Computation of Ventilation-Perfusion Ratio with Kr-81m in Pulmonary Embolism

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Diagnostic difficulties occur in pulmonary embolism (PE) during visual analysis of ventilation-perfusion images in matched defects or in chronic obstructive lung disease (COPD). In 44 patients with angiographically confirmed PE and in 40 patients with COPD, the regional ventilation-perfusion ratios ($\dot{V}/\dot{Q}$) were therefore computed using krypton-81m for each perfusion defect, and were displayed in a functional image. In patients with PE and mismatched defects, a high $\dot{V}/\dot{Q}$ (1.96) was observed. A $\dot{V}/\dot{Q} > 1.25$ was also found in nine of 11 patients having PE and indeterminate studies (studies with perfusion abnormalities matched by radiographic abnormalities). COPD was characterized by matched defects and low $\dot{V}/\dot{Q}$. The percentage of patients correctly classified as having PE or COPD increased from 56% when considering the match or mismatched character to 88% when based on a $\dot{V}/\dot{Q}$ of 1.25 in the region of the perfusion defect. This quantitative analysis, therefore, seems useful in classifying patients with scintigraphic suspicion of PE.

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Although ventilation-perfusion imaging with a gamma camera is a common approach to the diagnosis of pulmonary embolism (PE), regional ventilation-perfusion ratios ($\dot{V}/\dot{Q}$) are not usually computed. It is generally admitted that a mismatch between ventilation and perfusion images is diagnostic of pulmonary embolism (*1–4*). Nevertheless, McNeil et al. (*5,6*) and more recently Cheely et al. (*7*) and Goris et al. (*8*), have shown that angiography must be performed in a large proportion of cases to make the diagnosis. Diagnostic difficulties occur particularly when a ventilation defect is noted, since it could be related either to pulmonary embolism or to another cause such as chronic obstructive pulmonary disease (COPD) (*9–11*). However, the diagnosis of a matched or a mismatched defect of perfusion relies on qualitative and obviously subjective visual analysis of the two images, ventilation and perfusion, which is especially difficult when perfusion and ventilation are both reduced. Recently a new method for the study of the regional distribution of $\dot{V}/\dot{Q}$ with a gamma camera in normal subjects has been described (*12*). This method requires continuous inhalation and infusion of Kr-81m during tidal breathing. Since pulmonary embolism must be characterized by a high $\dot{V}/\dot{Q}$ due to reduction of the perfusion, the aim of this work is:

1. To assess the distribution of regional $\dot{V}/\dot{Q}$ ratios in pulmonary embolism.
2. To determine whether or not the value of the $\dot{V}/\dot{Q}$ computed in the region of a perfusion defect can be used to improve the diagnosis of pulmonary embolism in the cases previously described.

Two groups of patients were therefore studied, one with proved pulmonary embolism, and a second with COPD without pulmonary embolism.

MATERIALS AND METHODS

Patients. The study was performed on 44 patients (19 M, 25 F, aged 19 to 83 yr) who had pulmonary embolism confirmed by angiography and were admitted between

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January 1980 and September 1981 to two general hospitals.

For each of these patients the indication for pulmonary angiography was a clinical suspicion of pulmonary embolism together with a defect of perfusion on an initial image with Tc-99m macroaggregated albumin (MAA), and additionally one of the following criteria: (a) the scintigraphic abnormalities corresponded to radiographic abnormalities in the same regions of the lung (these cases are usually called indeterminate lung images); (b) the scintigraphic perfusion defects were small; (c) inferior vena cava interruption was contemplated; or (d) fibrinolytic therapy was being considered.

Following angiography, ventilation-perfusion measurements were performed using Kr-81m, immediately followed by a second Tc-99m MAA perfusion image. Informed consent of the patients was obtained. In 90% of the patients, the two studies were separated by less than 48 hr. The maximum delay between ventilation-perfusion measurement and pulmonary angiography was 72 hr. The mean delay between the onset of the clinical symptoms and the study was 5 days. The mean arterial oxygen tension of the patients, breathing air, on the day of the study was 67 mm Hg ± 2.35 s.e.m. No patient had a history of chronic obstructive lung disease. Eight patients had massive pulmonary embolism with arterial obstruction greater than 60% as defined by U.P.E.T. criteria (*13*). Eleven patients had radiographic opacities in the region of the pulmonary embolism.

