypercapnoea. The values obtained have been presented, however, if the gas collection period was longer than 1 min. The blood sampling and gas collection period was longer than 1 min. The blood sampling and gas collection were more simultaneous when the gas collection period was shorter. This should reduce the methodological error of the cardiac output measurements caused by the non steady state conditions (12) in the oxygen uptake measurement. Kilburn et al. (22) showed in patients inhaling 10% CO_2 that cardiac output measurements after about 7 min compared with 12 min CO_2 breathing were reliable though steady state conditions had not yet been achieved. In this laboratory the error of a single determination, calculated from 10 duplicate determinations during a conventional Fick measurement, at rest, was 6.1% for cardiac output, 5.1% for arteriovenous oxygen difference and 4.1% for oxygen uptake (48). The oxygen uptake during ambient air breathing was used for calculations of the cardiac output during hyperoxia.

The pressures reported, which refer to the midthoracic level, might not exactly represent the whole respiratory cycle, as they comprise of arithmetic mean values of the highest and lowest pressures. The variations were caused by breathing. As this same principle was followed throughout the entire study, the pressures obtained in different experimental situations should be comparable. Some of the inter-individual discrepancies might have been due to differences in the lengths of the inspiratory and expiratory phases of the breathing cycle. Pulmonary capillary venous pressures were considered in this study to correspond to left ventricular filling pressures, as investigations by Rao et al. (34), Lockhart et al. (26) and Ježek & Boudík (24) have confirmed that simultaneously measured left ventricular end-diastolic (LV_{ED}) and PCV pressures are equal in patients with respiratory failure and also moderately severe chronic obstructive lung disease. Some other authors (1, 15, 19, 20, 23) have also found increased PCV pressures in patients with this type of disease, but they have considered this to be due to increased intrapleural, alveolar pressure or bronchopulmonary anastomoses. Lockhart et al. (26) have shown, however, that the increased PCV pressure, but not the oesophageal pressure, increased further during exercise. In this material the PCV pressures did not change significantly in most patients during either hypoxia or hyperoxia. Therefore, the PVR values obtained from PCV values calculated from the mean changes in the material should be fairly correct. During induced hypercapnoea the individual changes of PCV pressure were greatly variable and the individual PVR values obtained from the mean PCV pressure increase in the material might not, therefore, have been very exact.

Under habitual conditions (rest, air breathing), the pulmonary hypertension was so variable among both R- and C-group patients that in spite of the fact that $S_{a_{O_2}}$ seemed to be lower and the PA pressure higher in the R-group patients, the only significant difference between the groups was a higher pulmonary vascular resistance in the R-group. One of the reasons for the differences in pulmonary hypertension was increased PCV pressure in a few patients of both groups. This was considered, as mentioned earlier, to be a sign of deranged left ventricular function either due to coronary artery disease or to left ventricular hypertrophy.

Left-ventricular hypertrophy could in some cases be explained as due to increased arterial blood pressure, but in other cases there was no such obvious reason and the lung disease may have been responsible (6, 44). The highest diastolic arterial blood pressure (direct measurement) in the present

material at rest was 96 mmHg. Also the studies of Baum et al. (4) suggest that left ventricular function in chronic obstructive lung disease may be deranged. The patients with increased PCV pressures at rest during ambient air breathing (e.g. R5, R8, C1 and C5) had relatively low pressure gradients over the capillary bed compared with the rest of the patients in this material.

These patients had near to normal or normal arterial oxygen saturations and normal carbon dioxide tensions. The reasons for this might have been that the increased PCV pressure hindered capillary collapse from increased alveolar pressure. The lung might have become more uniformly perfused and the ventilation/perfusion inequalities might have decreased. That an increasing PCV pressure has a reducing effect on the pressure gradient over the pulmonary capillary bed has been shown, among others, by Harvey et al. (18). This is best seen in normal subjects and in patients with no pulmonary vascular changes. In the above mentioned patients the low cardiac output might also have contributed to the fact that the saturation levels were normal or near to normal.

Acute exposure of patients with severe chronic obstructive lung disease, in their habitual state, *to decreased or increased inspiratory oxygen concentrations* alters the level of their pulmonary hypertension without changing their pulmonary capillary venous pressure significantly in most of the present patients. That PVR increases during hypoxia is supported among others by the findings of Westscott et al. (46). Fishman et al. (12) found a significant increase ($\geqslant 5$ mmHg) in one third of their patients. In case PCV changed during hypoxia or hyperoxia this happened in patients in whom it was elevated. As mentioned earlier these changes were small, however, with the exception of patient C5. The PA pressure changes were greatest with the highest pulmonary arterial pressures at rest during ambient air breathing. This is in agreement with the findings of most authors that oxygen has its greatest effect in decreasing the high pulmonary arterial pressures in connection with respiratory failure (1, 16). Several authors (8, 12, 30, 39, 47), have observed small or no significant decrease of the pulmonary hypertension in patients exposed to high oxygen concentrations in resting conditions.

