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Image of patients suspected of having pilmonary thromboembolic disease the value of chest XRay combined with perfusion scan

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ORIGINAL ARTICLES

IMAGING OF PATIENTS SUSPECTED OF HAVING PULMONARY THROMBO-EMBOLIC DISEASE; THE VALUE OF CHEST X-RAY COMBINED WITH PERFUSION SCAN

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Abstract

Objective: To determine the value of a recent chest x-ray (done within 24 hours of the perfusion scan) combined with perfusion in diagnosing acute pulmonary thromboembolism in clinical settings.

Methodology: Retrospective analysis of 155 consecutive patients clinically suspected with pulmonary thromboembolism between January 2017 and January 2019, who underwent a lung scintigraphy.

Results: Most of the study participants (75.5%) were black Africans. The overall population studied had a mean age of 50.09 years (SD 16.78). A recent chest x-ray was found in 40.1% of the projected sample size of 386 patients. The sensitivity and specificity of the PISAPED 1 reader were 96% and 97%, respectively, with a NPV and PPV of 99% and 89%. The sensitivity and specificity of the PISAPED 2 reader were both 96%, with a NPV and PPV of 86%and 99%, respectively. The PIOPED II and the PISAPED 1 had an agreement of 88.39% (Kappa value of 0.7348) while the PIOPED II and the PISAPED 2 had an agreement of 88.39% (Kappa value of 0.7444).

Conclusion: Chest x-ray in conjunction with perfusion scintigraphy is accurate and can be used where ventilation/perfusion scintigraphy cannot be done in the diagnosis of pulmonary embolism.

Key words: *Pulmonary thromboembolism, chest x-ray, ventilation perfusion scintigraphy, PISAPED criteria.*

Introduction

Pulmonary thromboembolism (PE) is the partial or complete occlusion of the lungs' central or peripheral artery by an embolus[1] . Acute PE is the 3rd most common cause of death after cardiovascular diseases and malignancies and the 3rd most common cause of cardiovascular death after myocardial infarction and stroke[1,2].

Globally, over 650,000 cases of PE are diagnosed annually, with more than 100,000 deaths yearly[3]. The mortality rate is approximately 30% but could be reduced to 3-10% if anticoagulation is commenced timeously or inferior vena cava filters, when indicated, are placed in time. In South Africa, however, there is a lack of data on the disease prevalence. Both PE and anticoagulation therapy for PE may be detrimental to the health of the patient. There is, therefore, a need for prompt and accurate diagnosis.

Even with recent advances in technologies aimed at enhancing medical diagnostics, diagnosing individuals suspected of having PE remains a challenge in medicine. To arrive at a diagnosis, a thorough clinical examination and risk assessment are required[4–6]. The imaging modalities employed in the workup of patients with suspected with PE include chest radiograph, lung ventilation/perfusion scintigraphy (V/Q), computed tomography pulmonary angiography (CTPA) and magnetic resonance angiography (MRA) [7,8].

A chest x-ray (X) is required as part of the initial evaluation, and lung scintigraphy is frequently performed after that. The V/Q scintigraphy was first introduced in 1964 to assess pulmonary blood flow[9]. Over the past five decades, it has become an essential modality for assessing PE[9].V/Q scintigraphy is a diagnostic nuclear medicine imaging procedure that compares the pattern of distribution in the lungs of intravenously injected radiopharmaceuticals labelled with metastable technetium 99 with inhalation of inert gases or aerosols. A gamma camera is then employed to acquire two-dimensional (2D) or three-dimensional image (3-D) images (10). A conventional V/Q study is performed with planar imaging (2-D).

V/Q scintigraphy, is the imaging of choice in the setting of suspected PE with a normal chest radiograph. Also, it has an advantage over other PE assessment techniques like CTPA in that it does not require the use of contrast agents. Patients having a history of iodinated contrast allergy and renal impairment will benefit from this property[9]. Furthermore, obese patients who cannot fit in the CT gantry or exceed the table's weight limit will also benefit from V/Q scintigraphy[4]. Finally, in pregnancy, where reduced radiation exposure to the

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breast and developing fetus is desired, V/Q scintigraphy is also the imaging modality of choice.

