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Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease

E WEITZENBLUM, C HIRTH, A DUCOLONE, R MIRHOM, J RASAHOLINJANAHARY, M EHRHART

From the Pulmonary Function Laboratory, Pavillon Laennec, University Hospital, Strasbourg, France

ABSTRACT In 175 patients with chronic obstructive lung disease (157 chronic bronchitic and 18 emphysematous patients) exhibiting moderate to severe airway obstruction (mean FEV_1/vital capacity = 40·2 ± 11·1%), cumulative survival rates calculated by the actuarial method were compared in subgroups according to the initial level of mean pulmonary artery pressure, pulmonary volumes, and arterial blood gases. Patients were catheterised between 1968 and 1972 and were followed for at least five years. The results emphasise the high prognostic value of $\bar{P}_{AP}$ since survival rates after four and seven years were significantly lower in the subgroup with $\bar{P}_{AP}$ > 20 mmHg (2·7 kPa). Certain other parameters ("driving" pressure across the pulmonary circulation, FEV_1 and $Paco_2$) appear to be equally good at predicting survival as $\bar{P}_{AP}$ in these obstructed patients. The effect of age should be taken into account in prognostic studies such as ours since survival rates were significantly lower in patients over 60 years of age. In 64 patients who underwent a second right heart catheterisation at least three years after the first (average delay: 5·5 ± 2 years), the prognostic value of changes in $\bar{P}_{AP}$, arterial blood gases, and pulmonary volumes was studied but with the exception of Pao_2 was unremarkable. Further studies are needed in this field.

In chronic obstructive pulmonary disease (COPD) and especially in chronic bronchitis, the presence of cor pulmonale is associated with a poor prognosis.[1-3] However pulmonary arterial hypertension is measurable and therefore easier to assess than cor pulmonale and prognostic studies have usually been related to the presence of pulmonary hypertension and its severity.[4-7] Most of these studies have included cases of severe COPD with a high proportion of patients having experienced episodes of right-sided heart failure. Only one recent study[7] was devoted to the prognosis of pulmonary hypertension in a large series of patients with mild or moderate airflow obstruction. Follow-up data were generally not taken into account.

We have investigated the prognostic value of mean pulmonary artery pressure ($\bar{P}_{AP}$) taking into account the influence of age, and compared it with other functional data (FEV_1, arterial blood gases) in our series of patients with moderate to severe airway obstruction. The actuarial method was used to assess survival rate. In 64 patients who underwent a second catheterisation at least three years after the first the prognostic significance of follow-up data was evaluated.

Address for reprint requests: Dr E Weitzenblum, Pavillon Laennec, Centre Hospitalier Régional de Strasbourg, Boîte Postale 426 67091 Strasbourg Cédex, France.

Methods

One hundred and seventy-five patients aged between 36 and 82 years (mean 59·8) with chronic bronchitis or emphysema or both were included in this study. All but two were male. All patients underwent a right heart catheterisation between 1968 and 1972. The fate of all patients at least five years after right heart catheterisation was known. Dyspnoea on exertion was present in all cases. Chronic airflow limitation was assessed by a FEV_1/vital capacity ratio constantly less than 60%. Cases with associated left heart disease, systemic hypertension (diastolic arterial pressure > 100 mmHg, 13·3 kPa), and other severe disease were excluded. Patients were never investigated during an acute exacerbation. Twenty-five patients were excluded from the study having been lost to follow-up. We do not consider that the loss of this small number has introduced significant bias.

Patients could be separated according to clinical,

Table 1 *Initial pulmonary function and haemodynamic data*

	Mean	± *1 SD*
Vital capacity (ml)	3070	± 810
FEV_1 (ml)	1237	± 467
FEV_1/vital capacity (%)	40·2	± 11·1
Pa_{O_2} (mmHg*)	63·2	± 10·7
Pa_{CO_2} (mmHg*)	39·7	± 6·2
$\bar{P}_{AP}$ (mmHg*)	19·8	± 7·6
Pulmonary artery systolic pressure (mmHg*)	31·1	± 10·4
Pulmonary artery diastolic pressure (mmHg*)	12·8	± 6·0
Right ventricle systolic pressure (mmHg*)	31·6	± 10·2
Right ventricle diastolic pressure (mmHg*)	1·6	± 2·2
Pulmonary artery wedge ("capillary") pressure (mmHg*)	6·4	± 2·9
Driving pressure** (mmHg*)	12·6	± 5·5
Brachial artery systolic pressure (mmHg*)	139·8	± 18·0
Brachial artery diastolic pressure (mmHg*)	81·5	± 10·0
Cardiac output (l min^{-1})	5·65	± 1·62
Cardiac index (1 $min^{-1}m2$)	3·24	± 0·93