In this material there were some deviations from the general tendency that the highest pressures change most. These might have been due in some patients to differences in acid–base balance. The metabolic compensation was most apparent in the R-group patients who inspite of carbon dioxide retention had normal arterial pH. During hyperoxia the R-group female patients showed a tendency to be more hypercapnic (43). The difference between the R-group male and female patients was not statistically significant ($p < 0.20$). The C-group patients showed correspondingly a tendency to be less hypercapnic than the R-group ($p < 0.20$) and least metabolically compensated, with normal arterial pH. If a patient with pulmonary hypertension, arterial hypoxaemia and hypercapnoea and with a normal or acidotic arterial pH is exposed to hypoxia, the effect of decreasing $P_{a_{O_2}}$ on the pulmonary arterial pressure may be reduced or abolished by the increasing arterial pH due to the hypoxic hyperventilation. Therefore, the pressure changes observed may be smaller than if only one variable had been studied. On the other hand, at an alkalotic pH the pulmonary hypertension obtained should be due mostly to hypoxia. The question of the influence of oxygen tension, pH and the role of sympathetic stimulation in pulmonary hypertension is still open though many studies have been performed on heart–lung preparations, on intact animals and on man (5, 9, 10, 12, 16, 17, 18, 21, 29, 32, 41).

As an example of patients with different reactions to induced hypoxia, may be mentioned patient R1 with the severest pulmonary hypertension of the whole material. His PA mean pressure increased from 42 to 69 mmHg at the same time as his $P_{a_{O_2}}$ decreased from 56 to 31 mmHg. $P_{a_{CO_2}}$ (48 mmHg) remained unchanged and the arterial pH decreased from 7.51 to 7.48. The pH decrease occurred in spite of marked hyperventilation. Another example is patient R3, in whom the PA diastolic pressure was unchanged in spite of increased hypoxaemia and decreasing cardiac output and arterial blood pressure. His pH increased from 7.44 to 7.51, at the same time as $P_{a_{CO_2}}$ decreased, due to hypoxic increase in ventilation, from 48 to 39 mmHg. The alkalosis might have rendered the sympatho-adrenal system insensitive to hypoxia. That the sympatho-adrenal system was deranged in patient R3 is supported by the finding that there was no increase in heart rate during hypoxia despite the extremely decreased cardiac output and arterial blood pressure. Richardson et al. (35) have suggested that in normal man hypoxia might increase the cardiac output

by direct stimulation of the cardiac sympathetic nerves. According to Downing et al. (9) centrally mediated autonomic activity is of great importance for the maintainance of cardiac function during hypoxia. The previously mentioned patient (R1) might have had a different reaction, though his arterial pH was alkalotic at rest, because his arterial pH in working conditions (W_{max} = 150 kpm/min) rapidly sank to acidotic levels in contrast to R3 in whom it remained on alkalotic levels in submaximum working conditions. As discussed earlier the alkalotic pH of patient R3 might have been due to chloride depletion, which by Robin (37) has been found to prolong the period of metabolic alkalosis even after a period of manifest respiratory insufficiency has subsided. The difference in H^+ concentration might also explain the difference in the stimulation of the sympatho-adrenal system.

A further example is patient C2 who had an unchanged pulmonary artery pressure in spite of an increased cardiac output and a $P_{a_{O_2}}$ value of 33 mmHg while his pH simultaneously increased from 7.35 to 7.44. A further decrease of $P_{a_{O_2}}$ to 20 mmHg was needed to increase the PA pressure in alkalotic conditions. This patient was one of those who had a marked reduction of PA pressure during hyperoxia. In patient R12 there was a reduction of PA pressure inspite of an increased $P_{a_{CO_2}}$ from 61 to 74 mmHg, but probably the pressure level in this patient, as in others, was also influenced by the decreased pH during hyperoxia. There were also a few patients, who inspite of a normal pH and $P_{a_{CO_2}}$ in their habitual state reacted only with small changes to varying inspiratory oxygen concentrations (e.g. C3).