The lung scintigraphy makes use of ionizing radiation, just as the chest x-ray. The lung scintigraphy is made up of two aspects, a ventilation study (V) and a perfusion study (Q) component. In nearly a third of all patients suspected of having a PE, normal perfusion scintigraphy usually rules out PE[4,11]. However, when there are perfusion abnormalities, ventilation scintigraphy is required to determine whether these defects seen on the perfusion study are matched or unmatched on the ventilation scintigraphy. If these defects are unmatched, the diagnosis of PE is confirmed. However, if these defects are matched, this disproves the diagnosis of PE[5,7].

Although ventilation scintigraphy is an essential tool in this diagnostic strategy, there have been concerns about increased radiation exposure to patients, especially the developing foetus in pregnant women and the lactating breasts[8,12]. The study's high cost, non-availability of the tracer, time commitment, and low compliance in patients with respiratory distress are significant limitations in performing ventilation/perfusion (V/Q) studies[7,12]. Several guidelines propose a chest x-ray prior to lung scintigraphy as part of the diagnostic process [7,8,13]. We investigated if a chest x-ray could substitute the ventilation scintigraphy in defining these segmental perfusion defects because the chest x-ray has a similar role in increasing the specificity.

In Nuclear Medicine, there are several diagnostic criteria used in the assessment of PE. Available criteria include the Prospective investigation of pulmonary embolism diagnosis II (PIOPED II), Modified PIOPED II and the prospective investigative study of acute pulmonary embolism diagnosis (PISAPED) and the ventilation/perfusion single-photon emission computer tomography (V/Q SPECT) criteria. The modified PIOPED II and the PISAPED criteria are the two most widely used protocols in diagnosing acute PE. In the modified PIOPED II, a perfusion scan is read against a ventilation scan to make a diagnosis. Perfusion lung scanning was enhanced with ventilation imaging to increase accuracy, hoping to distinguish pulmonary vascular occlusion due to embolism from perfusion anomalies caused by respiratory disorders. In diagnosing PE using the PISAPED criteria, the ventilation study is omitted. The perfusion scan is read against a recent chest x-ray for interpretation[14]. The diagnosis made using these criteria could be a positive, negative and indeterminate study.

In a couple of studies to compare the modified PIOPED II and the PISAPED parameters, statistics showed that the sensitivity and specificity were not significantly different (84.9% and 92.7%, respectively, for modified PIOPED II and 80.5% and 96.6%, respectively, for PISAPED) [15,16]. Furthermore, Miniati et al. (1996), in their study, suggested that using the PISAPED criteria reduces the percentage of patients with indeterminate findings that will require an additional test to arrive at a diagnosis of positive or negative study for PE[16]. Pre-test probability tools such as the Wells score and the Geneva score when used in conjunction with the PISAPED criteria further increases its diagnostic accuracy. The Wells score objectively assign points based on patient history, symptoms, and physical findings[17–19].

In South Africa, patients referred for assessment for acute PE usually have undergone a radiological chest x-ray examination to assist in identifying the cause of the patients' chest symptoms. This study compares the ventilation and perfusion scan findings using the modified PIOPED II criteria and the perfusion chest x-ray combination using the PISAPED criteria. If the results are similar, then, if already performed, the chest x-ray can replace the ventilation scintigraphy in selected investigations. The direct consequences of this study will be reduced radiation dose to the patient, the developing fetus and breasts of pregnant women and lactating mothers, respectively. It may also assist in cost reduction and save time, thus assisting in service delivery. Finally, although not proven, the ventilation component of the study might be associated with an increased risk of spread of COVID-19 and many centers have eliminated this technique in patients with COVID-19 infection[36].

Materials and Methods

Study design and participants

This retrospective cross-sectional analysis focused on secondary data obtained at the Charlotte Maxeke Academic Hospital's Nuclear Medicine Department, Johannesburg, South Africa from January 2017 to January 2019.-Patients above 18 years who had a chest x-ray done within 24 hours prior to lung scintigraphy were recruited. Patients with uninterpretable chest x-ray were excluded.