Forty patients with COPD and no history of pulmonary embolism were also selected on the basis of pulmonary function tests: $FEV_1/VC = 41.6 \pm 2.8\%$. Thin layer chromatography as percent of predicted was (93 ± 5.7)% (mean ± s.e.m.). Gas tensions in their arterial blood was 59 ± 2 mm Hg for oxygen, and 46.6 ± 1.6 mm Hg for carbon dioxide (mean ± s.e.m.). Fifteen of them had bullous emphysema. All these patients had ventilation-perfusion studies with krypton-81m, and a Tc-99m MAA perfusion image.

Methods. The scintigrams were made with a gamma camera, equipped with a medium-energy collimator, and linked to a computer with 64K, 16-bit words. Krypton-81m, a short-lived radionuclide ($T_{1/2}$ = 13 sec, E = 190 keV), was produced from a rubidium-81 minigenerator ($T_{1/2}$ = 4.95 hr). It was first proposed for lung study by Fazio (*14*). The theoretical considerations have been developed recently by Amis (*15*). Patients were supine, breathing quietly, with back to the gamma camera. Three scintigraphic studies were performed sequentially without moving the patient: a ventilation study with Kr-81m; a perfusion study with Kr-81m for the computation of $\dot{V}/\dot{Q}$ ratios, which need to be performed using tracer of the same energy in ventilation and perfusion (*12*); and a perfusion study with Tc-99m MAA. This last was performed for the delineation of the perfusion defect, since it has been shown that a Kr-81m perfusion image could overestimate the perfusion in obstructive lung diseases (*16*). For each study 200,000 cumulative counts of the posterior view of the regional radioactivity distribution were collected by the computer memory in a 64 × 64 matrix, and transferred to magnetic disc. Sequential images of the evolution of the radioactivity were also stored during 30 sec after the onset of the infusion of Kr-81m. Ventilation and perfusion images with Kr-81m and a perfusion image with Tc-99m were recorded concurrently on film. For the krypton studies a 20% window of the gamma camera was centered on the 190-keV peak of Kr-81m. For the ventilation study krypton was flushed out by passing air at about 1 l/min through the rubidium generator and delivered continuously into a face mask. At the end of this study, krypton inhalation was discontinued, and the lung count rate allowed to decrease by radioactive decay and ventilatory washout (30 sec). The perfusion study was then performed by eluting krypton with a 5% dextrose solution at a rate of 10 ml/min and infusing it into an antecubital vein. A 2-min background count was recorded before each inhalation and infusion study. The window of the camera was then switched to 140 keV and a single injection of 2 mCi of Tc-99m MAA was given. The total time required for this study was about 10 min. The procedure was completed by obtaining the anterior, left lateral, and right lateral views of the Tc-99m perfusion. The dose to the lung delivered by the Kr-81m study was less than 35×10^{-5} Gy and from the Tc-99m MAA study less than 3×10^{-3} Gy (*16*).

Conventional chest radiographs of all patients were obtained in anterior and lateral views within 12 hr of the ventilation-perfusion study. Pulmonary angiography was performed by global injection of 1 ml/kg of ioxitalamic acid into the main pulmonary artery. If the angiographic diagnosis was uncertain, additional studies by selective or segmental hyperselective injection were obtained. To minimize injection of contrast material in cases of multiple defects, the injections were directed first to the major defect on the perfusion image, then successively to the smaller defects until an embolus was found. Oblique angiographic views were obtained when the embolus could not be visualized on standard projections.

In both groups of patients the perfusion defects on the posterior Tc-99m MAA images were classified visually by two independent observers according to their sizes on Kodak films, without the knowledge of the diagnosis. Since perfusion defects in COPD are generally not segmental (*9*), a classification derived from that of Taplin was used (*17*). Defects of perfusion were thus expressed as percentage reduction of lung perfusion in three ranges 0–15%, 15–25%, or greater than 25%. The defects were classified as matched if a ventilation defect whose size was closely related to that of the perfusion defect was present in the same region of the Kr-81m ventilation

scintigram; it was mismatched when ventilation was normal or mildly reduced in a poorly perfused area. Defects were classified as indeterminate if they were matched by a radiological opacity.

