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Diagnostic evaluation of planar and tomographic ventilation/perfusion lung images in patients with suspected pulmonary emboli

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Summary

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Planar lung ventilation/perfusion scintigraphy (V/P_{PLANAR}) is a standard method for diagnosis of pulmonary embolism (PE). The goals of this study were to test whether the diagnostic information of ventilation/perfusion tomography (V/P_{SPET}) applied in clinical routine might enhance information compared with V/P_{PLANAR} and to streamline data processing for the demands of clinical routine. This prospective study includes 53 patients suspected for PE referred for lung scintigraphy. After inhalation of $^{99\text{m}}\text{Tc}$ -DTPA planar ventilation imaging was followed by tomography, using a dual-head gamma camera. $^{99\text{m}}\text{Tc}$ -MAA was injected i.v. for perfusion tomography followed by planar imaging. Patients were examined in supine position, unchanged during V/P tomography. Two reviewers evaluated V/P_{PLANAR} and V/P_{SPET} images separately and randomly. Mismatch points were calculated on the basis of extension of perfusion defects with preserved ventilation. Patients were followed up clinically for at least 6 months. With V/P_{SPET} the number of patients with PE was higher and 53% more mismatch points were found. In V/P_{SPET} interobserver variation was less compared with V/P_{PLANAR} . Ancillary findings were observed by both techniques in half of the patients but more precisely interpreted with V/P_{SPET} . V/P_{SPET} shows more and better delineated mismatch defects, improved quantification and less interobserver variation compared with V/P_{PLANAR} . V/P_{SPET} is amenable to implementation for clinical routine and suitable even when there is demand for a high patient throughput.

Introduction

Planar lung scintigraphy is a frequently used method for the diagnosis of pulmonary embolism (PE) (Burkill *et al.*, 1999) due to its non-invasive character, ease of application, low cost, low radiation burden and high sensitivity (Maki *et al.*, 1999). The value of scintigraphy is questioned, primarily because of a high incidence of non-diagnostic findings reported in studies based on PIOPED and modified PIOPED interpretative strategies (Gottschalk *et al.*, 1993). However, recent studies show much more favourable results because of improved techniques for planar lung ventilation/perfusion scintigraphy (V/P_{PLANAR}) (Howarth *et al.*, 1999; Barghouth *et al.*, 2000; Tagil *et al.*, 2000) and alternative interpretation strategies (Bajc *et al.*, 2002a). Accordingly, a technique allowing V/P_{PLANAR} within 1 h after referral showed a higher sensitivity and similar low rates of non-diagnostic findings as compared with spiral computer tomography (CT) (Bajc *et al.*, 2002a). Studies by Palla *et al.* (1988); Eustace *et al.* (1993); Corbus *et al.* (1997);

Magnussen *et al.* (1999); Wenger *et al.* (2000); Lemb & Pohlabein (2001); showed that ventilation/perfusion tomography (V/P_{SPET}) further improves specificity by reducing the proportion of uncertain results. Palmer *et al.* (2001) recently showed that V/P_{SPET} is clinically feasible with short examination time, low cost and low radiation dose. Their preliminary data indicate that tomography is superior to V/P_{PLANAR} . The method was validated on pigs using lung emboli labelled with ^{201}Tl as a golden standard (Bajc *et al.*, 2002b), thus circumventing imperfections of other modalities, such as angiography. The latter study showed that V/P_{SPET} was significantly more sensitive than V/P_{PLANAR} with respect to detection of small emboli.

The objective of PE diagnostics is not only to confirm or deny the presence of PE, but also to provide quantitative data on degree of PE so as to meet the demands by rapidly evolving therapeutic modalities. Massive embolization should be treated with thrombolysis, while modest embolization requires inpatient treatment. At a low degree of PE, outpatient treatment may be offered. It appears even possible that we in the future may

abstain from treatment of single sub-segmental emboli. Accordingly, diagnostic methods should allow quantitation. Also evaluation and development of new therapeutic strategies require recognition of all embolized areas at the time of diagnosis and at follow up.