One hundred and fifty-five (155) consecutive patients of the 389 participants were examined to reflect the appropriate referral pattern of patients who required a chest x-ray in less than 24 hours. Data extracted from patients' laboratory results such as D-dimer and kidney function were retrieved from the National Health Laboratory System (NHLS). Patients' chest radiograph and images from ventilation/perfusion and their reports were retrieved from the hospital database. Data analysis was limited to patients with chest x-ray done within 24 hours before lung scintigraphy. All patients' clinical characteristics and risk factors for pulmonary embolism were recorded from the request forms/report. This study utilised two experienced nuclear medicine physicians who were unaware of the results of the V/Q scan. They read only the perfusion images against the chest x-ray. These nuclear medicine physicians were coded as P1SAPED 1 and PISAPED 2, respectively. An experienced radiologist also reviewed the same chest x-rays to determine the accuracy of the two nuclear medicine physicians' interpretations and to measure

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interobserver agreement. Any abnormalities on the chest x-ray, such as pleural effusion, atelectasis, tumor or consolidation was labelled as abnormal. The perfusion scan was subsequently compared with the chest x-ray, and the findings were classified based on interpretation using the PISAPED criteria. The readers interpreted the X/Q scans according to the PISAPED criteria. A descriptive statistic reporting on frequencies and proportions was computed to describe study participants' demographic characteristics. Cohen Kappa statistics was utilized to assess percentage agreement between PIOPED II (the gold standard) and PISAPED 1 and PISAPED 2 readers.

Ethical Considerations

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC), with ethics clearance number MP191138.

Results

As shown in table 1, about half of the participants (78/155) were hospitalized patients. Also, 95% (147/155) of the patients did not have their Wells score calculated before being referred to the Nuclear Medicine department. Only 6 (constituting 4%) of the referred patients had a high Wells score (Wells score >2), while only 2 (1%) had a low Wells score. Also, about 60% (92/155) of the patients had a D-dimer done prior to lung scintigraphy. However, out of the 92 patients referred for a D-dimer examination, 41% (75/92) had high D-dimer levels (>0.5mcg/ml), while just 12% (17/92) had normal D-dimer levels (<0.5mcg/ml).

Table 1 Demographics

Indicators	All respondents N=155	Frequencies	Percentage (%)
Race of participants			
Black Africans		117	75.5
Mixed-race		9	5.8
Indian		2	1.3
Caucasians		27	17.4
Gender of participants			
Male		51	33
Female		104	67
Age group (years)		**Mean= 50.09**	**Std= 16.78**
18-29		24	15
30-39		27	17
40-49		16	10
50-59		35	23
60-69		34	22
Above 70 years		19	13

Assessing sensitivity and specificity of the diagnosis

As illustrated in table 2, PISAPED 1 successfully identified 97% of the 132 outcomes utilized in this analysis. PISAPED 1 found 24 of the 25 positive results, giving it a sensitivity of 96%. Similarly, PISAPED 1 correctly recognized 104 of the 107 results categorized as negative by modified PIOPED II, yielding a 97% specificity. PISAPED 1 identified 24 of the 27 records as positive, with a PPV of 89%. The NPV was 100%. The sensitivity and specificity results for PIOPED II and PISAPED 2 may be seen in table 2. PISAPED 2 correctly identified 126 out of 131 samples, resulting in a 96% accuracy rate. Furthermore, the sensitivity rate was 96% for 24 of the 25 positives. In comparison, modified PIOPED II recognized 102 of the 106 instances as negative, while PISAPED 2 identified 102 of the 106 cases as negative, yielding a 96% specificity rate. PIOPED II and PISAPED 2 also projected PPV and NPV of 86% and 99%, respectively. This is the percentage of PISAPED 2 positive records that were also true positive by modified PIOPED II (24/28).

Table 2: Sensitivity, specificity positive and negative predictive values of modified PIOPED II versus PISAPED 1 and PISAPED 2 readers.