The distribution of regional ventilation-perfusion ratios was assessed by a method similar to that previously described, i.e., a normalized, regional, ventilation-perfusion ratio was obtained by dividing the Kr-81m ventilation image by the perfusion Kr-81m image (*12*).

For each patient, the ventilation and perfusion images stored in the computer were displayed on a TV screen after background subtraction and a nine-point smoothing. The limits of each lung were drawn electronically on the TV screen to determine two regions of interest (ROI). The regions of the lung corresponding to the projections of the radioactivity during Kr-81m infusion contained in the subclavian vein, the superior vena cava, and the right atrium and ventricle were determined on sequential images and subtracted from the lung ROI. Total counts on the resulting lung ROIs were computed from ventilation and perfusion images, then normalized. For every patient, in addition, ROIs were drawn by the two observers on the Tc-99m perfusion image for each defect of perfusion. In drawing these ROIs the operator was guided by the shapes of the defects detected on the analog images. The ventilation and perfusion images acquired in a 64 × 64 matrix were then contracted to 32 × 32. The number of counts in each pixel of the surface of the lung was therefore about 1000. The signal-to-background ratio was always >10 in both ventilation and perfusion.

$\dot{V}/\dot{Q}$ were computed in two ways:

1. In each of the pixels of the lung area, $\dot{V}/\dot{Q}$ was computed by dividing the normalized krypton ventilation image by the normalized krypton perfusion image. These regional $\dot{V}/\dot{Q}$s are therefore normalized to an overall value of 1, which is considered the normal $\dot{V}/\dot{Q}$. The topographical distribution of these values was displayed on the TV screen in a color-coded functional image, each color corresponding to a range of $\dot{V}/\dot{Q}$. The error in the $\dot{V}/\dot{Q}$ values is between 5% to 10% for high $\dot{V}/\dot{Q}$ but is less than 1% in normal subjects.

2. $\dot{V}/\dot{Q}$ was also computed by the same process (Kr_{vent}/Kr_{perf}) in each area of interest located on the perfusion defects previously drawn on the perfusion Tc-99m image.

For statistical analysis the patients were classified according to the size of their largest perfusion defect. Matched and indeterminate defects were grouped together. Comparisons between the groups used either chi-squared (χ^2) tests or one- or two-way variance analysis as appropriate (*18*). The number and percentage of patients correctly classified—either on the basis of the qualitative analysis or on the $\dot{V}/\dot{Q}$ analysis of the image—were computed a posteriori.

RESULTS

Qualitative analysis of images. The usual visual analysis of ventilation images with Kr-81m and Tc-99m MAA for perfusion showed that the two groups of patients are comparable taking into account the size of the perfusion defect, as shown in Fig. 1. However, the analysis of the 167 defects of perfusion showed that mismatched defects are significantly more frequent (69/93) in PE than defects matched by a ventilation defect or a radiological opacity ($\chi^2 = 11.9$, $p < 0.001$) and matched defects are predominantly observed in COPD (54/74) ($\chi^2 = 9.3$, $p < 0.01$).

Twenty-five patients (57%) of the PE group had all their defects mismatched and therefore could be correctly classified as having PE on the visual analysis of

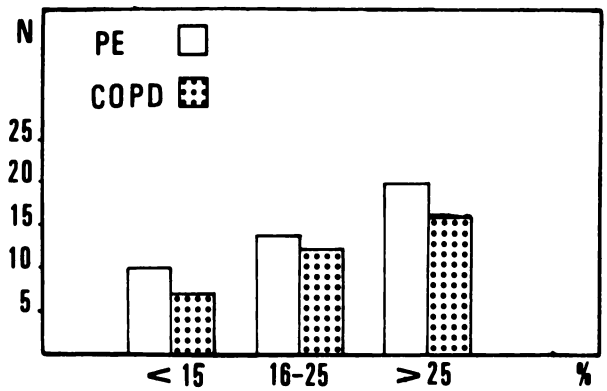

FIG. 1. Distribution of patients (N) according to size of perfusion defect (percentage of unperfused lung field) in pulmonary embolism (PE) and in chronic obstructive pulmonary diseases (COPD). There is no reliable difference between two groups.

