Pulmonary Hemodynamics in Patients With Chronic Obstructive Pulmonary Disease Before and During an Episode of Peripheral Edema*

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We have investigated pulmonary hemodynamics in 16 patients with COPD with respiratory insufficiency, exhibiting marked peripheral edema. All the patients had previously undergone, within the last 6 months (T1), a right heart catheterization, in a stable state of their disease, when they were free of edema. Patients were subdivided into two groups according to the level of right ventricular end-diastolic pressure (RVEDP) during the episode of edema (T2): patients with a markedly elevated RVEDP (>12 mm Hg) indicating the presence of right ventricular failure (RVF)=group 1, n=9; patients with a normal or slightly elevated RVEDP (<12 mm Hg)=group 2 (no RVF), n=7. In group 1 pulmonary artery mean pressure (PAP) increased very significantly from T1 (27±5) to T2 (40±6 mm Hg, p<0.001) as did RVEDP, from 7.5±3.9 to 13.4±1.2 mm Hg (p<0.001). These hemodynamic changes paralleled a marked worsening of arterial blood gases, PaO_2 falling from 63±4 to 49±7 mm Hg (p<0.01) and $PaCO_2$ increasing from 46±7 to 59±14 mm Hg (p<0.01). On the other hand, in group 2, PAP was stable during the episode of edema (from 20±6 to 21±5 mm Hg), as was RVEDP (from 5.5±2.4 to 5.1±1.5 mm Hg), and changes in arterial blood gases from T1 to T2 were small and nonsignificant. It is concluded that RVF is effectively present in at least some patients with COPD with peripheral edema and is associated with a significant increase of PAP from baseline, probably accounted for by hypoxic vasoconstriction. Thus, pressure overload may contribute to the development of RVF. In other patients there are no hemodynamic signs of RVF, PAP is stable, and the origin of edema is not well understood.

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PAP=pulmonary artery pressure; PH=pulmonary hypertension; RVEDP=right ventricular end diastolic-pressure

Patients with advanced chronic obstructive pulmonary disease (COPD) often exhibit peripheral edema during acute exacerbations of their disease. The origin of this edema was generally attributed to right heart failure, but it has long been known that other mechanisms could be involved.[1] Furthermore, the possible occurrence of right heart failure in patients with COPD has been questioned,[2] especially as cardiac output is generally maintained or even elevated in these patients in the presence of edema.[3,4] Pulmonary hypertension (PH) is most often of mild degree in patients with COPD,[5] and that worsening of PH, during exacerbations of the disease, could lead to right heart failure, has been denied by Macnee et al[6] who observed that mean pulmonary artery pressure (PAP) was almost identical in patients with severe COPD with or without peripheral edema. In fact, different results were reported very recently by Anand et al.[7]

We thus decided to investigate patients with COPD exhibiting marked peripheral edema. A right heart catheterization was performed during the episode of edema, but also during a stable period of the disease when patients were free of edema. The aim of our study was to answer two questions: (1) Was right heart failure, assessed on hemodynamic data, present in some patients? (2) Was there a worsening of pulmonary hypertension, which could have favored the development of right heart failure, during the episode of edema?

Methods

We have investigated 16 patients with COPD. All had a history of chronic bronchitis defined on usual grounds,[8] and a spirographic pattern of airway obstruction defined by an FEV_1/VC ratio <60 percent. Pulmonary volumes, measured in a stable state of the disease, are shown in Table 1; it can be seen that bronchial obstruction was generally severe since the average values of FEV_1 and FEV_1/VC were respectively 1,000 ml and 40 percent. Hypoxemia was mild to moderate in most of the patients (Table 2). Half of the patients (8/16) had hypercapnia, which was mild in all individual cases, $PaCO_2$ ranging between 46 and 53 mm Hg (Table 2). Two patients (patients 9 and 10 [Table 2]) had a persistent hypocapnia; clinically, these patients had the "emphysematous" type of COPD.