Method	Diagnostic Reading	Sensitivity	Specificity	PPV	NPV
Modified PIOPED II vs PISAPED 1	97% (128/132)	96% (24/25)	97% (104/107)	89% (24/27)	99% (104/105)
Modified PIOPED II vs PISAPED 2	96% (126/131)	96% (24/25)	96% (102/106)	86% (24/28)	99% (102/103)

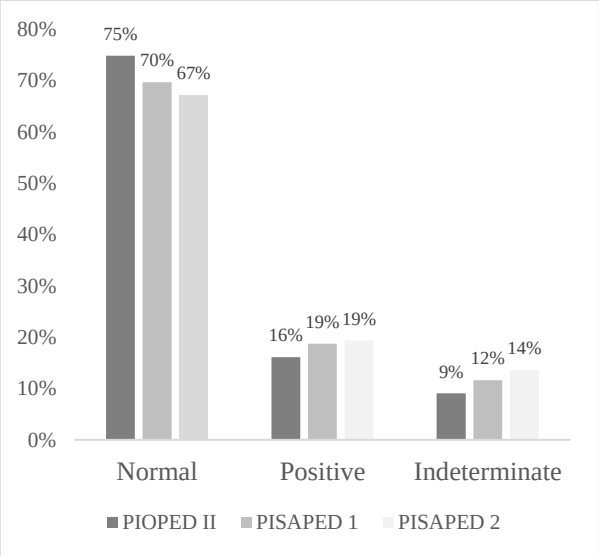


Figure 1: Percentage score for diagnostic accuracy comparing PIOPED II with PISAPED 1 and PISAPED 2 readers.

Figure 1 shows that out of the 155 instances, 137 agreements between modified PIOPED II and PISAPED 1 were established. One hundred and four (104) instances were classified as normal, 24 as positive, and 14 as indeterminate using modified PIOPED II and PISAPED 1. Between modified PIOPED II and PISAPED 1, the observed agreement rate is 88.39%. The Kappa value of 0.7348 suggests that modified PIOPED II and PISAPED 1 are strongly correlated and that the observed agreement is not due to chance. On the other hand, 102 instances were classified as normal, 24 as positive, and 11 as indeterminate using the modified POIPED II and PISAPED 2. For both modified PIOPED II and PISAPED 2, 137 (or 57%) of the cases were classified as normal, positive, or indeterminate. The observed agreement cannot be attributed to chance, given the Kappa value of 0.7444, the observed proportion of agreement between modified PIOPED II and PISAPED 2 (88.39%), and the proportion of agreement that would be projected merely by chance expected agreement (54.56%). The results of the study show that the radiologist identified 98% (152/155) abnormal chest x-rays. At the same time, reader 1 and reader 2 found 48% (75/155) and 54% (85/155) abnormal chest x-rays respectively. Cardiomegaly was the most common abnormal finding on chest x-rays in this investigation. The radiologist recognized cardiomegaly in around 36% of all chest x-rays, while the PISAPED 1 and PISAPED 2 readers both found 21% cardiomegaly in their findings. Also, small pleural effusions accounted for 94% (34 out of 36) of the 36 pleural effusions identified on chest x-rays, while massive pleural effusions accounted for 6% (2 out of 36).

PISAPED 1 reader misclassified 77 of the 152 instances designated as abnormal by the radiologist. Both the radiologist and reader 1 classified a total of 78 cases as either normal or abnormal. Given the extremely low Kappa value of 0.0363, the observed proportion of agreement between the radiologist and PISAPED 1 reader 1 (50.32%) and the proportion of agreement that would be expected simply by chance expected agreement (48.45%), there is poor or weak agreement between the radiologist and PISAPED 1 reader. The PISAPED 2 reader, on the other hand, identified 71 instances as normal. Both the radiologist and the PISAPED 2 reader correctly diagnosed 87 instances as either normal or abnormal. Given the extremely low Kappa value of 0.0363, there is only a slight agreement between the radiologist and the PISAPED 2 reader.