The aim of the present study was to compare V/P_{PLANAR} and V/P_{SPET} with respect to the diagnosis of PE, quantification of emboli and ancillary findings, against the clinical diagnosis at discharge from hospital. Before applying V/P_{SPET} in routine, we wanted to validate its usefulness. Based on initial clinical experience of the V/P_{SPET} technique, we wanted to improve the normalization of images, their mode of presentation, and to automate data processing.

Patients and methods

This prospective study embraces 51 patients with symptoms suggestive for PE and additional two patients on treatment for PE. All were examined with V/P_{PLANAR} and V/P_{SPET} . Referred patients were included whenever the dual head gamma camera was available. Accordingly, patient selection was not specific for the purpose of the study. The study included 19 inpatients (one with trauma, four from surgical and 14 from medical specialties) and 34 outpatients. The patients gave informed consent to be examined both by V/P_{PLANAR} and V/P_{SPET} . Approval was obtained from the ethical committee.

When patients left hospital, the responsible clinicians established the final diagnosis, based on symptoms, blood specimens, chest X-ray (and some with spiral CT), V/P scintigraphy, changes due to therapy, according to a local consensus program on venous thromboembolism. Patients with PE were followed during 6-month periods by one of us, up to 24 months. They were controlled at an outpatient clinic with physical examination, blood specimens and scintigraphy, if considered necessary. Patients without PE were not given anticoagulant therapy and were followed for at least 6 months, by their medical records.

According to the protocol, a new V/P scintigraphy should be performed in case of recurrent symptoms, which did not occur.

For the ventilation study patients inhaled aerosolized $^{99\text{m}}\text{Tc}$ -DTPA (TechneScan DTPA; Mallinckrodt Medical, Petten, The Netherlands) in supine position, by spontaneous breathing from a pressurized air driven nebulizer. Inhalation stopped when 30 MBq had been deposited, as measured by a shielded Geiger-Müller tube (Mini-Instruments Ltd, Burnkam-on-Crouch, Essex, UK). Planar images in anterior, posterior and posterior oblique projections were taken in the supine position and followed by ventilation tomography. Immediately thereafter and without patient movement, 100 MBq $^{99\text{m}}\text{Tc}$ -MAA (TechneScan LyoMAA; Mallinckrodt Medical) was given by i.v. injection for perfusion study. Then, tomography was followed by planar imaging. A large field-of-view dual-head gamma camera with low energy all-purpose collimators was used (SMV DST-XLi, Buc Cedex, France). For SPET a 64×64 matrix was used with 128 projections over 360° . Sixty-four steps of 10 and 5 s were used for the ventilation and the perfusion studies, respectively.

$^{99\text{m}}\text{Tc}$ -DTPA clearance was calculated from the initial and final SPET projections, and was used for correction of the ventilation projection set prior to reconstruction. Iterative reconstruction was performed using OSEM with eight subsets and two iterations. The ventilation background was subtracted from the perfusion tomograms, and a normalized V/P image set calculated. As manual processing would be prohibitive in clinical routine the procedure, from raw data to a complete set of images for final review was made fully automatic. Tagil et al. (2000) and Palmer et al. (2001) described details of the planar and tomographic techniques. In short, the main consideration in the creation of quotient images is to define a suitable scaling factor between the reconstructed and appropriately smoothed ventilation and perfusion data sets. The scaling was designed with the aim to produce quotient images that would be displayed in a fixed grey-scale value in lung regions deemed to be normal from a simple automatic criterion. In the original work (Palmer et al., 2001) the normal region was selected by thresholding from the maximum count after automatic hot-spot removal in the reconstructed volumes. In the present work, a more robust normalization thresholding was applied. Thus, the reconstructed volume was first truncated at a lower threshold of 10% of its maximum value. An upper threshold was then obtained by iteration to the count level at which 90% of the lung volume was included. The voxels within the count range 50–100% of the upper threshold defined a preliminary 'normal' subvolume. This process was applied to ventilation and perfusion independently. The volume in which both ventilation and perfusion were 'normal' comprised the final normalization volume. When, in exceptional cases, no such common volume was recognized, each region was used separately. The average voxel count in the normalization volume was scaled to be equal for ventilation and perfusion. The final display was set to always span a quotient range of 0–4000, with equality being represented by 1000.