Patients were investigated during two distinct periods: first, during a stable state of their disease when they were free from chest infection and from peripheral edema (T1); secondly, during an episode of marked peripheral edema (lower limbs), often but not necessarily associated with an acute exacerbation

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Table 1—*Anthropometric Data and Pulmonary Volumes in the Two Groups of Patients During a Stable State of the Disease (No Edema)**

	Group 1	Group 2	*t* Test
Sex, M	9/9	7/7	
Age, yr	61±6	65±10	NS
Vital capacity, ml	2,553±613	2,354±657	NS
Vital capacity /predicted, %	69±9	73±22	NS
FEV_1, ml	1,044±358	936±348	NS
FEV_1/vital capacity, %	39±13	40±11	NS

*Mean values±SD. For the definition of groups 1 and 2, see text. NS=the difference between group 1 and group 2 is statistically nonsignificant.

of the disease (T2). The time interval between T1 and T2 was at least of 1 month and always less than 6 months. No patient had any causes other than COPD, such as renal insufficiency or hepatic cirrhosis, that could have accounted for edema. Patients were excluded if they had any clinical, electrocardiographic, or echocardiographic evidence of systemic hypertension, valvular heart disease, coronary artery disease, or primary myocardial disease. Also excluded were patients with an abnormally high (>12 mm Hg) pulmonary artery wedge pressure.

The long-term treatment of the patients generally included theophylline derivatives, β_2-agonist aerosols and/or anticholinergic drug aerosols, and physiotherapy. Two patients received long-term oxygen therapy at home. During the episode of peripheral edema, patients were in hospital and received, in addition, antibiotics and continuous O_2 therapy when their PaO_2 was <60 mm Hg. Diuretics were given only after the right heart catheterization had been performed.

Pulmonary function studies (vital capacity, FEV_1) were performed at T1. Arterial blood gases (PaO_2, $PaCO_2$, pH) were measured at T1 and T2 during right heart catheterization. Right heart catheterization was performed at T1 and T2 as previously described.[9] For the purpose of this study, we used small-diameter flotation catheters, either Grandjean[10] F4 catheters (Plastimed, Saint-Leu-La-Forêt, France) or Swan-Ganz F5 catheters (Edwards Lab Inc, Anasco, Puerto Rico). The catheters were introduced percutaneously into an antecubital vein or into the right femoral vein. A Cournand needle was inserted into the humeral artery and arterial and mixed venous (pulmonary artery) blood gases were measured with standard electrodes. The cardiac output was calculated according to Fick's principle applied to oxygen, the oxygen uptake being measured in steady-state conditions during at least 10 min, with simultaneous sampling of arterial and mixed venous blood during the last minute. Oxygen uptake was measured with an open circuit system (Oxycon, Minjardt, the Netherlands). Oxygen therapy, which was given at T2 in all patients whose PaO_2 was <60 mm Hg, was withdrawn at least 2 h before the onset of right heart catheterization.

An informed consent was obtained from every patient and the study protocol was approved by the Ethical Committee of our University Hospital.

Statistical Analysis

All data were expressed as mean±SD. Within a given group, the significance of changes from T1 to T2 was assessed by Student's *t* test for paired data. The comparison between groups was assessed by Student's *t* test for unpaired data. The level of statistical significance was $p<0.05$.

Results

According to the hemodynamic results at T2, that is during the episode of edema, the patients were

Table 2—*Evolution of Weight and Arterial Blood Gases From Baseline (T1) to the Episode of Edema (T2)**

	Weight, kg		PaO_2, mm Hg		$PaCO_2$, mm Hg	
	T1	T2	T1	T2	T1	T2
Group 1						
1	88	93	64	59	38	60
2	71	78	62	50	41	45
3	72	80	58	36	49	68
4	81	88	70	45	53	66
5	86	93	63	51	46	54
6	54	61	60	55	48	66
7	46	52	66	46	50	64
8	85	91	63	45	51	75
9	52	55	55	56	32	28
M	70.6±16.1	76.3±16.6†	63±4	49±7‡	46±7	59±14‡
Group 2						
10	50	55	67	56	36	33
11	41	45	62	60	52	45
12	54	62	56	69	37	48
13	58	64	74	50	39	47
14	65	71	58	56	47	52
15	49	54	68	54	43	46
16	82	87	73	68	41	41
M	57.0±13.3	62.6±13.6†	66±7	59±7	42±6	45±6

*M=Mean values±SD.
†Difference between T1 and T2 statistically significant ($p<0.001$).
‡Difference between T1 and T2 statistically significant ($p<0.01$).