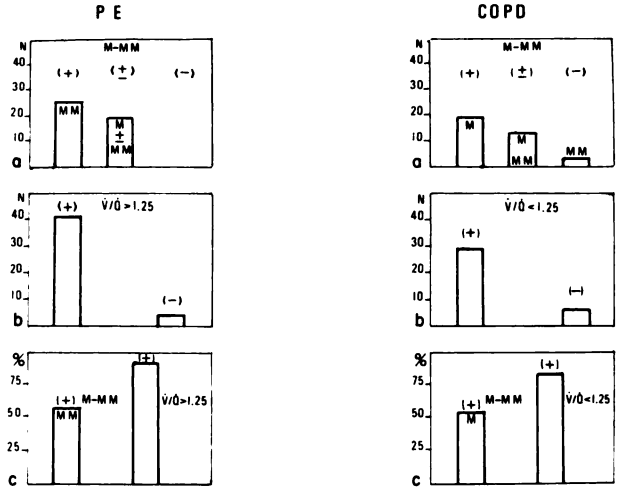

FIG. 2. (a,b): Classification of patients in two groups (PE and COPD) performed on basis of qualitative (M. MM),* a, or quantitative ($\dot{V}/\dot{Q}$ < or >1.25), b, analysis of images (N number of patients); (c): Percentage of patients correctly classified in two groups by *M = matched, with or without radiological opacity; MM = mismatched; (+) clinical and/or angiographic diagnosis confirmed; (−) clinical and/or angiographic diagnosis not confirmed (apparently refuted); (±) inconclusive.

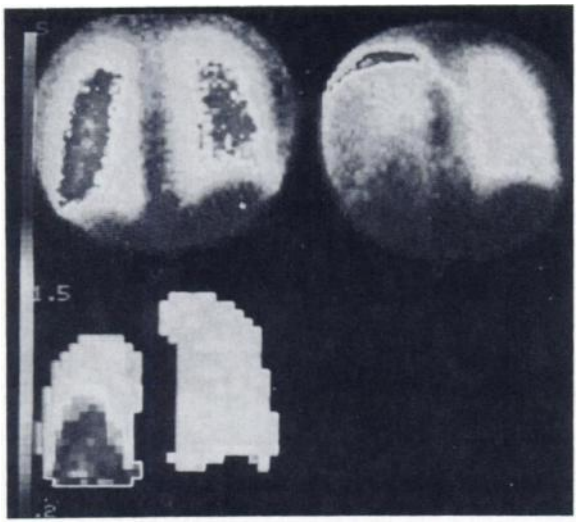

FIG. 3. Pulmonary embolism in left lung (posterior view, patient supine), V = ventilation image with Kr-81m. Q = perfusion image with Kr-81m. On perfusion image note perfusion artifact due to radioactivity contained in subclavian vein. $\dot{V}/\dot{Q}$ = functional image of $\dot{V}/\dot{Q}$ ratios, with scale of $\dot{V}/\dot{Q}$ values at left side. High $\dot{V}/\dot{Q}$ ratios are obvious in embolized left lung.

ventilation and perfusion images (Fig. 2a,c). Eleven patients had indeterminate scintigrams, that is, one or more defects matched by radiographic abnormalities (infiltrate, atelectasis, or effusion). An additional mismatched defect was present in four of them. Eight patients had a mixed pattern of matched and mismatched defects (Fig. 2a). Thus, 19 patients (43% of the group with proved PE) could not be classified accurately as having PE by the qualitative analysis. In the group with COPD, 19 patients (54%) had all their defects matched, and thus could be correctly classified (Fig. 2a,c). A mixed pattern was observed in 13 patients, and three patients had all their defects mismatched and could be erronously classified as PE (Fig. 2a). Five patients had no defects of pefusion detectable in the posterior view and were therefore excluded. Forty-four percent of all patients lacked a definitive diagnosis following the qualitative analysis of the ventilation-perfusion images according to the mismatched or matched character of the perfusion defects.

Quantitative analysis. In acute pulmonary embolism, functional images display a characteristic pattern that reflects the nonhomogeneity of the distribution of $\dot{V}/\dot{Q}$ (Fig. 3). The more striking feature is the existence of large regions with high $\dot{V}/\dot{Q}$. The highest $\dot{V}/\dot{Q}$ computed in a pixel in the whole group was 12. These high $\dot{V}/\dot{Q}$s are obviously a consequence of the vascular obstruction.