Mean values and standard deviation, n = 175, except for wedge pressure and driving pressure (n = 105).
$\bar{P}_{AP}$ = mean pulmonary artery pressure.
*Conversion factor between mmHg and kPa: 1 mmHg = 0·133 kPa.
**Driving pressure is $\bar{P}_{AP}$ − P wedge.

radiological, and functional criteria[8 9] into a bronchitic group (n = 157) and an emphysematous group (n = 18) but clinical features of chronic bronchitis (sputum) were sometimes present in emphysematous patients, as were radiological signs of emphysema in bronchitic patients.

The following measurements of lung function were obtained in all patients: vital capacity, FEV_1 (measured with a closed circuit spirograph), arterial blood gases (Pa_{O_2}, Pa_{CO_2}, pH) measured with Radiometer electrodes. Haemoglobin saturation was calculated from Pa_{O_2} and pH according to Severinghaus.[10]

The procedure for right heart catheterisation used in our laboratory has been described.[11] Float catheters were used. Patients were studied in the supine position in the morning without premedication. The zero reference point was situated 7·5 cm below the angle of Louis. Cardiac output was calculated in steady state conditions (10 to 15 minutes of quiet breathing) according to the Fick equation. In 64 patients pulmonary haemodynamics were reinvestigated at least three years after the first measurements (range 36-119 months, mean 67 ± 24 months). At the same time lung function studies (pulmonary volumes, arterial blood gases) were repeated.

The fate of patients at least five years after the initial investigation was known in all cases. The first catheterisations were performed in 1968 and data were collected in 1978; thus the period of observation varied from a few months (early deaths) to 10 years.

The survival rate was calculated according to the actuarial method.[12] The advantage of this method is that it takes into account patients who might be lost after five years of observation. Its value in this kind of study has been emphasised recently by Massin *et al.*[7] Survival rates of subgroups (separated according to $\bar{P}_{AP}$, FEV_1, arterial blood gases, and so on) could

Table 2 *Comparison of the cumulative survival rates after four and seven years according to the initial level of the main parameters (for statistical methods, see text)*

	Number of cases	*Survival rate after four years (%)*	*Comparison of survival rates after four years*	*Survival rate after seven years (%)*	*Comparison of survival rates after seven years*
$\bar{P}_{AP}$ < 20 mmHg*	113	71·8	p < 0·01	55·6	p < 0·01
$\bar{P}_{AP}$ > 20 mmHg*	62	49·4		29·2	
Driving pressure** < 15 mmHg*	71	77·4		61	p < 0·001
Driving pressure > 15 mmHg*	34	41·2	p < 0·001	26·5	
Pa_{O_2} > 60 mmHg*	104	70·4	p < 0·05	53·7	NS
Pa_{O_2} < 60 mmHg*	71	54·9		35·8	
Pa_{CO_2} < 45 mmHg*	133	69·9	p < 0·001	53·2	p < 0·001
Pa_{CO_2} > 45 mmHg*	42	45·3		24·1	
FEV_1 > 1200 ml	90	81·2	p < 0·001	61·9	p < 0·001
FEV_1 < 1200 ml	85	45·9		30	
Age < 60 years	81	79·0	p < 0·001	61·7	p < 0·01
Age > 60 years	94	51·1		33·4	

NS = not significant. Driving pressure = $\bar{P}_{AP}$ − P wedge.
*Conversion factor between mmHg and kPa: 1 mmHg = 0·133 kPa.
**Driving pressure could not be measured in all cases (n = 105).