Discussion

Demographics of eligible patients

The majority (75%) of the patients who participated in this study as shown in table 1 were black Africans; this is similar to Dentan et al. (2014), Bulajic et al. (2019) and Danwang et al. (2017), who found a higher prevalence of PE in blacks and associated this to the presence of communicable diseases such as tuberculosis (TB) which are themselves a hypercoagulable state (2,32,33). Interestingly, there were 27 people in the 30–39-year-old age bracket (representing 17%) of the total eligible candidates compared to the 19 people in the 70+ age group representing only 13% of the total population investigated. Increased risk factors such as obesity and the use of hormonal contraceptives could account for the major cause of high PE suspicion among young people. Additionally, patient lifestyle and socioeconomic status could add value to the study if the association and findings in the research group could be linked.

Almost half of the patients in our study were hospitalized patients. This is particularly important in the chest x-ray findings because in-patients are most likely to have cardiopulmonary problems, abnormal x-ray findings and increased indeterminate interpretation. This was the main flaw of the PIOPED study, where 68% of in-patients were utilized, resulting in a 44% of indeterminate diagnosis of PE[15]. In the modified PIOPED study, the number of in-patients was reduced to 11%, thus reducing the indeterminate results. Giving the high PPV of a normal chest x-ray by Stein et al. (2007) of 86%, the present study had indeterminate results of between 18-21%[34]. This was slightly higher than their findings in the PIOPED II study, where the indeterminate findings were 14%. Our higher indeterminate rate could also be due to the significant number of suboptimal quality x-ray images as described by the radiologist.

Value of chest x-ray and diagnostic accuracy of chest x-ray/perfusion scan

Out of our estimated sample size of 386, only 40.1% of patients had a recent chest x-ray. Although there is limited data on the physician's chest x-ray referral pattern within 24 hours prior to V/Q studies, de Groot et al. (2000) reported that about 83% of patients had a chest x-ray done 48 hours before V/Q studies[4]. However, a more recent chest x-ray is preferred for symptomatic patients. Further studies could be done to compare the value of chest x-ray done within 24 hours and 48 hours in PE assessment.

The study showed almost double the percentages of radiologists' abnormal chest x-rays compared to the PISAPED 1 and PISAPED 2 readers. According to our findings, PIASPED reader 1 and PISAPED reader 2 both recorded close identical proportions of chest x-rays classified as normal or abnormal. This contradicts the radiologist's results, which revealed that 98% of the chest x-rays were abnormal. As a result, the interobserver variabilities between the radiologist's findings (designated as the goal standard) and PISAPED 1 and PISAPED 2 readers were exceptionally low (Kappa 0.0363). Various studies, including that of Al aseri et al. (2009), Gatt (2003) and Espinosa (2000), also confirm that chest x-ray evaluation interpretation is very varied among physicians and even more so among experienced radiologists[20–22]. However, this was contrary to the studies by Tranovich et al. (2019), who

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found a good inter-reader agreement between emergency medicine physicians and radiologists[23]. These discrepancies may require further investigations on the criteria of reporting between the two specialties. To increase the interobserver variabilities, a standard template for the diagnosis will be beneficial. Out of possible abnormalities that could be visualized on chest x-ray in patients suspected of having PE, our study was similar to many others, including the ICOPER study by Goldhaber et al(1999), which found cardiomegaly to be the most common abnormalities[24,25]. Since the majority of our participants are of the child-bearing age, further studies should be conducted to understand the high frequency in this study population.

This study showed that the majority (95%) of patients referred for assessment for PE in the Nuclear medicine department did not have a Well's score calculated (table 1). An indication that the majority of participants did not have an objective patient assessment to rule out PE before referral. This finding is higher than that of Smith et al. (2008), who found that there was no documentation of pre-test probability assessment in 64% of known VTE suspicious cases[26]. The results of Runyon et al. (2007) may explain the low utilization of the Well's ratings[17]. In their study, 68% of respondents said they were familiar with at least one of two pre-test likelihood tools for PE. However, due to medico-legal considerations, difficulty memorizing and applying the guidelines, the assumption that clinical configuration is easier, and the belief that none of the rules has been tested to their satisfaction, the physicians did not use the pre-test likelihood methods. The low use of pre-test probability in our study is evident and close to that of Adams et al. (2013) in South Africa, who found that the recommendation to risk-stratify patients prior to CTPA using a pre-test algorithm (Well's score or updated Geneva score) was ignored, with less than half of CTPA referrals adopting these recommendations[27]. The cause for exclusion of pre-test probability may need to be investigated further.