Table 3—*Hemoynamic Findings During the Episode of Edema (T2)**

	RVEDP, mm Hg	PAP, mm Hg	PWP, mm Hg	Q, L/mn/m^2	PvO_2, mm Hg
Group 1					
1	15	39	11	4.68	39
2	12.5	50		1.83	26
3	15	40	8	4.01	27
4	12.5	35		3.73	33
5	15	30		2.53	35
6	13	41	10	2.97	32
7	13	35		2.40	32
8	12.5	41		4.48	34
9	12.5	48	9	2.05	27
M	13.4±1.2	40±6		3.19±1.07	31.7±4.3
Group 2					
10	7	16	8	3.89	38
11	5	26	8	3.32	34
12	6	29	9	3.01	29
13	3	18		2.23	27
14	3	16	7	2.02	32
15	6	22		5.92	38
16	5.5	17	7	2.6	30
M	5.1±1.5	21±5		3.29±1.32	32.6±4.3

*PWP=pulmonary artery wedge pressure; Q=cardiac output; PvO_2=mixed venous oxygen partial pressure; M=mean value (±SD). For the definition of groups 1 and 2, see text.

subdivided into two groups: those with markedly elevated (>12 mm Hg) right ventricular end-diastolic pressure (RVEDP) (group 1) and those with normal or near normal RVEDP (<12 mm Hg) (group 2). A marked increase of the filling pressures of the right heart (right atrial pressure, RVEDP) is generally considered as reflecting right ventricular failure. Patients exhibiting both peripheral edema and an elevated RVEDP have a high probability of belonging to the category "decompensated cor pulmonale."

Table 1 shows that the pulmonary volumes, and particularly FEV_1, at T1 were identical in the two groups. Individual results of weight at T1 and T2 are given in Table 2. It can be observed that the weight gain during the episode of edema was identical in the two groups, being about 6 kg as a mean.

Individual hemodynamic results at T2 are given in Table 3. Group 1, defined by an elevated RVEDP ("decompensated cor pulmonale" group), comprised nine patients. Their cardiac output was normal whereas PAP was moderately and sometimes severely increased (range, 30 to 50 mm Hg). In group 2, which comprised seven patients, RVEDP was by definition normal or slightly elevated; cardiac output was normal; PAP was in the normal range (<20 mm Hg) or slightly elevated (<30 mm Hg) in all patients. The difference in PAP between groups 1 and 2 was highly significant ($p<0.0001$).

The evolution of the main hemodynamic parameters from T1 (no edema) to T2 (edema) in the two groups of patients is shown in Table 4 (mean values). It can be seen that RVEDP and PAP were stable in group 2, whereas in group 1 we observed a marked and significant increase of both RVEDP ($p<0.001$) and PAP ($p<0.001$) from their baseline value during a stable state of the disease. In this group, PAP increased in all individual patients (range of variation from +4 to +19.5 mm Hg, with a mean of +12.5±6.7 mm Hg). On the contrary, PAP

Table 4—*Evolution of the Main Hemodynamic Data From T1 to T2**

	RVEDP, mm Hg		PAP, mm Hg		Q, L/min/m^2	
	T1	T2	T1	T2	T1	T2
Group 1 (n=9)	7.5±3.9	13.4±1.2†	27±5	40±6†	3.23±0.82	3.19±1.07
Group 2 (n=7)	5.5±2.4	5.1±1.5	20±6	21±5	3.63±0.36	3.29±1.32

*For the definition of T1, T2, group 1, and group 2, see text.
†Difference between T1 and T2 statistically significant ($p<0.001$).

never increased by more than 6 mm Hg in group 2 (range, from −10 to +6 mm Hg, with a mean of +0.6 ± 5 mm Hg).