Whether they were assessed by visual analysis as matched by a ventilation defect (12 defects), or a radiological opacity (12 defects), or mismatched, perfusion defects in pulmonary embolism had a high computed $\dot{V}/\dot{Q}$ (Table 1). The $\dot{V}/\dot{Q}$ value is related both to the mismatched or matched feature and to the size of the defect. For mismatched defects $\dot{V}/\dot{Q}$ remains high (1.67) even for the smallest perfusion defects. For the matched defects $\dot{V}/\dot{Q}$ is still statistically >1, but to a lesser degree. Among these defects, 12 images had been classified qualitatively as indeterminate; even in these cases the $\dot{V}/\dot{Q}$s were high (1.34 ± 0.1 s.e.m., n = 12). Moreover, $\dot{V}/\dot{Q}$ could reach 3.2 in a pixel in spite of the presence of a large radiological opacity (Fig. 4 and 5). The results observed in COPD for either type of defect were significantly different (Table 1): the size of the defect did not modify the value of its $\dot{V}/\dot{Q}$, and matched defects had low $\dot{V}/\dot{Q}$ and thus differed significantly from the matched defects observed in pulmonary embolism ($p < 0.001$). Mismatched defects had lower $\dot{V}/\dot{Q}$s than those in pulmonary embolism ($p < 0.001$).

TABLE 1. $\dot{V}/\dot{Q}$ IN MATCHED (M) AND MISMATCHED (MM) PERFUSION DEFECTS (IN PE AND COPD) ACCORDING TO THEIR SIZE

Percentage of unperfused lung field	PE		COPD	
	M	MM	M	MM
1–15	1.25 ± 0.43* (15)†	1.67 ± 0.56 (19) xxx	0.85 ± 0.20 (25) xxx	1.30 ± 0.36 (7)
16–25	1.28 ± 0.20 (7) xxx	1.80 ± 0.60 (27) xxx	0.88 ± 0.19 (17) xx	1.45 ± 0.34 (7) x
25	1.84 (2)	2.38 ± 1.00 (23) xxx	0.90 ± 0.16 (12)	1.31 ± 0.33 (6) x
Total	1.31 ± 0.39 (24) xxx	1.96 ± 0.80 (69) xxx	0.87 ± 0.19 (54) xxx	1.36 ± 0.33 (20) xxx

* Values are expressed as mean ± standard deviation.

† Number of defects is in parentheses—For each value difference from one is expressed by level of significance (x = $p < 0.05$; xx = $p < 0.01$; xxx = $p < 0.001$); For PE, M means perfusion defects matched by ventilation defect or radiographic opacity.

