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Prognostic factors in restoration of pulmonary flow after submassive pulmonary embolism: a multiple regression analysis

R. Menéndez, D. Nauffal, M.J. Cremades

Prognostic factors in restoration of pulmonary flow after submassive pulmonary embolism: a multiple regression analysis. R. Ménendez, D. Nauffal, M.J. Cremades. ©ERS Journals Ltd 1998.

ABSTRACT: Defects as evaluated by lung perfusion scans may persist even 6 months after pulmonary embolism (PE), when treatment is withdrawn. The aim of this study was to evaluate the effect of several potential factors on the resolution of lung perfusion defects, both during the first days and at 6 months, when patients were discharged.

In a retrospective follow-up cohort study we included 102 patients with PE, diagnosed lung from a ventilation/perfusion (V'/Q') scan, following Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria, together with a phlebographic study of lower extremities or angiography. Lung perfusion scan was performed at diagnosis, and in two follow-up evaluations, at 7–10 days and at 6 months. Potential factors studied were: age; sex; presence of underlying cardiac or pulmonary disease; venous insufficiency; alveolar-arterial pressure difference for oxygen; delay in diagnosis; abnormalities in electrocardiogram or chest radiograph; and the size of defects as shown in lung perfusion scans. All factors were studied with regards to the size of the defects at the two follow-up evaluations, through a univariate statistical analysis and two multiple stepwise regression analysis.

Multivariate statistical analysis selected four factors: size of defects at diagnosis; prior cardiopulmonary disease; delay in diagnosis; and sex, as synergistic variables to predict defect size at 7–10 days. On the other hand, the defect size at 7–10 days was the only variable selected as a predictor of the size of defects at 6 months.

Resolution of pulmonary defects during the first days after diagnosis of pulmonary embolism is influenced by the initial defect size, prior cardiopulmonary diseases and sex. The size of residual defects at 6 months depends mainly on the size of defects at 7–10 days.

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Service of Pneumology, University Hospital La Fe, Valencia, Spain.

Correspondence: R. Ménendez
Servicio De Neumologia
Hospital Universitario La Fe
Avda de Campanar 21
46009 Valencia
Spain
Fax: 34 63868789

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The conventional treatment of submassive pulmonary embolism (PE) includes initial intravenous heparin followed by oral anticoagulation therapy for 6 months [1–3]. Although heparin does not directly act on dissolution of thrombi, it favours the action of the fibrinolytic system, and prevents the production of new thrombi. Thus, early appropriate anticoagulation therapy improves the restoration of pulmonary flow and the resolution of lung defects, as evaluated by lung perfusion scans, in the first days. It is known that residual defects may persist after 6 months [4–6], and that resolution is insignificant thereafter. However, there is not much information about factors associated with resolution of pulmonary defects. Underlying cardiopulmonary diseases have been proved to worsen restoration of pulmonary flow, and effects have been quantified through a multivariate analysis [7].

Nevertheless, other factors which may influence the recovery of perfusion have not been very precisely studied. The aim of our work was to evaluate the role of several potential factors on restoration of pulmonary flow in patients with treated PE, both during the first days, when recovery is more evident, and at 6 months, when it is almost completed and patients are usually discharged. Secondly, we have tried to quantify the effect of these factors, in order to develop a mathematical model to more accurately predict the size of residual defects.

Patients and methods

We retrospectively studied 102 consecutive patients with a diagnosis of PE, from the Service of Pneumology of a tertiary teaching hospital. The diagnosis of PE was suspected on clinical grounds: chest radiograph electrocardiogram (ECG); and arterial blood gas analysis, and confirmed in 96 patients by lung scan or angiography. Lung ventilation/perfusion (V'/Q') scans were interpreted according to Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria [8]. Accepted criteria of PE in lung scanning were: a high probability pattern of PE in a lung V'/Q' scan, or an intermediate probability pattern tog-ether with deep venous thrombosis.