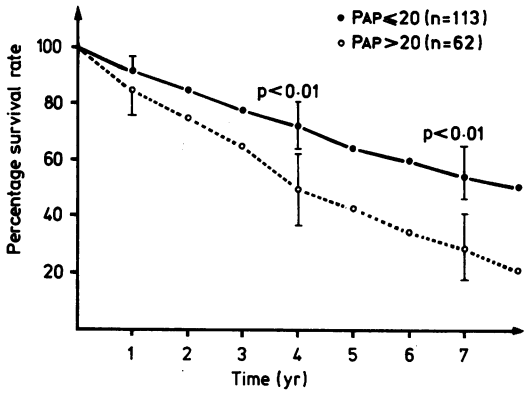

Fig 1 *Survival rates according to the initial level of pulmonary artery mean pressure ($\bar{P}_{AP}$) (< 20 mmHg, 2·7 kPa or > 20 mmHg). The comparison of survival rates between the two subgroups shows significant differences ($p < 0·01$) after four and seven years.*

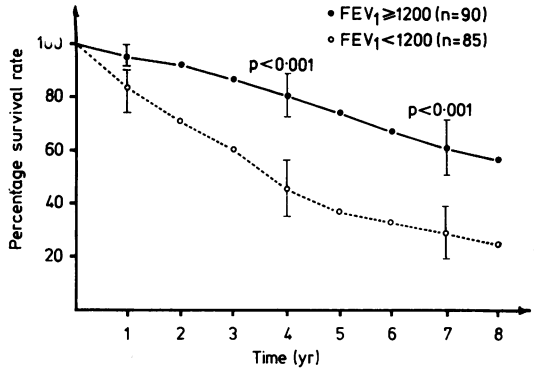

Fig 2 *Survival rates according to the initial level of FEV_1 (> 1200 ml or < 1200 ml). Survival rates in the two subgroups are significantly different ($p < 0·001$) after four and seven years.*

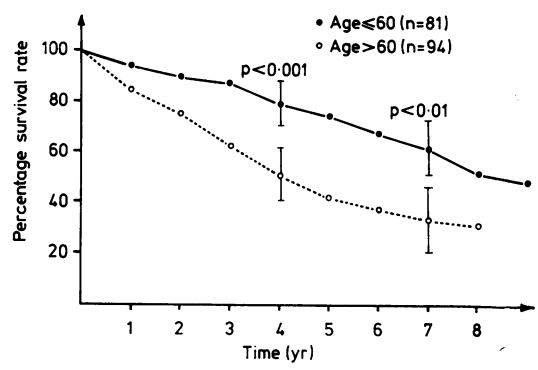

Fig 3 *Survival rates according to age (< 60 years or > 60 years). Survival rates in the two subgroups are significantly different after four years ($p < 0·001$) and seven years ($p < 0·01$).*

be compared using appropriate statistical methods.[12] The average figures for the main parameters in patients not surviving five years and in survivors were compared using Student's *t* test for unpaired data.

In patients who underwent a second right heart catheterisation, the average values of haemodynamic measurements, pulmonary volumes, and arterial blood gases between the first and the second investigation were compared by Student's *t* test for paired data. These patients were divided into two subgroups: dead patients and survivors of seven years or longer, and rates of change in $\bar{P}_{AP}$, Pa_{O_2}, Pa_{CO_2}, vital capacity, and FEV_1 between these two subgroups were compared (Student's *t* test).

Results

Average values for pulmonary volumes, arterial blood gases, and pulmonary haemodynamics are listed in table 1. Airway obstruction was moderate to severe and the mean FEV_1/vital capacity ratio for the whole group was markedly abnormal (40·2 ± 11·1%). Hypoxaemia was observed in almost all cases but was generally moderate (Pa_{O_2} < 60 mm Hg,

Table 3 *Comparison of the average figures of age, FEV_1, arterial blood gases, $\bar{P}_{AP}$, and driving pressure between the group of subjects who died within five years and the group of survivors*

	Subjects who died within five years (n = 76)	*Subjects still alive after five years (n = 99)*	*Significance (Student's t test)*
Initial age (yr)	63·0 ± 9·2	57·2 ± 8·7	4·28 p < 0·001
FEV_1 (ml)	1056 ± 378	1375 ± 482	5·10 p < 0·001
Pa_{O_2} (mmHg*)	62·2 ± 11·0	63·9 ± 10·6	1·03 NS
Pa_{CO_2} (mmHg*)	40·8 ± 6·7	38·7 ± 5·5	2·29 p < 0·025
$\bar{P}_{AP}$ (mmHg*)	21·7 ± 7·9	18·3 ± 7·2	2·89 p < 0·005
Driving pressure (mmHg*)	15·1 ± 5·9 (n = 42)	10·9 ± 4·5 (n = 63)	4·09 p < 0·001

*Conversion factor between mmHg and kPa: 1 mmHg = 0·133 kPa.