Ventilation, perfusion and V/P quotient tomograms were simultaneously presented in 13.6 mm thick coronal, sagittal and transverse slices, and as rotating volume rendered 'Maximum Intensity Projection' images. The computer display allowed adjustment of thresholds and colours.

For clinical purpose physicians on duty read the planar images. These reports were used by clinicians for treatment-decisions and also, in the study, for comparison with results of the two expert reviewers. For the purpose of the study these two reviewers interpreted SPET images. No results from SPET were given to clinicians.

The clinical readers and the reviewers had access to clinical data. Planar and tomographic images were related for interpretation to anatomical charts of lung segments. The two reviewers read separately all planar and tomographic images. The two modalities were interpreted with at least 3 weeks interval. In each session the identification of patients was hidden and the order was randomized.

The time needed for V/P examination is about 30 min including acquisition time of 16 min. Reconstruction, automatic

processing including all slices and 3D rendered cine images take 9 min. Interpretation and reporting takes 5–10 min.

Interpretation criteria

Ventilation and perfusion defects were quantified with respect to segmental/subsegmental character of defects, 'RoVent' points (reduction of ventilation) and 'RoPer' points (reduction of perfusion) (Palmer et al., 2001; Olsson et al., 2002). A segmental reduction or a subsegmental total deficiency was attributed 1 point; a segmental total deficiency was attributed 2 points. For each lung, we calculated the number of points reflecting a P defect with preserved V, to a total mismatch score.

Within a holistic principle of image reading the following guidelines were applied.

- No embolism, PE–: absence of unmatched perfusion defects.
- Embolism, PE+: >1 segmental or subsegmental defect of mismatch, i.e. at least 2 points.
- Other pathology than PE: matched defects with typical patterns for other lung diseases.
- Non-diagnostic, ND: Grave V/P defects rendering the judgement of mismatch impossible.

We adhere to a holistic principle of clinical image reading, in line with concepts recently described by Freeman et al. (2001). Accordingly, ancillary scintigraphic findings and clinical data were considered in the interpretation. The readers considered the number of mismatched areas, their distinctness, peripheral or central position, as well as segmental or non-segmental location. Signs of obstructive or parenchymal lung disease, tumour and heart failure were included in clinical and reviewed reports. Increased clearance of DTPA from the lungs was considered to indicate alveolar inflammation.

Statistics: linear regression was used for comparison between readers. Wilcoxon Signed Rank Test was used for comparisons between V/P_{SPET} and V/P_{PLANAR}, using Sigma Stat, Statistical Software, version 2, SPSS Inc.

Results

According to the final clinical diagnosis, 11 patients were treated for recent PE. Another two patients were on continuous treatment since a previous episode of PE (Table 1). In the 11 cases of recent PE the diagnosis reflected a positive reading of

the routine V/P_{PLANAR}. The reviewers judged the V/P_{PLANAR} positive for PE in the same 11 and 10 cases, respectively. In the 11th case, one reviewer expressed strong suspicion for PE and recommended CT to confirm the suspicion. In two patients with 'old PE' the routine and the reviewers' report on V/P_{PLANAR} were negative. On V/P_{SPET} both reviewers reported PE in all 11 new cases with a clinical diagnosis of PE and in two patients already on therapy for PE (Fig. 1). In the remaining 40 patients all routine and review reports of V/P_{PLANAR} were negative. In three of these 40 patients V/P_{SPET} showed PE according to one reviewer. The other reviewer reported two of these, while the third was considered ND (Table 1).

The inter-observer agreement between reviewer A and B, with respect to the number of mismatch points recognized for each patient, MMP_A and MMP_B, respectively was illustrated with regression analysis:

For V/P_{PLANAR}:

$$\text{MMP}_B = 0.79(\pm 0.04); \quad \text{MMP}_A - 0.2(R^2 = 0.88)$$

For V/P_{SPET}:

$$\text{MMP}_B = 0.96(\pm 0.03); \quad \text{MMP}_A - 0.2(R^2 = 0.95)$$

Numbers in brackets indicate standard error. The intercept 0.2 was not significantly different from zero.

On average mismatch points in V/P_{SPET} were for both reviewers 53% higher than in V/P_{PLANAR}. This difference between the methods was significant (reviewer A, $P = 0.003$ and B, $P = 0.001$).