This was demonstrated in a phlebographic study when a filling defect was visible in at least two projections. In six patients with interme-diate probability *V'*/*Q'* scan and negative phlebographic study, the diagnosis of PE was established by pulmonary angiography; in these cases the criteria of DALEN *et al*. [9] were followed. We excluded patients who had suffered a previous PE episode to avoid misinterpretation of lung scan due to possible residual defects. By design, patients with massive PE, treated with fibrinolytic therapy, and pa-tients who died during evolution of PE were not includ- ed (13 patients). The patients were managed according to a specific diagnosis (firstly, clinical assessment of probability of PE and lung *V'*/*Q'* scan; secondly, a plebographic study; and thirdly, an arteriography if prior studies are in-conclusive) and treatment protocol; anticoagulation therapy was always started on the suspicion of PE. All of them were treated with *i.v.* heparin in the first week after diagnosis, followed by oral acenocumarol during a period not shorter than 6 months, monitored in our hospital.

The following data, which may be gathered at the moment of diagnosis, were collected from the medical records in all patients: age; sex; abnormalities in electrocardiogram and/or chest radiograph; immobilization; venous insufficiency; underlying cardiopulmonary disease; blood gas analysis; number of days between onset of symptoms and diagnosis; and lung scan results. The alveolar-arterial pressure difference for oxygen ($P_{A\text{-}a,O_2}$) was calculated according to the following equation:

$$P_{A\text{-}a,O_2}\ (\text{mmHg}) = (150\text{-}1.25\ P_{a,CO_2}) - P_{a,O_2}$$

where P_{a,CO_2} is the arterial carbon dioxide tension, and P_{a,O_2} is the arterial oxygen tension. Cardiopulmonary disease was defined as the presence of valvular heart or coronary artery disease, myocardial infarction and left- or right-sided heart failure. Pulmonary disease comprised chronic obstructive pulmonary disease (COPD), asthma, pneumonia and any other acute or chronic lung diseases at the time of PE. Most of them had been previously diagnosed in our hospital or consulting areas by pneumologists or cardiologists, according to their clinical history, chest radiography, functional respiratory studies and ECG patterns. Some cases were diagnosed during hospitalization in our Pneumology Department. Venous insufficiency was defined as chronical oedema and varicose veins without any other disease.

Pulmonary scintigraphy

Lung perfusion scan was performed with a gamma camera after injecting the patient with an *i.v.* dose of 60,000 ^{99m}Tc-labelled serum albumin microespheres (2–4 mCi.). The same procedure was repeated in each evolutive control. A pulmonary ventilation scintigraphy was also performed 24 h after lung perfusion scan. Ventilation lung scan was performed with ^{99m}Tc-diethylenetriaminepenta-acetic acid (DTPA) radioaerosol placed into a nebulizer with 3 mL of sterile saline solution. Patients inhaled radioaerosol in the supine position for 5 min, breathing at tidal respiration.

Both perfusion and ventilation lung scans were evaluated simultaneously, using a lung segment reference chart [10], in six projections: anterior; posterior; oblique; and lateral views [11]. Size of perfusion defects was quantified in lung perfusion scans according to the following pre- established numerical score: three points for each lung segment not perfused or with a defect higher than 75%; two points for segments perfused between 25 and 75%; and one point for perfusion defects <25%. The final score was obtained by addition of all defects in each perfu- sion scan. Every scintigraphy was examined by two skilled pneumologists to give the final score; if there was dis-agreement between them, the mean of the two scores was used. The size of defects in lung perfusion scans was quan-tified in three occasions at diagnosis: at the first follow-up evaluation; 7–10 days after initiation of anticoagulation therapy; and at 6 months.

Statistical analysis

The statistical analysis was performed with the commercial package: Statistical Package for Social Sciences (SPSS). As a preliminary measure, interobserver variability in the quantification of size defects in lung scans was evaluated with an analysis of variance (ANOVA).