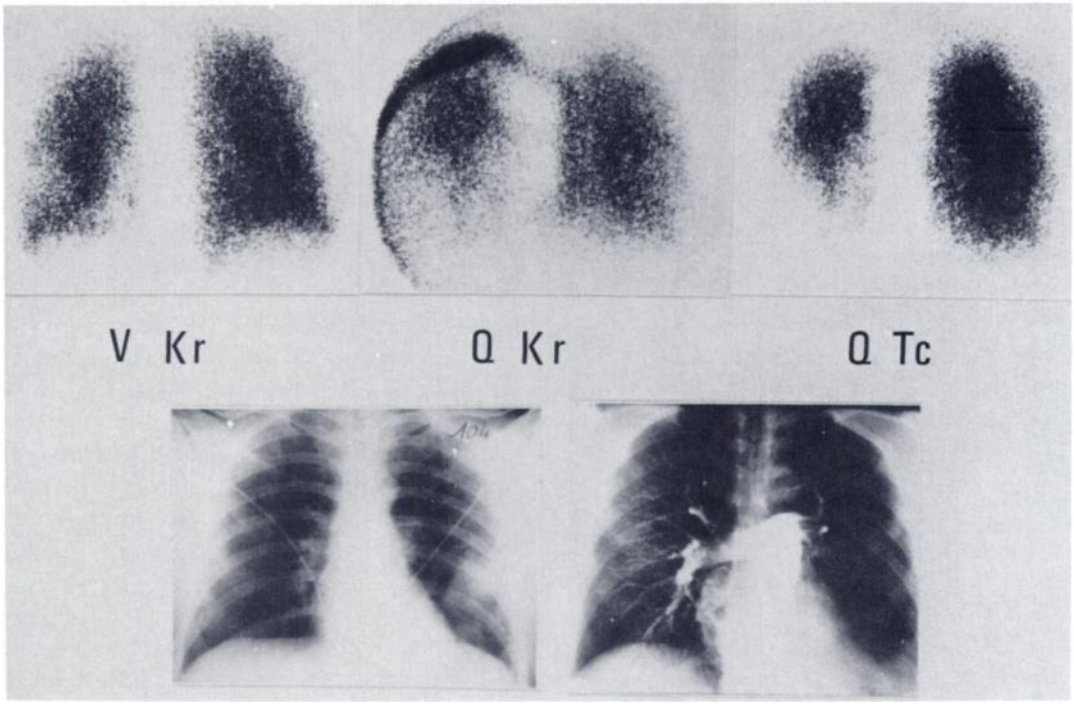

FIG. 4. Laennec infarction (patient supine, posterior view). Ventilation and perfusion images with Kr-81m, and perfusion image with Tc-99m, of patient with radiologic opacity in left lung. Note defect of ventilation and perfusion in left lung corresponding to radiological opacity, and slight defect of perfusion in right lung. Angiographic study demonstrates massive PE in left lung as well as embolism in base of right lung.

From this analysis, the following criterion has been chosen to classify the patients a posteriori. A patient with a $\dot{V}/\dot{Q}$ higher than 1.25 in a perfusion defect was considered as having a PE. If all the defects had a $\dot{V}/\dot{Q}$ below 1.25, this diagnosis was excluded. This value has been chosen because it gives the best χ^2 values for separating the two groups ($\chi^2 = 36.8$, df = 1). Only three patients out of the 44 patients with PE could not be classified using this criterion (Fig. 2b); one had a small mismatched defect, and two had indeterminate scintigrams. Thus, among the 11 patients with indeterminate lung images, nine could be correctly classified by this way. In the COPD group, however, six patients with mismatched defect and $\dot{V}/\dot{Q}$ higher then 1.25 were erroneously classified as having PE (Fig. 2b). Nevertheless on the whole, with this criterion the percentages of patients correctly classified increased drastically compared with those observed using qualitative analysis of the scintigrams (Fig. 2c).

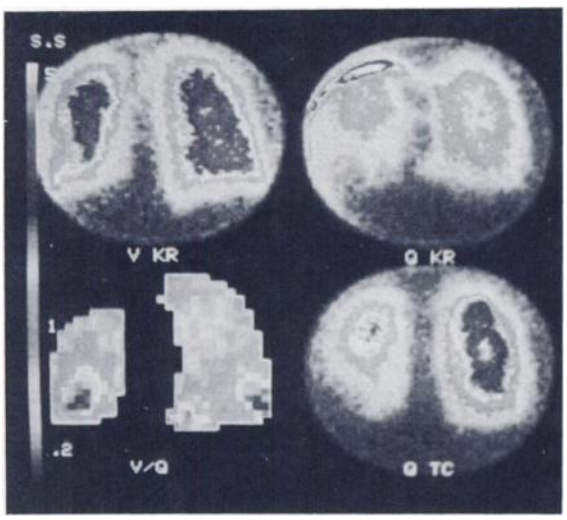

FIG. 5. Functional imaging of Fig. 4 patient shows very high $\dot{V}/\dot{Q}$ in region of radiological opacity (2.4 computed in total area of this perfusion defect), and high $\dot{V}/\dot{Q}$ in region of small defect, suggesting PE.

DISCUSSION

The computation of regional $\dot{V}/\dot{Q}$ with Kr-81m presents some advantages. The low solubility and short half-life of Kr-81m eliminates the effects of recirculation and extrathoracic diffusion on count rate. Radiation exposure is very low. The fact that only tidal breathing is required makes such measurements easy to perform on patients with acute pulmonary embolism (*12*,*15*,*16*). The process of dividing the krypton ventilation image by the krypton perfusion image allows the computation of a correct regional value of the $\dot{V}/\dot{Q}$ ratio, as discussed previously (*12*).

