The Predictive Value of Ventilation-Perfusion Scanning for the Diagnosis of Pulmonary Embolism in Patients with Impaired Renal Function

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ABSTRACT: **Background:** Computed tomography pulmonary angiography (CTPA) is considered the method of choice for diagnosing pulmonary embolism (PE). In most patients with impaired renal function, ventilation-perfusion (V/Q) scanning is the preferred modality.

Objectives: To evaluate the predictive value of V/Q scanning in patients with impaired renal function.

Methods: We assessed all patients with impaired renal function who underwent V/Q scanning. The patients studied included those who also had CTPA (group 1) and those who did not (group 2). We recorded the results of V/Q scanning, chest X-rays, CTPA, D-dimer levels, ultrasound of deep veins, and clinical probability for PE (Wells' score) in group 1. CTPA results were considered true results. Anticoagulant treatment was documented in all the patients.

Results: Of the 45 patients in group 1, 12 (22%) had positive CTPA for PE. The positive predictive value (PPV) for patients with high probability results on V/Q scanning for PE was 30%. Restricting results to D-dimer levels ≥ 1000 ng/ml added little to this value. Restricting results to Wells' score ≥ 7 resulted in 72% PPV. The negative predictive values for low or moderate probability were ~79 % and ~67% respectively. Of the 95 patients in group 2, all those with high probability for PE were treated with anticoagulants.

Conclusions: Patients with impaired renal function and high probability for PE on V/Q scanning had very low PPV for PE. Due to the lack of CTPA studies, patients with high probability for PE on V/Q scanning were treated with anticoagulants.

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KEY WORDS: ventilation-perfusion (V/Q) scanning, impaired renal function, predictive value, pulmonary embolism, computed tomography pulmonary angiography (CTPA)

Pulmonary embolism is an important entity in medical practice since it is associated with high morbidity and mortality [1]. Computed tomography pulmonary angiography is considered the modality of choice for the diagnosis of PE [2]. It is highly sensitive and specific for this purpose [3]. Regardless of the results of this examination, usually no further investigation is required to rule out, or confirm, PE – unless the study is inconclusive. However, this study had some limitations and contraindications, such as impaired renal function, allergy to the contrast material, and fear of radiation especially in patients with high risk for breast cancer. The mechanism of radio-contrast nephropathy is hypoxic tubular injury due to vasoconstriction with release of free oxygen radicals. Major risk factors for the development of radio-contrast nephropathy are prior impaired renal function and diabetes mellitus [4]. In facilities where magnetic resonance imaging is available, MR-angiography could be an option [5]. It has a better renal safety profile and no radiation [6]. Yet, gadolinium-related nephrogenic systemic fibrosis could occur. In centers where MRI is not available, ventilation-perfusion scanning then becomes the modality of choice [7]. This modality is not as sensitive or specific as CTPA, and usually other tests like D-dimer levels and venous ultrasonography of the deep veins in the lower extremities in addition to clinical probability (pretest probability) are taken into account when assessing the likelihood of PE [8]. Usually, the results of the V/Q scanning are documented as low, moderate or high probability for PE. This classification is based on the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) criteria [9]. Generally, the positive predictive value of high probability and negative predictive value of low probability on V/Q scanning reach ~90% and ~100% respectively [10]. These figures are affected by other variables including clinical probability and prevalence of PE in the population studied.

Impaired renal function is a medical condition that is encountered more and more frequently in the emergency room and medical ward. Patients with impaired renal function who are suspected of having PE are usually referred for V/Q scanning to avoid the potential injury to the kidneys from contrast material in CTPA. The results of this modality

PE = pulmonary embolism
CTPA = computed tomography pulmonary angiography
V/Q = ventilation perfusion

may profoundly affect the treating physician's decision with regard to anticoagulant treatment. It must be remembered that impaired renal function is associated with increased D-dimer levels that could lead to further unnecessary V/Q scanning or anticoagulant treatment [11]. D-dimer levels were significantly elevated in 46% and 72% of the patients with mild and moderate impairment of kidney function, respectively.