A Kolmogorov-Smirnov test was performed to evaluate Gaussian distribution of variables. The variables were analysed with regards to the size of defects at follow-up evaluations after 7–10 days and 6 months, through a univariate statistical analysis. The Mann-Whitney U-test and Spearman's correlation were employed because some variables were not normally distributed. All the variables were also included in a multivariate analysis to identify those factors which act as independent synergistic variables. Two different multiple regression analyses were performed. Firstly, the dependent variable was the size of defects at the 7–10 days follow-up evaluation. Secondly, the size of defects at 6 months was the dependent variable, and the defect size at the first follow-up evaluation was included among the independent variables. The multiple regression analyses [12, 13] were performed with a stepwise method to sequentially include variables in the model, using the following pre-established criteria: inclusion of a variable when its level of significance was <0.05 (p in <0.05), exclusion of a variable when its level of significance was >0.10 (p out >0.10) and when the value of tolerance, as a measure of collinearity was >0.01 (tolerance >0.01). This method selects significant variables one by one, and every time a new variable is included, the rest of those previously selected are examined to check if any of them may be removed from the model. The significance of coefficients were evaluated by a Student's t-test. A p-value <0.05 was considered significant. A study of residuals was performed for the two multiple regression equations to test their normal distribution and homocedasticity.

Results

The study included 102 patients (46 male, 56 female), with a mean age of 64 yrs (range 21–88). In the study period, 13 additional patients died during evolution of PE and were excluded from the study analysis. Thirty patients had prior cardiopulmonary diseases; and in 85 patients chest radiograph or ECG abnormalities were present at the

Table 1. – Evolution of perfusion defects in the whole group and according to qualitative variables

	Defect size		
	At diagnosis	At 7–10 days	At 6 months
Whole group	12.8±7.7 (11)	7.5±5.2 (6.0)	4.1±4.2 (3)
Sex (Male/Female)	12.6±7.7 (10)/13.1±7.2 (11)	6.8±5.2 (5.5)/8.2±5.2 (7.5)	3.4±3.6 (3)/4.9±4.7 (3)
Cardiopulmonary disease (No/Yes)	12.9±7.8 (11)/12.7±6.5 (11)	6.8±5.3 (5.5)/9±4.7 (9.0)*	3.4±3.8 (2)/5.6±4.6 (5)*
Immobilization (No/Yes)	13.4±7.9 (11)/11.4±6.0 (11)	7.7±5.4 (6.0)/6.5±4.5 (6.0)	4.2±4.1 (3)/3.7±4.3 (3)
Venous insufficiency (No/Yes)	12.8±7.7 (11)/12.1±7.0 (11)	7.6±5.6 (6.0)/7.1±4.4 (6.0)	3.8±4.2 (3)/4.2±3.0 (3)
ECG or Rx abnormalities (No/Yes)	14.7±7.4 (13)/12.1±7.2 (10)	9.4±5.1 (9.5)/7.1±5.2 (6.0)	5.3±5.0 (3)/3.5±4.0 (3)

Values are expressed as mean±SD with median in parenthesis. Size of perfusion defects calculated with a score (see text). ECG: electrocardiogram; Rx: chest radiograph. Univariate analysis was performed using the Mann-Whitney U-test. *: p<0.05.

initial evaluation. In the whole group median diagnosis delay was 4 days (interquartile range 3–11 days). Increased $P_{A\text{-}a,O_2}$ of >2.7 kPa (>20 mmHg) was found in 92 patients (29 with prior cardiopulmonary disease). There were no statistical differences between scintigraphic scores as evaluated by the two observers (p>0.05).

Lung perfusion scans were evaluated at diagnosis, and potential factors involved in resolution of pulmonary defects at the two follow-up evaluations were studied through univariate (tables 1 and 2) and multivariate statistical analyses (tables 3 and 4).

Evaluation of defect size in perfusion scans at diagnosis

There were no differences in the defect size for any of the qualitative factors, although a positive correlation of the initial size of the defects with age and $P_{A\text{-}a,O_2}$ was found. Patients with prior cardiopulmonary diseases were older (p<0.01).