No patient developed signs or symptoms of new PE during the follow up period of 6 months.

Ancillary findings

The reviewers together reanalysed V/P_{PLANAR} and V/P_{SPET} images with respect to ancillary findings indicating other diseases than PE.

Ancillary findings were concordant between V/P_{PLANAR} and V/P_{SPET} in 25 patients.

V/P changes were of obstructive type, i.e. central deposition of aerosols and matched ventilation perfusion changes in 12 (Fig. 2). Lobar V/P defects were observed in 4, and minor

Table 1 Clinical diagnosis and scintigraphic findings.

Clinical diagnosis of PE	Routine reading of V/P _{PLANAR}	Reviewers' reading of V/P _{PLANAR}		Reviewers' reading of V/P _{SPET}	
		Reviewer A	Reviewer B	Reviewer A	Reviewer B
13 PE+					
11 New	11 PE+	11 PE+	10 PE+ 1 ND	11 PE+	11 PE+
2 Old	1 PE– 1 ND	2 PE–	2 PE–	2 PE+	2 PE+
40 PE–	40 PE–	40 PE–	40 PE–	37 PE– 3 PE+	37 PE– 2 PE+ 1 ND

PE+, patient with and PE–, patient without pulmonary embolism; ND, non-diagnostic.

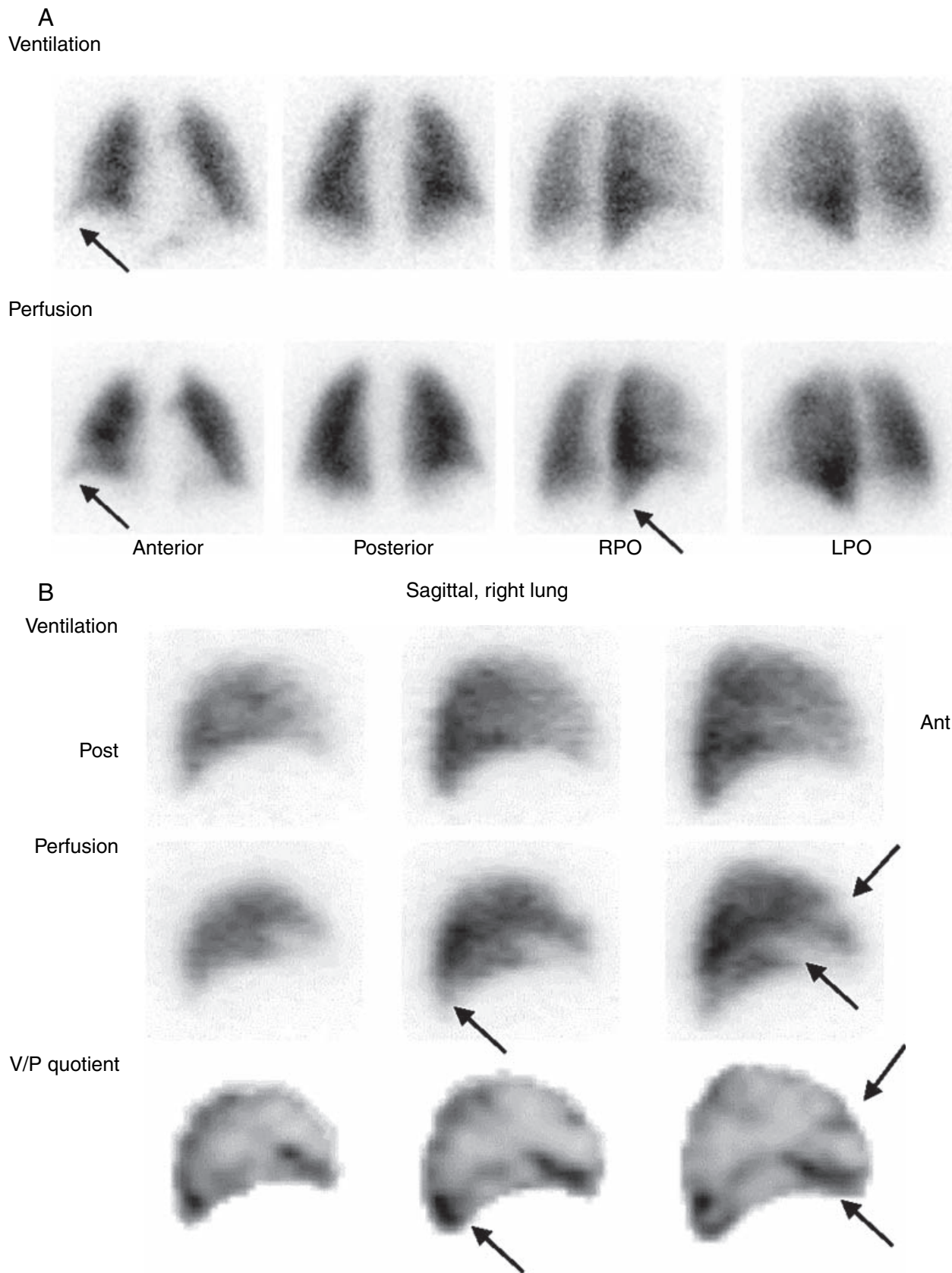


Figure 1 Patient with known PE, 6 month after therapy: (A) planar images: reduction and uneven distribution of V and P in lower lobe of right lung (arrows); (B) tomography: sagittal slices from anterior to posterior – a perfusion defect in lower lobe is clearly visible, enhanced by V/P quotient (arrows).