To date no studies have addressed the PPV or NPV of V/Q scanning in patients with impaired renal function. In this retrospective study we evaluated the PPV and NPV of V/Q scanning in patients with impaired renal function who were suspected of having PE and who eventually also underwent CTPA. We also documented the outcome of renal function, eventual anticoagulant treatment, recurrent PE, and mortality.

PATIENTS AND METHODS

All the registered V/Q scans that had been performed at Carmel Medical Center since 2005 were located. The files of all those who underwent the scanning due to clinical suspicion of PE were reviewed. Patients who had ventilation in addition to perfusion, impaired renal function at the time of V/Q scanning, and CTPA studies were classified as group 1. Patients with impaired renal function who underwent V/Q scanning but not CTPA were assigned to group 2. The aim of this differentiation was to evaluate the eventual impact of V/Q results on the anticoagulant treatment in group 2 patients. The files were also reviewed for explanations as to why CTPA was performed after the V/Q scanning in group 1 patients. Impaired renal function was defined as serum creatinine level higher than the upper normal level corrected for gender.

The results of the V/Q scanning, chest X-rays, CTPA, D-dimer levels, ultrasound of the deep veins of the lower extremities, and pretest probability for PE in group 1 were documented. Ventilation was performed using Biodex-Pulmonex Xenon System and V/Q scanning using Vari Cam gamma cameras (General Electric, USA) or E. Cam (Siemens, Germany). First, perfusion was performed using labeled macro-aggregates of albumin and planar acquisition, followed by ventilation using 133Xe. The interpretation of the V/Q scanning was based on the PIOPED II criteria where mismatch with segmental hypoperfusion or large sub-segmental hypoperfusion is indicative of moderate probability for PE. Mismatch with less than that is indicative of low probability and mismatch with two segments of hypoperfusion or more are indicative of high probability.

The CTPA scans were performed using spiral CTs (multiple detector, 64–128 slices) (Philips, Germany) and interpreted according to filling defects compatible with thrombi at the pulmonary arterial tree up to the segmental branches.

For ultrasonographic investigation of the proximal deep veins of the lower extremities, a modern version of Philips ultrasound Doppler machines (HD 11 and IU 22) with linear transducers 4/8 were used and the interpretation was based on the compressibility of the deep veins and/or visualization of an intravenous clot of the proximal deep veins. The common femoral vein down to the trifurcation of the popliteal vein was evaluated. All the results of chest X-rays, CT, V/Q scanning and ultrasound were signed by senior and very experienced radiologists, each in his or her own field.

D-dimer values were evaluated by immunoenzymatic determination of fibrin degradation products using Vidas D-Dimer Exclusion (bioMerieux Inc. France). Pretest (clinical) probability was assessed by the authors using Wells' scoring system [12]. Reports of X-rays were classified as either normal lung fields or abnormal lung fields including pleural effusion, congestion, infiltrate and/or consolidation.

We also documented creatinine levels at the time of the CTPA study, 2–4 weeks later (whichever was available, with preference for 4 weeks), and 1 year following the CTPA in group 1 patients.

The PPV and NPV were calculated for all the patients in group 1 with low, moderate or high probability for PE with or without the restriction to D-dimer levels, ultrasound status of the lower extremities, and pretest probability. PPV and NPV of V/Q scanning for the diagnosis of PE were based on the assumption that CTPA results were true. Although the normal range of D-dimer levels is 0 to 500 ng/ml, we evaluated PPV and NPV with D-dimer levels higher or lower than 500 and 1000 ng/ml due to the fact that impaired renal function is associated with increased D-dimer levels. Mortality and recurrent PE, in addition to anticoagulant treatment, in all patients from both group 1 and group 2 were documented.

For statistical analysis, paired *t*-test was used to compare between creatinine levels of all patients in group 1 at 2–4 weeks and 1 year following the CTPA compared to the levels at the time of the CTPA study. Chi-square test was used to compare between the number of deaths and recurrent PE cases in both groups.

RESULTS

During the period 2005–2008, 173 V/Q scanning studies were performed in 161 patients (after 2008 ventilation was not performed). All the studies were requested due to clinical suspicion of PE. The reason for V/Q scanning was impaired renal function in 140 patients, allergy to contrast material in 7, and different causes in 14. There were 45 patients in group 1 and 95 in group 2.