Table 4 *Initial and final average figures of the main parameters in the 64 patients who underwent a second catheterisation, at least three years after the first one*

	Initial	*Final*	*Significance*
Vital capacity (ml)	3170 ± 720	2610 ± 635	$p < 0.001$
FEV_1 (ml)	1210 ± 370	910 ± 305	$p < 0.001$
FEV_1/vital capacity (%)	38·3 ± 9·1	35·5 ± 10·5	$p < 0.005$
Pa_{O_2} (mmHg*)	60·7 ± 10·0	65·1 ± 11·3	$p < 0.01$
Pa_{CO_2} (mmHg*)	40·7 ± 5·6	44·7 ± 9·3	$p < 0.001$
$\bar{P}_{AP}$ (mmHg*)	20·9 ± 7·6	23·2 ± 10·9	$p < 0.02$
P.wedge pressure (mmHg*)	5·8 ± 2·6**	6·7 ± 2·3**	NS
Driving pressure (mmHg*)	11·5 ± 3·7**	12·8 ± 5·7**	NS
Cardiac index ($1min^{-1}m2$)	3·29 ± 0·84	3·56 ± 0·91	NS

Comparison of initial and final figures by Student's *t* test.
*Conversion factor between mmHg and kPa: 1 mmHg = 0·133 kPa.
**n = 34.

8 kPa in 71 cases, 40·6%). Hypercapnia defined by a Pa_{CO_2} > 45 mmHg (6 kPa) was present in only 42 subjects (24%).

Pulmonary arterial hypertension was defined as $\bar{P}_{AP}$ > 20 mmHg (2·7 kPa) and was observed in 62 patients (35·4%). In only 17 cases (9·7%) was $\bar{P}_{AP}$ > 30 mmHg (4 kPa). The pulmonary capillary (wedge) pressure was normal (< 12 mmHg, 1·6 kPa) in all but four cases. The driving pressure across the pulmonary circulation was defined as the difference between $\bar{P}_{AP}$ and the pulmonary capillary pressure.

The survival rate of the whole group was compared to that of a general population with a comparable age distribution and with the same mean age (60 years).[13] The survival rate was strikingly lower in our group of patients after three years: 73·8% versus 96% in the general population. After five years the survival rate was 56·6% versus 92%. After eight years it was only 40·6% versus 86%. At the end of the study 99 subjects had died. Death was directly or indirectly related to cardiorespiratory causes in 56 cases. In 20 cases, it was due to other causes. In 23 cases the exact cause of death was not known.

Survival rates were calculated according to the initial level of $\bar{P}_{AP}$ (> 20 mmHg, 2·7 kPa, n = 62, < 20 mmHg, n = 113), Pa_{O_2} (< 60 mmHg, 8 kPa, n = 71, > 60 mmHg, n = 104), Pa_{CO_2} (> 45 mmHg, 6 kPa, n = 42, < 45 mmHg, n = 133), FEV_1 (< 1200 ml, n = 85, > 1200 ml, n = 90), driving pressure (> 15 mmHg, 2 kPa, n = 34, < 15 mmHg, n = 71). The influence of age on survival rates was also investigated (> 60 years, n = 94, < 60 years, n = 81). It would have been preferable to divide each range into more than two groups, especially the age range which is very large (36-83 yr). This was not done because the actuarial method is invalid when groups are numerically small. The division into two groups for each parameter was either arbitrary in

Table 5 *Changes in pulmonary volumes, arterial blood gas and $\bar{P}_{AP}$ between the first and the second right heart catheterisation (delay between the two investigations = three to 10 years): comparison between survivors after seven years, and subjects who died after three to seven years*

	Survivors after seven years (n = 27)	*Dead after seven years (n = 24)*	*Significance (Student's t test)*
Initial vc (ml)	3178 ± 733	3112 ± 625	NS
Δ vc (ml)	− 567 ± 614	− 581 ± 500	NS
Δ/year (ml)	− 79 ± 83	− 150 ± 155	NS
Initial FEV_1 (ml)	1203 ± 331	1154 ± 335	NS
Δ FEV_1 (ml)	− 264 ± 378	− 253 ± 302	NS
Δ/year (ml)	− 47 ± 41	− 67 ± 88	NS
Initial Pa_{O_2} (mmHg*)	58·7 ± 8·3	60·4 ± 11·6	NS
Δ Pa_{O_2} (mmHg)	+ 8·4 ± 12·0	+ 1·0 ± 14·0	$p < 0.05$
Δ/year (mmHg)	1·3 ± 2·1	+ 0·15 ± 3·2	NS
Initial Pa_{CO_2} (mmHg*)	39·5 ± 5·6	43·0 ± 5·8	$p < 0.05$
Δ Pa_{CO_2} (mmHg)	+ 5·5 ± 11·5	+ 3·0 ± 6·2	NS
Δ/year (mmHg)	+ 0·7 ± 1·7	+ 0·6 ± 1·3	NS
Initial $\bar{P}_{AP}$ (mmHg*)	20·4 ± 8·7	23·4 ± 6·7	NS
Δ $\bar{P}_{AP}$ (mmHg)	+ 2·7 ± 8·6	+ 3·0 ± 8·0	NS
Δ/year (mmHg)	+ 0·5 ± 1·5	+ 0·8 ± 2·0	NS