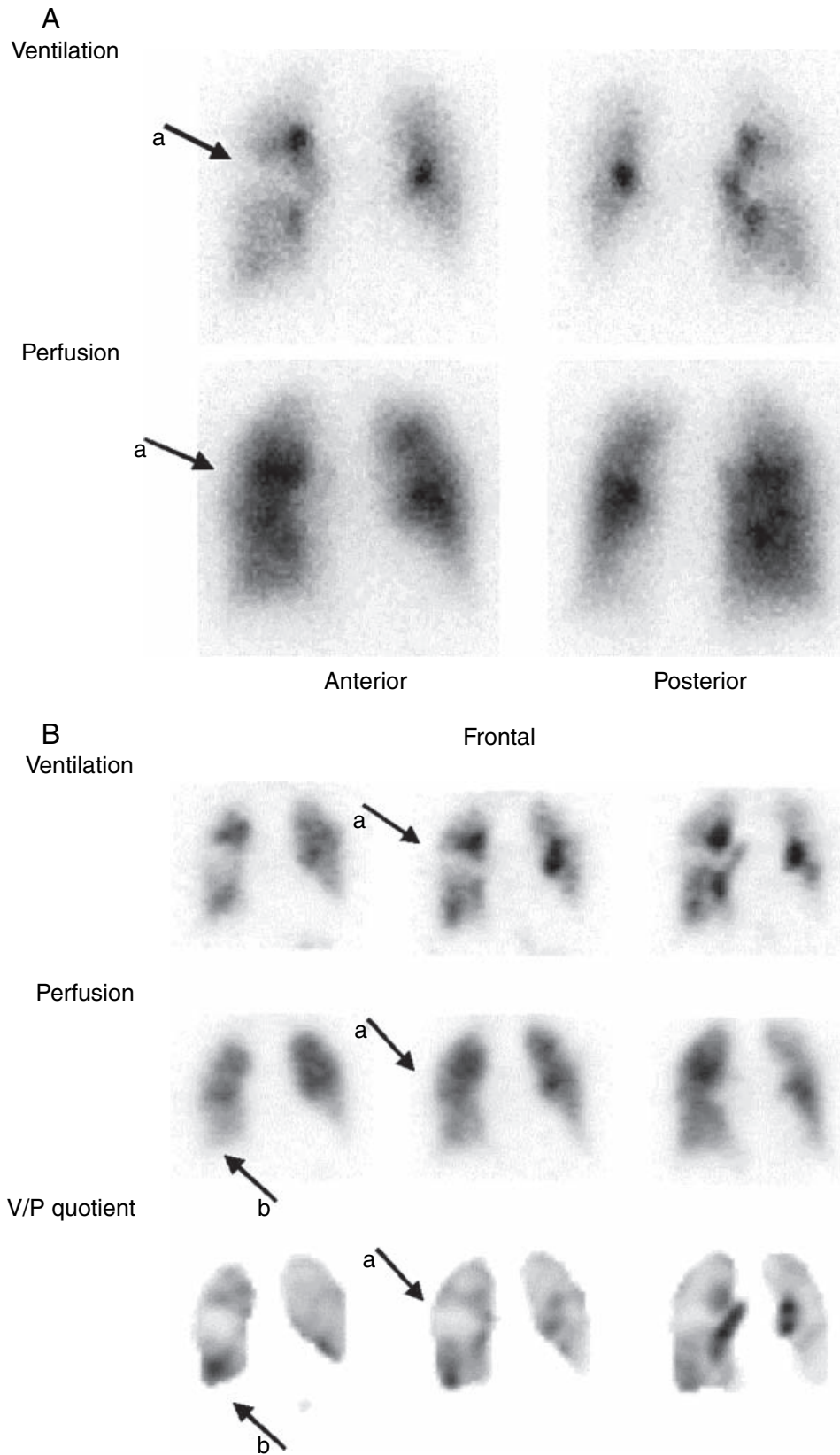


Figure 2 Patient with known obstructive lung disease: (A) planar images: V/P are uneven and reduced in some segments (a) and central deposition of aerosol; (B) tomography: coronal slices – reduction of V and P (a) and also clear mismatch on V/P quotient typical for subsegmental PE (b).

defects of the same type in 5 (Fig. 3). Two others had pattern of heart failure, i.e. diminished ventilation and perfusion in dorsal and basal part of the lung. Alveolitis was diagnosed by high clearance of DTPA in two patients.

Ancillary findings were discordant in four patients. In one patient obstruction was only recognized on V/P_{SPET} . Two patients with enlarged hearts and one patient with uptake in oesophagus clearly observed on V/P_{SPET} showed false V/P changes on V/P_{PLANAR} .

Discussion

In this study, we compare planar and tomographic imaging in a clinical material. In a previous experimental study we showed that both sensitivity and specificity was enhanced by tomography (Bajc et al., 2002b). In that study artificial emboli were marked with ^{201}Tl providing a 'true gold standard'. A limitation of clinical studies is that no similar standard is available. Traditionally, pulmonary angiography has been regarded as the gold standard for diagnostics of PE. However, according to a recent article on state of the art 'the status of pulmonary angiography as the standard of reference for diagnosis of PE is in doubt' (Schoepf & Costello, 2004). A similar opinion has since several years been advocated by the British Thoracic Society, Standards of Care Committee, 1997. These considerations were based upon several studies showing limited sensitivity