Nevertheless, this method has some limitations. The main practical problem is due to the radioactivity contained in the subclavian veins, which impedes the computation of $\dot{V}/\dot{Q}$ in this small region of the lung. The

process of normalization does not permit knowledge of the absolute $\dot{V}/\dot{Q}$, but only the distribution of the regional $\dot{V}/\dot{Q}$s, since the mean $\dot{V}/\dot{Q}$ is arbitrarily defined as one. Nevertheless, for a given group of patients the distribution of the regional $\dot{V}/\dot{Q}$ is the important factor that monitors correct gas exchange (*19*). The quantitative analysis used in this study is closely related to arterial oxygenation in normal subjects (*12*) and may be of interest for interpretation of hypoxemia in PE, which could be related to the heterogeneous distribution of $\dot{V}/\dot{Q}$ (*20–22*).

The use of quantitative assessment of ventilation-perfusion imaging has been suggested, since the diagnosis of PE by a visual analysis of the images is often difficult (*8,23–27*). The interpretation pitfalls, due to observer performance, are the small and the matched defects of perfusion (*28,29*). The association of matched to mismatched defects in COPD is another diagnostic problem (*10,11,30*). As a matter of fact, many of our patients could not be easily classified on the basis of the qualitative analysis. Although the population we studied is highly selected, being biased toward those cases with indeterminate scintigrams, our results are consistent with those of Goris (*8*) Even using ventilation images with Kr-81m and perfusion images with Tc-99m, he failed with a qualitative analysis in the diagnosis in 42% of the cases.

Conversely, through use of the $\dot{V}/\dot{Q}$ ratio in the region of the perfusion defect, with a threshold of 1.25, patients having or not having PE or COPD were much better classified. High $\dot{V}/\dot{Q}$s are indeed the functional consequence of pulmonary embolism due to the reduction of blood flow associated with normal ventilation, which results in the well-known dead-space effect (*19–21*). The percentage of patients correctly classified increased from 56%, based only on the match or mismatch character of the defect, to 88% with this quantitative criterion. In the indeterminate images the quantitative analysis classified accurately nine of 11 patients demonstrating high $\dot{V}/\dot{Q}$ in the perfusion defect, in spite of the radiological opacity. Although some authors have stressed that a careful assessment of the relative size of perfusion defects and radiographic abnormalities could improve the diagnosis, this approach failed in patients having PE and abnormalities of equal size (*31*). High $\dot{V}/\dot{Q}$s have already been demonstrated by Bass in one patient with a Laennec infarction (*32,33*). These high values expressed the preferential reduction of perfusion with respect to ventilation. They were generally observed at the periphery of the radiologic abnormalities, and the highest values were measured in the cases of embolism of the proximal artery. Conversely, a low or normal $\dot{V}/\dot{Q}$ has been reported by others in pneumonia, which can be the differential diagnosis (*34*). Patients with mismatched defects, or with matched defects without radiological opacity, were easily classified on basis of the $\dot{V}/\dot{Q}$s. A $\dot{V}/\dot{Q}$ higher than 1.25 suggested a PE even in the presence of a matched defect, and a $\dot{V}/\dot{Q}$ lower than 1.25 excluded the diagnosis, as in the majority of the detects caused by COPD.

Nevertheless, in COPD the quantitative analysis showed a large range of $\dot{V}/\dot{Q}$s (Table 1). Low $\dot{V}/\dot{Q}$s (0.87) and matched defects seemed the rule. The predominant decrease of ventilation in COPD, leading to a moderate hypoperfusion by hypoxic vasoconstriction, explains these low values (*35*). High $\dot{V}/\dot{Q}$s (1.36) and mismatches were also observed as in a previous study (*24*). These values were lower than those observed in PE, but there was some overlap between the two groups for the mismatched defects. Thus, 17% of patients with COPD having mismatches and $\dot{V}/\dot{Q}$ greater than 1.25 were erroneously classifed as PE.

Although, these patients were carefully selected on the absence of any clinical suspicion of pulmonary embolism, we cannot exclude the chance that these high $\dot{V}/\dot{Q}$s might correspond to an old, unrecognized embolus. Nevertheless, in COPD high $\dot{V}/\dot{Q}$s have been reported with the inert-gas technique and have been attributed to a reduction in local perfusion compatible with the loss of alveolar tissue (*35*).

With this quantitative analysis, two regional qualitative values are replaced by a single regional physiological value: the $\dot{V}/\dot{Q}$ ratio. This allows one to quantitate objectively the regional inequalities between ventilation and perfusion, and to demonstrate that PE may be characterized by a high $\dot{V}/\dot{Q}$ even if the ventilation is reduced, thus increasing the number of correctly diagnosed patients.

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