Δ vc = change in vital capacity during the observation period.
Δ/year = change per year.
*Conversion factor between mmHg and kPa: 1 mmHg = 0·133 kPa.

order to have groups with comparable numbers of patients or was based on the usual criteria of "normality"—for example, $\bar{P}_{AP}$ > 20 mmHg (2·7 kPa) = pulmonary hypertension, P_{aCO_2} > 45 mmHg (6 kPa) = hypercapnia and so on.

Table 2 displays survival rates after four and seven years and the statistical significance of the comparison between subgroups. Survival rate curves according to $\bar{P}_{AP}$, FEV_1, and age are illustrated by figs 1-3 (other curves (P_{aO_2}, P_{aCO_2}, driving pressure, survival rate curve for the whole group) may be obtained from the authors on request). It may be seen that survival rates differ significantly according to the initial level of all the above-mentioned parameters except for P_{aO_2} after seven years. The largest differences between subgroups were observed for P_{aCO_2}, FEV_1, and driving pressure.

Average values of the main parameters in the group of subjects who died within five years (n = 76) and the group of survivors (n = 99) were compared by Student's *t* test. Table 3 shows that more effective discrimination between the two groups was provided by FEV_1, age, and driving pressure.

In 64 patients who underwent a second right heart catheterisation at least three years after the first, we compared initial and final pulmonary haemodynamic measurements, pulmonary volumes and arterial blood gases. These results are presented in table 4. This subgroup of 64 patients is fairly representative of the whole group (except for age: 56·7 ± 7·7 years) since initial mean values are very close in the whole group (table 1) and in this subgroup (table 4). During the observation period pulmonary volumes decreased significantly, P_{aO_2} and P_{aCO_2} both increased and changes in $\bar{P}_{AP}$ were small although statistically significant.

The fate of 51 patients who underwent a second right heart catheterisation was known seven years after the initial investigation. These patients were divided into two subgroups: subjects who died within seven years (n = 24) and subjects who survived seven years or more (n = 27). Changes in $\bar{P}_{AP}$, arterial blood gases, and pulmonary volumes in these two subgroups were compared and the results are shown in table 5. Mean changes were not significantly different, except for P_{aO_2} which increased in the group of survivors but did not vary appreciably in the group of patients who died within seven years.

Discussion

In patients with moderate to severe airway obstruction the prognosis was significantly worse when pulmonary hypertension was present. Patients without initial pulmonary hypertension had a survival rate of 71·8% after four years compared with a survival rate of 49·4% in patients with initial pulmonary hypertension. After seven years the differences were also very marked, there being 55·6% of survivors in the group without pulmonary hypertension compared with 29·2% in the group with pulmonary hypertension. The prognostic significance of $\bar{P}_{AP}$ is also illustrated by the comparison of the average $\bar{P}_{AP}$ in survivors after five years and in patients who died within five years (table 3), but it should be emphasised that overlap of individual values between groups was important. Thus the prognostic value of pulmonary hypertension in COPD patients agrees fairly well with the results of previous investigators.[4 7 14] Ourednik *et al*[4] observed that survival rates were significantly different after three and five years when $\bar{P}_{AP}$ was greater or less than 20 mmHg (2·7 kPa) and when $\bar{P}_{AP}$ was > 40 mmHg (5·4 kPa) survival rate was lower than in patients with a $\bar{P}_{AP}$ 20-40 mmHg (2·7-5·4 kPa), as early as one or two years after the first examination.