The changes in arterial blood gases in individual patients appear in Table 2. The average values of PaO_2 and $PaCO_2$ were almost identical at T1 in groups 1 and 2 (no significant difference), but differed significantly at T2 ($p<0.05$ for both PaO_2 and $PaCO_2$). This was due to a relative stability of arterial blood gases in group 2 from T1 to T2, while hypoxemia and hypercapnia markedly worsened in group 1 ($p<0.01$ for both PaO_2 and $PaCO_2$). During the acute phase of edema, group 2 patients had slight hypoxemia ($PaO_2=59\pm7$ mm Hg) compared with severe hypoxemia in group 1 (49 ± 7 mm Hg) and slight hypercapnia ($PaCO_2=45\pm6$ mm Hg) compared with marked hypercapnia in group 1 (59 ± 14 mm Hg).

We have analyzed the linear correlations between changes in arterial blood gases and changes in pulmonary hemodynamic variables from T1 to T2. The only significant correlation was that between changes in PaO_2 and PAP in group 1 patients ($r=-0.75$, $p=0.02$).

Discussion

Our results show that among patients with COPD with marked peripheral (ankle) edema, it was possible to distinguish two groups: a group of patients exhibiting a worsening of pulmonary hemodynamics, compared with baseline value, and hemodynamic signs of right heart failure (elevated RVEDP); and a group of patients whose hemodynamic data were stable, compared with those obtained when the patients were free of edema; RVEDP was normal in these patients. In the first group, the worsening of pulmonary hemodynamics paralleled the deterioration of arterial blood gas values. In the second group, there was relative stability of arterial blood gas values from the reference period to the episode of edema.

Indeed, the cause of edema was not clear in group 2 patients. Obviously, they did not have any right ventricular failure and their clinical and hemodynamic picture was not that of the classic "decompensated cor pulmonale."[6,11] Thus, the presence of peripheral edema in patients with COPD is not synonymous with right heart failure, a fact that has been emphasized earlier by Richens and Howard.[2] In our series, nearly half of the patients (7/16) had marked peripheral edema without evidence of right ventricular failure and without significant worsening of their respiratory insufficiency.

Patients with obvious causes of edema (renal failure, hepatic cirrhosis) were excluded from that study. In one patient in group 2, water retention could have been caused by the prolonged use of oral steroids. We have no definite explanation of the origin of edema in the remaining six patients in this group. The presence of associated left heart failure is very unlikely since patients with left heart disease were excluded and the pulmonary arterial wedge pressure, when it could be measured (in five of seven patients in group 2 [Table 3]), was constantly <12 mm Hg. In the two patients in whom wedge pressure could not be measured (patients 13 and 15 [Table 3]), PAP was, respectively, of 18 and 22 mm Hg, which is not compatible with left heart failure.

On the other hand, in group 1 patients, the presence of peripheral edema was associated with hemodynamic signs of right heart failure (markedly elevated RVEDP), realizing the classic picture of "decompensated cor pulmonale." Using RVEDP as an indicator of right ventricular failure has been criticized earlier,[11] but interestingly, in the six patients with gross edema investigated by Macnee et al,[6] right ventricular function was markedly impaired, taking into account the numerous hemodynamic variables measured in this elegant study, and the mean RVEDP was 12 mm Hg, which is near our mean value of 13.4 mm Hg. Our group 1 patients (n=9) are rather similar to the edematous patients of Macnee et al.[6] We did not investigate right ventricular function as they did, but we can assume from the measurements of RVEDP the presence of right heart failure, despite maintained cardiac output, in agreement with earlier studies.[3,4,6]

The most important finding in group 1 patients was the marked increase of PAP from baseline conditions (27 ± 5 mm Hg) to the episode of edema (40 ± 6 mm Hg). This worsening of pulmonary hypertension paralleled that of hypoxemia and hypercapnia. It thus appears that right heart failure is present in some patients with COPD exhibiting peripheral edema, and is probably accounted for by pressure overloading, PAP increasing very significantly from its baseline value. Indeed, an average value of 40 mm Hg is not synonymous with severe pulmonary hypertension, but it must be reminded that PAP may largely exceed this resting value during any form of activity (*eg*, walking) or simply during sleep and particularly during REM sleep.[12-14]