Approximately half of the patients in our sample did not have their D-dimers tested prior to referral. In a country with limited resources, such as South Africa, a less expensive D-dimer test would be a cost-effective method of patient risk stratification. In our study, 12 patients had a normal D-dimer. These patients could have avoided additional diagnostic test for PE had their Well's score been calculated as recommended by Goodacre et al. (2005), Quiroz and Shoepf (2005), and Ravel et al. (2005) given the high NPV of D-dimer [28–30]. This was also similar to Lee and Zierler's (2010) retrospective review of 1,161 patients, which found that the diagnostic technique of pre-test probability and D-dimer as an initial screening for suspected VTE was underutilized[31].

Diagnostic accuracy and interobserver agreement

When PIOPED II and the two PISAPED readers are compared, the readings are remarkably close. In PIOPED II, 75% of the patients had a normal study, 16% had scans positive for PE, and 9% had inconclusive studies. The PISAPED 1 group had 70% normal studies, 19% positive studies, and 12% indeterminate studies, whereas the PISAPED 2 reader saw 67% normal studies, 19% positive scans, and 14% indeterminate studies. The PISAPED 1 reader had a sensitivity and specificity of 96% and 97%, respectively, and an NPV and PPV of 99% and 89%. The PISAPED 2 reader had a sensitivity and specificity of 96% and an NPV and PPV of 86% and 99%, respectively. The agreement between the PIOPED II and the PISAPED 1 and PISAPED 2 was 88.39% (Kappa value of 0.7348) and 88.39% (Kappa value of 0.7444), respectively. Given their Kappa values, this remarkable agreement in interpretation is unlikely to be attributable to coincidence. These findings were similar to those of da Silva et al. (2014) and Miniati et al. (1996), who found that the modified PIOPED II and PISAPED parameters had comparable sensitivities and specificities (84.9% and 92.7% for modified PIOPED II and 80.5% and 96.6% for PISAPED) as well as similar NPV and PPV (96% and 90% for the PIOPED II criteria and 95% and 96% for the PISAPED criteria respectively) (15,16). Our results, however, had higher sensitivity, specificity, NPV and PPV than the study by J vans et al. (2015), which found a sensitivity of 60%, specificity of 86%, NPV of 83 and PPV of 71.4% in their research. However, with a Kappa value of 89%, both investigations demonstrated very strong interobserver agreement. This demonstrates that the diagnostic accuracy of the PISAPED criteria is highly dependent on the reader's level of experience and ability to include other parameters, such as pre-test probability tools, to improve diagnostic accuracy. However, in this analysis, the number of indeterminate studies was substantially larger than in other studies, such as that of Sostman et al. (2008), who had no patients in their indeterminate category[35]. This is most likely due to the high number of suboptimal x-ray quality found in this investigation.

Conclusion

This study demonstrates that using a chest x-ray in conjunction with perfusion scintigraphy (PISAPED) is accurate and can be used where ventilation/perfusion scintigraphy (Modified PIOPED II) cannot be done in the diagnosis of PE. Although in our environment, majority of the chest x-rays are of sub-optimal quality, the PISAPED criteria had a comparably good accuracy and very good interobserver agreement. Even while the PISAPED readings yielded more uncertain results than the PIOPED II criteria, they seem to be more beneficial in the hands of an experienced reader who uses pre-test probability tools to improve diagnostic accuracy. The PISAPED criteria are also more helpful in younger patients, pregnant and breastfeeding mothers, and other settings where reduced exposure to ionizing radiation is desired. Also, in a resource limited country like South Africa, the ventilation portion of lung scintigraphy could

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be omitted to reduce cost and save time, thus assisting in service delivery.

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