Follow-up evaluation of perfusion scans at 7–10 days

Perfusion scans normalized in six patients, and were not available in five. The size of remaining defects in the group as an whole was 59% of defect size at diagnosis. At this evaluation, patients with prior cardiopulmonary diseases showed a increased size of defects, and there was a significant correlation with age, the initial size of defects, the $P_{A\text{-}a,O_2}$ and an almost significant correlation with the delay in diagnosis. In order to investigate what variables were independent and synergistic to predict defect size at 7–10 days (dependent variable y), a multiple regression analysis was performed. The results are displayed in table 3. Four of the variables were selected as independent predictors and yielded the following mathematical formula:

$$y = 0.51x+0.09z+2.57s+1.36q-2.5$$

where: x is defect size at diagnosis, the numerical score obtained in the initial perfusion scan; z is diagnosis delay, the number of days until diagnosis; s is prior cardiopulmonary disease (n=0, yes=1); q is sex (male=1, female=2; multiple correlation coefficient r=0.79, F=38; p<0.001). We may predict the remaining defects at 7–10 days substituting variables included in the model by their respective value for a given patient.

Table 2. – Results of correlation between perfusion defects and quantitative variables at diagnosis and follow-up evaluations

	Defect size					
	At diagnosis		At 7–10 days		At 6 months	
	r	p-value	r	p-value	r	p-value
Age	0.25	0.01	0.32	0.001	0.25	0.01
$P_{A\text{-}a,O_2}$	0.34	0.005	0.32	0.001	0.19	0.058
Diagnosis delay	0.13	NS	0.19	0.058	0.15	NS
DS at diagnosis		-	0.71	<0.001	0.53	0.001
DS at 7–10 days		-		-	0.73	<0.001

$P_{A\text{-}a,O_2}$: alveolar-arterial pressure difference for oxygen; DS: defect size; r: Spearman's correlation coefficient.

Table 3. – Multiple regression analysis. Selected variables to predict defect size at 7–10 days (y)

Variables in the equation	Coefficient (95% CI)	Student t-test	p-value
x	0.51 (0.6–0.42)	10.7	0.001
z	0.09 (0.14–0.03)	3.03	0.003
s	2.57 (4.03–1.11)	3.45	0.001
q	1.36 (2.7–0.01)	1.99	0.049
Constant	-2.5	-	NS

95% CI: 95% confidence interval. Multiple regression equation: y=0.51x + 0.09z + 2.57s + 1.36q -2.5. x: defect size at diagnosis; z: diagnosis delay; s: cardiopulmonary disease; q: sex.

Follow-up evaluation of perfusion scans at 6 months

Twenty six patients showed a complete resolution of defects, and in six patients perfusion scan was not available. In the group as a whole, remaining defects were 32% of those at diagnosis. Univariate statistical analysis showed that larger defect sizes at this follow-up evaluation were found in older patients, in those with cardiopulmonary diseases, and those with larger defect sizes at diagnosis and at the 7–10 days follow-up evaluation. Another multiple regression analysis to estimate the size of defects at 6 months (y') was performed. Only one variable the size of defects in the 7–10 days follow-up evaluation, was found to be significant, and the resulting formula was:

$$y'=0.61d-0.28$$

where d is the score of defect size; r=0.73; F=105; p< 0.001 (table 4). To calculate remaining defects at 6 months we must use the score obtained in the follow-up evaluation of 7–10 days.

Table 4. – Multiple regression analysis. Selected variable to predict defect size at 6 months (y')

Variables in the equation	Coefficient (95% CI)	Student t-test	p-value
d	0.61 (0.72–0.5)	10.2	<0.001
Constant	-0.28	-	NS

95% CI: confidence interval. Multiple regression equation: y' = 0.61d -0.28. d: score of defect size at 7–10 days; NS: nonsignificant.

Discussion

The main findings in our study are that resolution of pulmonary defects after submassive PE is about 40% during the first 7–10 days and that it depends on the initial defect size, prior cardiopulmonary disease and sex. Resolution achieved at 7–10 days will determine the residual defect size in the lung scan at 6 months.