and high inter-observer and intra-observer variability. Ethical concerns would also be raised against an invasive technique with some radiation hazards used for purely scientific reasons. In the absence of a standard reference for the diagnosis PE the outcome for patients should be regarded as appropriate endpoint (Fennerty, 1998).

The study reflects a transitory phase in our department during improvement and implementation of the tomographic method, previously described (Palmer et al., 2001). A minimum of technician intervention is now needed for reconstruction and V/P quotient calculations. The interpreter is helped by a new presentation form suitable for quality control and reviewing. Three sets of tomographic data (V , P and V/P quotient), viewed in coronal, sagittal and transverse plane as well as in simultaneous 3D volume images are directly available for interpretation.

Examination in supine position offered a stable and comfortable procedure even for critically ill patients. Moreover, it was convenient for the staff. Immobilization needed during the short acquisition time was well tolerated by all patients. There were only four patients that moved during examinations thus causing artefacts on V/P quotient images, which are easy to recognize.

The administered activity used here, 30 MBq for ventilation and 100 MBq for perfusion, were found to be adequate in most cases. Exceptionally we use up to 50 MBq for ventilation and up to 150 MBq for perfusion. The Procedure Guideline by the Society of Nuclear Medicine suggests, implicitly for planar technique, 20–40 MBq for ventilation, and a total count rate at perfusion of at least four times that at ventilation (ACCP, 1998).