Macnee et al,[6] comparing hemodynamic findings in patients with COPD with or without edema, concluded that the worsening of pulmonary hypertension could not be the cause of right heart failure: this worsening was not observed in their study, PAP being nearly the same in patients with and without edema. In fact, they did not follow up the same patients, as we did, but compared two different groups of patients. We believe that the best way is to

investigate the evolution of pulmonary hemodynamics from the baseline state to the episode of edema, the patients being their own controls, and this was the purpose of the present study. Our results are in good agreement with earlier data from Lockhart et al[4] and from Abraham et al[15] and particularly with the very recent study by Anand et al[7] who have observed comparable behavior of pulmonary hemodynamics and arterial blood gases in six patients with severe COPD investigated when they had edema and after recovery. The PAP decreased from 43±(SEM) 3.2 to 29.5±2.2 mm Hg ($p<0.006$) while PaO_2 increased from 41.5±3.1 to 50±2.9 mm Hg and $PaCO_2$ decreased from 58.3±1.8 to 45.1±3.5 mm Hg,[7] which is very similar to our findings in group 1. Thus, longitudinal studies show that hemodynamic worsening is observed in patients with COPD exhibiting both edema and an exacerbation of respiratory failure, and could explain the development of right heart failure.

In our group 1 as well as in the patients investigated by Anand et al,[7] the marked increase in PAP was probably accounted for by the worsening of hypoxemia which is known to induce peaks of pulmonary hypertension during acute respiratory failure of patients with COPD.[4,15] In the eight patients of Abraham et al,[15] PAP decreased from 52 to 36 mm Hg ($p<0.01$) after recovery from acute respiratory failure while PaO_2 increased very significantly. In the present study, we have observed a significant negative correlation between changes in PaO_2 and PAP in group 1 patients ($r= -0.75$, $p=0.02$) which is in good agreement with earlier results from our laboratory[16] and suggests the presence of hypoxic pulmonary vasoconstriction.

The fall in renal blood flow and the subsequent stimulation of the renin-angiotensin system have been proposed as the mechanisms of edema in COPD patients with "cor pulmonale."[1,2,17,18] This mechanism has been clearly established in edema associated with low output states,[19] but the role of these changes in renal hemodynamics has been discussed in patients with COPD with normal output states.[3] Hypoxemia and hypercapnia are the most likely causes of the fall in renal blood flow[2] even if renal hemodynamic changes are not closely related to arterial blood gas changes.[18] The presence of hyperaldosteronism with elevated plasma levels of renin and aldosterone has been documented by Farber et al[20] in patients with COPD exhibiting edema during acute respiratory failure. Hypoxemia and hypercapnia could have induced a fall in renal blood flow in group 1 patients, but the presence of functional renal insufficiency leading to secondary hyperaldosteronism is less probable in group 2 patients who, as a mean, were slightly hypoxemic and not significantly hypercapnic while they had edema. In fact, three patients from that group (patients 10, 13, and 15 [Table 2]) had a significant fall of PaO_2 from baseline to the episode of edema, but $PaCO_2$ increased by >5 mm Hg in only one of them (patient 13). The role of hypoxemia-hypercapnia inducing functional renal insufficiency cannot be ruled out in these patients.

In patients with COPD, hypoxemia and hypercapnia often worsen during sleep and particularly during REM sleep.[21,22] Consequently, daytime arterial blood gases may underestimate the importance of sleep-related hypoxemia and hypercapnia. On the other hand, it is known that severe nocturnal desaturation occurs only in patients with marked daytime hypoxemia.[23] It is thus unlikely that group 2 patients had a profound worsening of hypoxemia (and hypercapnia) during sleep.

We conclude that hemodynamic signs of right heart failure are present in at least some patients with COPD with peripheral edema. These patients show a significant increase of PAP from its baseline level, accounted for by a marked worsening of hypoxemia. This pressure overload probably contributes to the development of right heart failure. In the presence of normal cardiac output, the mechanism of edema is supposed to be mediated by a fall in renal blood flow and subsequent stimulation of the renin-angiotensin system, acute hypercapnia possibly being the triggering factor. On the other hand, some patients with COPD with peripheral edema do not exhibit hemodynamic signs of right heart failure, have no significant increase of PAP from baseline, and show very small changes of arterial blood gases. The origin and the mechanism of edema in these patients are not yet understood.

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