In most previous studies subjects have been divided, according to the level of $\bar{P}_{AP}$, into three,[7] four,[15] or five groups.[6 14] Thus pulmonary hypertension can be classified as mild (20-30 mmHg, 2·7-4 kPa), moderate (30-40 mmHg, 4-5·4 kPa) or severe (> 40 mmHg, 5·4 kPa) and survival rates clearly show that prognosis is particularly bad when $\bar{P}_{AP}$ is > 30 mmHg (4 kPa).[6 7 15] For instance Ourednik and Susa[6] observed that in their subgroup with $\bar{P}_{AP}$ > 50 mmHg (6·6 kPa) all patients had died within five years and that in the subgroup 30-50 mmHg (4-6·6 kPa) only 30% had survived after five years compared with 50% in the subgroup 20-30 mmHg (2·7-4 kPa). Conversely Bishop[15] observed that when $\bar{P}_{AP}$ was initially normal, 90% of subjects were alive five years later and Massin *et al*[7] had very similar results for patients in whom $\bar{P}_{AP}$ was < 20 mmHg (2·7 kPa). We have divided our patients into only two subgroups because although pulmonary hypertension was present in 62 subjects, it was moderate to severe (> 30 mmHg, 4 kPa) in only 17 subjects, the actuarial method would have been invalid for a group of this size.

Of the other haemodynamic parameters only driving pressure ($\bar{P}_{AP}$-wedge pressure) had a significant influence on survival rate, a finding which is in agreement with the results of others who have studied survival rate according to pulmonary vascular resistance.[7 15] We found that levels of cardiac output and wedge pressure did not influence prognosis. Massin *et al*[7] have recently investigated the prognostic value of more sophisticated haemodynamic parameters and have found that $\bar{P}_{AP}$-end-diastolic right ventricle pressure and change in $\bar{P}_{AP}$ from rest to exercise were as good predictors of mortality as $\bar{P}_{AP}$.

In our patients with chronic bronchitis and emphysema, FEV_1 and $Paco_2$ seem to be as good at predicting survival as $\bar{P}_{AP}$. Tables 2 and 3 show that the most significant differences were found when survival rates were compared in relation to initial FEV_1 and that the best discrimination between survivors after five years and patients who died within five years was provided by FEV_1. The high prognostic value of FEV_1 in patients with COPD is well known[16–21] and has been recently emphasised by Traver *et al.*[3]

The influence of age should be taken into account in this kind of prognostic study.[3] We observed that prognosis was significantly worse in patients > 60 years. The influence of age appears to be independent of functional and haemodynamic impairment. Mean values of $\bar{P}_{AP}$, driving pressure, Pao_2, and $Paco_2$ were almost identical in patients above and below 60 years, the only difference found being for FEV_1 which was lower in patients aged over 60 years (1130 ± 375 ml versus 1350 ± 530 ml in patients of under 60 years, $p < 0{\cdot}05$). As the effect of age on prognosis is significant it would have been justified, when studying the influence of haemodynamic and functional parameters, to further subdivide all groups according to age. This has not been done because the actuarial method of statistical analysis used in this study is inapplicable to small groups. The influence of age may partly account for the published differences observed between authors. Thus in the study of Massin *et al*,[7] survival rates for the whole group after five years (74·6%) and 10 years (51·1%) were markedly higher than our finding of 56·6% after five years and 38·4% after nine years. However Massin *et al* excluded patients over 65 years and the mean age of their group was 53·8 years.

Sixty-four patients underwent a second right heart catheterisation at least three years after the first, and we attempted to assess the prognostic value of follow-up data in addition to that of the initial "static" data. This group of patients was very similar to the whole group in terms of mean functional and haemodynamic data. In these patients changes in pulmonary haemodynamics were unremarkable, in agreement with recently published follow-up studies,[22–24] whereas pulmonary volumes had decreased markedly. Although survival rates in relation to changes in $\bar{P}_{AP}$, arterial blood gases, and pulmonary volumes could not be compared because of the limited number of cases, we did compare changes in these parameters in the survivors and the group of patients who died within seven years, using Student's *t* test. Decline of vital capacity and FEV_1 and increase of $\bar{P}_{AP}$ were generally more important in the group of patients who died but the differences were small. The only significant difference was related to change in Pao_2. It is probable that some differences would have become statistically significant had the number of patients been greater in each group. Some bias may have been introduced by the loss from follow-up of patients who died within the first three years. Further studies are needed to evaluate the prognostic significance of changes in pulmonary haemodynamics in patients with chronic obstructive lung disease.

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