Interpretation of lung scintigraphy according to initial and revised PIOPED criteria has caused confusion in nuclear and clinical medicine (Gray, 2002). The criteria for PE are based on the judgement of size of perfusion defects and ventilation, if studied, has not been standardized and often been performed with ^{133}Xe which we find inadequate. This has caused a high proportion of intermediate, non-diagnostic reports (Gottschalk et al., 1993). Difficulties are also caused by the reports expressed as probabilities and to use these in a clinical context. Recognition of patterns typical for PE represents a step forward as evidenced by the PISA-PED studies, even if ventilation was not studied (Miniati et al., 1996). Giordano & Angiolillo (2001), stressed that ventilation, if used should be performed using aerosols or Technegas. Finally, a holistic approach should be adopted for interpretation of scintigraphic images by using clinical information, segmental charts, and recognition of patterns typical for PE and for other diseases (Freeman et al., 2001; Palmer et al., 2001; Bajc et al., 2002a). Such a strategy has dramatically reduced the number of non-diagnostic reports and in general increased the diagnostic value of V/P scintigraphy (Bajc et al., 2002a). V/P_{SPET} used in recent studies showed particularly low numbers of non-diagnostic findings and high sensitivity and specificity for PE (Corbus et al., 1997; Lemb & Pohlbeln, 2001). In this respect our results are similar to these observations.

In the present study the comparison between V/P_{PLANAR} and V/P_{SPET} was based on the same holistic interpretation principles. The methods differed with respect to imaging technique. V/P_{PLANAR} showed diagnostic results superior to studies based on probabilistic criteria as by PIOPED. V/P_{SPET} further enhanced diagnostic accuracy both by visualizing remnants of PE in two patients under treatment and also by revealing findings typical for PE in another three patients, who were not treated (clinicians were not informed on the results of V/P_{SPET}). However, these results should be cautiously considered as the material is small and a real gold standard is not available.

V/P defects were quantified to describe the extent of PE in terms of new parameters RoVent and RoPer. Using this strategy V/P_{SPET} showed 53% more mismatch points than V/P_{PLANAR} . Furthermore, V/P_{SPET} with 3D visualization eliminates the influence of superimposed structures, thus clarifying segmental and subsegmental character of PE defects. Also the stripe sign indicating defects of other nature than PE is more obvious (Fig. 3). These qualities of V/P_{SPET} are particularly valuable when PE is combined with other diseases and explain the higher sensitivity observed by others and by us. An increased number of planar projections would probably marginally increased the sensitivity of planar technique at the cost of longer time for the whole procedure. Anyway with our planar technique the sensitivity is higher than that of CT (Bajc et al., 2002a). Another advantage of our V/P_{SPET} is the V/P quotient that facilitates both recognition and quantification of PE (Figs 1–3). Quantification is becoming important for choice of therapy, i.e. thrombolysis or conventional anticoagulants, and more importantly for identifying patients suitable for outpatient treatment (Kovacs