The recovery of pulmonary flow after acute PE is best monitored with perfusion lung scans [14, 15]. The method to quantify the size of defects in lung perfusion scans is relatively simple when using a reference chart [10]. Changes in blood gas analysis and chest radiograph have been proposed in the evaluation and early follow-up of PE, but after 1 month, only perfusion lung scans are useful, as reported by PREDILETTO *et al*. [15] using a similar score, which we have modified to distinguish between large, medium or small defects, as we have reported elsewhere [7]. Although some factors have been found which affect restoration of pulmonary flow, attempts to quantify their effect and the remaining defects at 6 months are few. After this time, the recovery of pulmonary flow is negligible [16].

In our study we quantified the size of defects after two different follow-up periods (at 7–10 days and at 6 months), in order to measure the effect of several potential factors as predictors of the restoration of pulmonary flow. It is known that recovery of pulmonary flow during the first 2 weeks is faster but not so evident afterwards, and we tried to investigate if evolution during these two different periods of time was affected by the same factors. Two factors were related with the size of defects at diagnosis: age and $P_{A\text{-}a,O_2}$, that is, larger defects in perfusion scans are to be expected in older patients and those with a greater $P_{A\text{-}a,O_2}$. In the first 7–10 days, about 40% of unperfused segments recovered, and the size of the remaining defects was related to several factors: age; the initial size of the defects; the initial $P_{A\text{-}a,O_2}$; and underlying cardiopulmonary disease. Some of those factors identified in the univariate analysis were previously recognized to be implied in the restoration of pulmonary flow during evolution of PE [4, 5, 17–19]. However, when a multivariate analysis was performed some different information was obtained. Multivariate analyses offer the advantage that they are capable of identifying those factors which act as independent variables and those which act as confounding ones. Thus, four factors were found to be synergistic and influence the size of defects at the 7–10 days follow-up evaluation (see table 3). This means that during the first 7 days, the resolution of pulmonary defects is delayed in patients with prior cardiopulmonary disease, and that the larger the initial size of defects, the larger the size of defects after 7–10 days. The same happens with the diagnosis delay and the effect of this variable has an additive effect on the other variables. Sex was also included in the model, and the $P_{A\text{-}a,O_2}$ and age were removed.

The joining of sex to the model means that it acts synergistically with the other factors. This information was not provided by the univariate study. The size of defects during evolution was higher in women, but not to a significant degree. The cardiopulmonary diseases are more frequent in men, and the deleterious effect they cause would counterbalance the effect of sex. Once the effect of these diseases is accounted for through a multivariate analysis, sex appears as a significant variable. This association has not been previously described and further studies would be needed to confirm this result. Contrary to sex, the $P_{A\text{-}a,O_2}$ and age, significant in the univariate study, were not included in the multivariate analysis model. Alterations in gas exchange following PE is influenced by the size of the embolized vessels (the size of the initial defect) and the prior haemodynamic status. Their association with the defect size at 7–10 days does not have value by itself, but as a reflection of the other two variables involved; initial defect size and prior cardiopulmonary disease. Once these factors are included in the model, no additional information is obtained from $P_{A\text{-}a,O_2}$. Similar reasons may be argued about age, since patients with prior cardiopulmonary diseases were older.

When studying the size of defects at 6 months, at the end of the follow-up period, four variables showed a statistically significant association in the univariate analysis. However, the multivariate analysis showed that the value of the defect size at 7–10 days is the most meaningful variable, and when considering this, no other factor has a significant role. That is, the evolution in the first days will potentiate subsequent recovery of pulmonary flow. Dissolution or fragmentation of emboli takes place during the first days, and if total resolution does not occur, the embolus will undergo organization [4], fibrosis becoming thus a hindrance for further recovery.

The effect of treatment was not evaluated because all our patients were treated with heparin. It is known that fibrinolytic therapy speeds resolution of thrombi during the first days [20], but our policy is to limit thrombolytic therapy, in patients with massive PE or haemodynamic derangement.

In summary, restoration of pulmonary flow after submassive pulmonary embolism is influenced during the first 10 days by the defect size at diagnosis; prior cardiopulmonary diseases; and sex. Once the acute phase is over, the size of remaining defects at 6 months will depend mainly on the defect size at 7–10 days.

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