The R-group patients seemed to have a greater tendency towards pulmonary vasoconstriction than the C-group patients, as they reached the same pulmonary arterial pressure level at a significantly higher level of $F_{I_{O_2}}$. The highest average PA mean pressure levels attained by the different groups under these conditions was about 37–38 mmHg. To produce these conditions the $F_{I_{O_2}}$ in the R-group was 0.1527 ± 0.088 and in the C-group 0.1134 ± 0.045 ($p < 0.005$). With these $F_{I_{O_2}}$ values $S_{a_{O_2}}$ in the R-group was $70.0 \pm 2.5\%$ and in the C-group $59.5 \pm 3.6\%$ ($p < 0.05$). Under corresponding conditions $P_{a_{O_2}}$ was 38.8 ± 2.1 in the R-group and 32.1 ± 2.1 mmHg in the C-group ($p < 0.05$); $P_{a_{CO_2}}$ was 48.9 ± 2.4 in the R-group and 39.3 ± 2.5 mmHg in the C-group ($p < 0.05$). As the pH was equal in these conditions the reason that pulmonary hypertension was the same at different oxygenation levels could not have been acidosis. During hyperoxia the PA diastolic pressures in R- and C-groups were fairly equal. Also this supports the view that the R-group patients were more prone to vasoconstriction.

The inhalation of gas mixture of about 5.5% CO_2 in air increased the PA mean pressure by a few mmHg in both R- and C-groups. As under these conditions, the arterial oxygen saturation was normal or near to normal the vasoconstrictive effect of hypoxia should have been abolished in all patients. An increase of PA diastolic pressure was hardly ever seen without an increase of the PCV pressure which elevation occurred in response to an increase in arterial blood pressure. The mean arterial blood pressure increase was about 20–30 mmHg, but, as shown in Fig. 4, the arterial diastotic pressure change varied from a slight decrease to an increase of about 35 mmHg. The arterial mean pressure remained unchanged or increased up to 63 mmHg. The mechanisms responsible for the interindividual differences in arterial blood pressure reactions are not quite clear, but as known from the literature several mechanisms are involved in the pressure changes caused by CO_2 inhalation (2, 3, 5, 13, 14, 25, 27, 28, 31, 32, 33, 38, 41).

CO_2 is known to have a depressive effect on the myocardium in isolated heart lung preparations and it has been known since the report of Führer & Starling (13) and Pattersson (33) that adrenalin is able to abolish the negative inotropic effects of CO_2. In both animal studies (31) and on man (38) the depressive effect of CO_2 has been found to be hindered by catecholamines, released either from the adrenal medulla or via sympathetic nerves directly to the myocardium. As both the diastolic pressure and the pulse amplitude increased in the patients of the present study, both noradrenaline and adrenalin should have been involved in the pressure reaction. As some authors (38) have found an increase of both 17-OH corticosteroids and catecholamines during exposure of normal subjects to CO_2 it has been speculated that the effect might be mediated by adrenalin which would stimulate a central nervous centre in the hypothalamus, which via increased production of ACTH would cause the release of both cortical and medullary adrenal hormones. Mechelke et al. (28) have in animal studies suggested that arterial blood pressure increase would be due to increasing ventilation. In this material the increase in blood pressure showed a tendency to be

greatest in patients with the lowest P_{aCO_2} levels. The question thus arises as to whether the circulation also is adapted to increased CO_2 levels.

There was a positive correlation between increase of ventilation and arterial blood pressure. Grollman (14) has suggested that the increased mechanical work during hyperventilation might be responsible for the changes. This possibility cannot be excluded in our patients. In normal subjects McGregor et al. (27) have found a greater increase of cardiac output during voluntary hyperventilation than during CO_2 inhalation. The improved filling of the heart might increase the cardiac output if myocardial function is normal and the heart able to increase the stroke volume.

In patients with emphysema, Fishman et al. (11) found increased PA pressure and increased flow and came to the conclusion that there was no proof of pulmonary vasoconstriction. These authors did not measure PCV pressures nor discuss the role of the increased arterial blood pressure, found in their patients. Tartulier et al. (45) and Ježek & Boudík (24) found increased PCV pressures in patients with chronic obstructive lung disease. Ježek & Boudík came to the conclusion that the increased PCV pressure was probably due to the cardiac depressant effect of CO_2 as they found a negative correlation between the stroke volume and the P_{aCO_2} level during carbon dioxide breathing. These authors did not give any report on the changes of arterial blood pressure. Røkseth (36) did not find any significant change of PCV pressure in patients with different types of lung disease. There was, however, no significant change of arterial blood pressure either in his patients. Kilburn et al. (22) found no increase of PCV pressure in their patients inspite of an increase in arterial blood pressure. The reason for differences between their findings and those in the present study and those of Ježek & Boudík could be the myocardial condition of the patients. The age of the patients might also play a role, as the myocardium is known to become less compliant with age and probably therefore increasing PCV pressures are found in a higher frequency in older subjects even during exercise (40).

Though this study does not give an answer on the mechanisms involved in the arterial blood pressure reaction during induced hypercapnoea, it is obvious that the sensitivity to CO_2 is inter-individually different. Whether this is due to an individual reaction pattern primarily or secondarily to the lung disease cannot be answered. The differences in arterial blood pressure reactions towards CO_2 (and perhaps other stimuli) might be the reason for that all patients with chronic obstructive lung disease do not develope left ventricular hypertrophy.

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