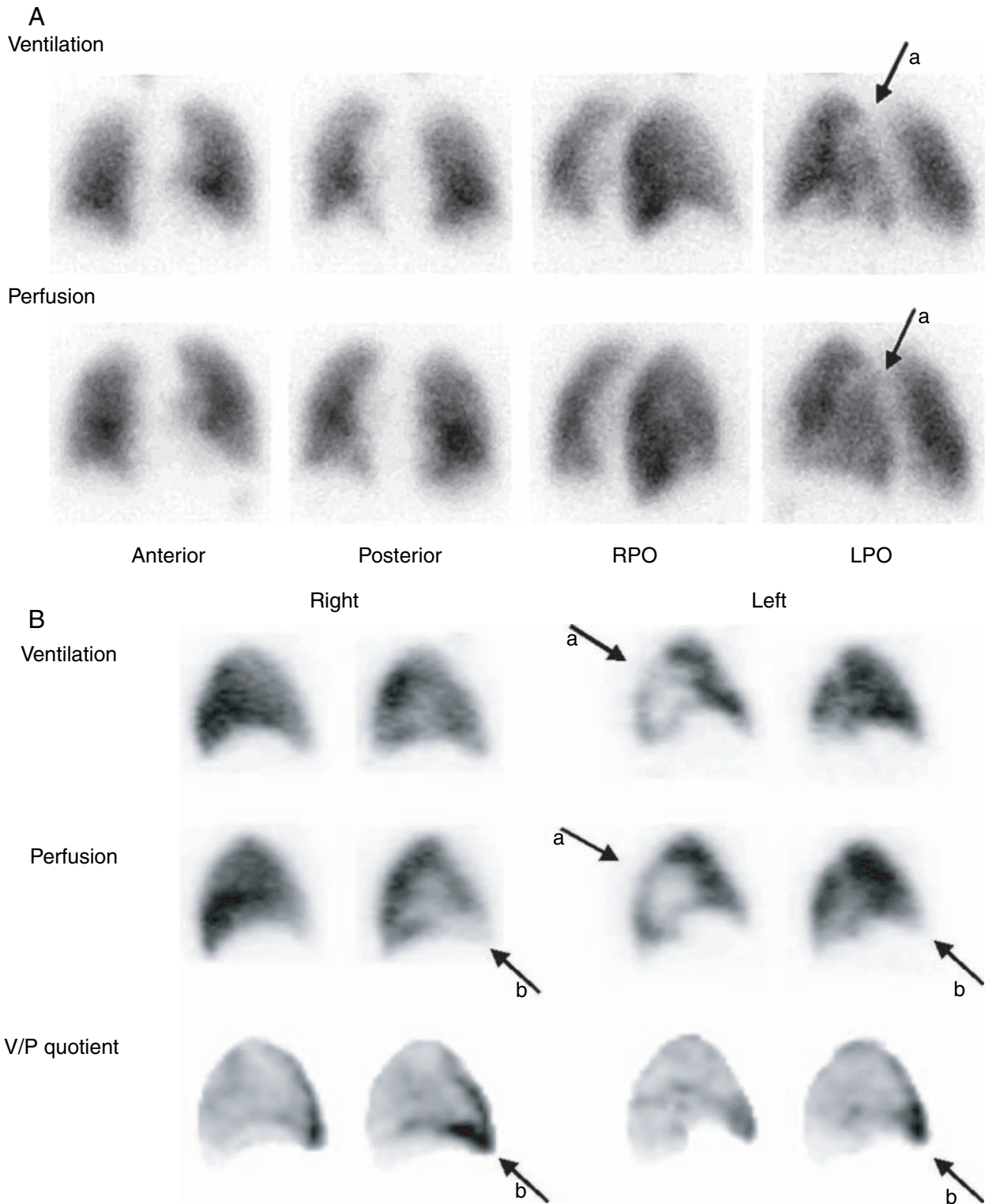


Figure 3 Patient with known pneumonia and PE: (A) planar images: reduced V and P posterior in left lung (a); (B) tomography: sagittal slices right to left lung – V and P defects posterior in the left lung are clearly delineated and stripe sign – typical for pneumonia (a). Perfusion defect in lingula and middle lobe are visible but mismatches are obvious from the V/P quotient (b).

et al., 2000; Olsson et al., 2002; Beer et al., 2003). The significantly lower interobserver variation and higher sensitivity observed by V/P_{SPET} compared with V/P_{PLANAR} is due to its

more clear patterns representing PE or other diseases. These qualities of V/P_{SPET} are important for a proper diagnosis, for the choice of therapy and for follow up of patients. A problem

which cannot be addressed on the bases of this study is the clinical significance and the indication to treat isolated subsegmental emboli.

The holistic attitude including ancillary findings should be used to recognize various differential diagnoses (Freeman et al., 2001). Both V/P_{PLANAR} and V/P_{SPET} imaging showed such findings in about half of the patients. The importance of ventilation studies is not limited to identification of mismatch but also allows the identification of patterns typical for alternative diagnoses such as obstructive disease, parenchymal diseases and tumours, heart failure and in our study also alveolitis. Experience from more than 1200 V/P_{SPET} examinations until today, combined with daily clinical feedback has for us confirmed the superiority of V/P_{SPET}.

Conclusion

V/P_{SPET} performed with recommended, low activity allows excellent imaging also of V/P quotient. V/P_{SPET} showed higher sensitivity with respect to demonstration of more emboli revealing more perfusion defects and had less interobserver variation than V/P_{PLANAR}. V/P_{SPET} enables better quantification that has impact on choice of therapy and improves follow up. Ancillary findings were more clearly delineated and correctly explained.

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