All the patients in group 2 with high probability on V/Q scanning (n=20) and 36% of those with moderate probability

PPV = positive predictive value
NPV = negative predictive value
PIOPED II = Prospective Investigation of Pulmonary Embolism Diagnosis II

were treated with anticoagulants, while only patients who had positive CTPA results for PE in group 1 were treated with anticoagulants, regardless of the result of the V/Q scan. Usually the CTPA studies were done within 0–2 days of V/Q scanning after renal preconditioning with acetylcysteine and fluids (all patients). There were no specific criteria as to who should be offered CTPA and who not. However, the general feeling from reviewing the files was that patients with low or moderate probability for PE who eventually proceeded with CTPA after the V/Q scanning had unexplained hypoxemia along with improving/stabilizing kidney function. Among the patients with high probability for PE on V/Q scanning, CTPA was undertaken mainly after improving/stabilizing kidney function, with the potential of increased risk of bleeding or inadequate monitoring when anticoagulants were considered or administered.

Table 1 summarizes the demographics, results of V/Q scanning, CTPA, ultrasound studies of the proximal deep veins, chest X-rays, and pretest probability scores of all patients in group 1. Ultrasound studies of the proximal deep veins of the lower extremities were performed in 25 patients only. Chest X-ray results of patients with high probability V/Q scan in group 1 (those who also had CTPA, 10 patients) included 7 patients with normal X-rays, one with pulmonary congestion, one with mild bilateral pleural effusion, and one with mild-moderate left pleural effusion. CTPA was positive in two of the three patients with abnormal X-ray findings (two with pleural effusion) but only in one patient of those with normal X-rays. Positive CTPA results were also seen in patients who had either normal or abnormal chest X-rays in both groups of low or moderate probability for PE.

The PPV and NPV of V/Q scans for the diagnosis of PE in all group 1 patients are summarized in Table 2. Table 3 presents the mean values of kidney function in group 1 patients at different time periods. Group 2 patients had significantly higher serum creatinine levels than group 1 at the time of V/Q scanning with a mean serum creatinine of 2.21 mg/dl ($P = 0.012$, data not shown). Table 4 shows the outcome of patients in both groups regarding recurrent PE or death, with no significant difference between the two groups. However, one patient from group 2 who was treated with anticoagulants for "PE" died following acute myocardial infarction due to severe anemia (hemoglobin 6.1 g/dl) with evidence of melena.

Table 1. Demographic and laboratory findings of patients in group 1

V/Q scan probability	Age (yr)*	Gender F:M	CTPA status +:-	Clinical probability score*	Ultrasound status +:-	Chest X-ray status** +:-
High probability (n=10)	67.8 ± 23.5 (18–91)	6:4	3:7	6.6 ± 2.0 (4.5–11.5)	3:6	3:7
Moderate probability (n=21)	62.6 ± 19.8 (28–87)	11:10	6:15	5 ± 1.7 (2–8)	3:6	10:11
Low probability (n=14)	69.9 ± 11.5 (40–82)	11:3	3:11	4.6 ± 1.6 (2–7)	0:7	7:7

*Mean ± SD (range)

**Abnormal lung fields for "+", and normal lung fields for "-"

+:- = positive:negative

Table 2. PPV and NPV results of V/Q scanning in group 1 patients with or without restriction for D-dimer levels, ultrasound status of deep veins of the lower extremities, and/or Wells' score

	All patients	DD › 0.5 K	DD › 1 K	DD ‹ 0.5 K	DD ‹ 1 K	DD › 1 K and + ultrasound	DD › 1 K + Wells' › 7	Probability
PPV	30%	30%	40%			~33%	~72%	High
PPV	~29%	40%	50%			~67%	~62%	Moderate
NPV	~67%			100%	~70%			Moderate
NPV	~79%			100%	100%			Low

DD = D-dimer, K = 10^3

Table 3. Mean values of kidney function in group 1 patients at different time points

	At CTPA	At 2–4 weeks	At 1 year
Mean creatinine level (mg/dl) (range)	1.41 (0.91–2.31)	1.18 (0.61–1.61)	1.32 (0.68–1.47)
No. of patients	45	38	31
P value		0.964*	0.432**

* *P* value comparing the results obtained at 2–4 weeks with those at CTPA

** *P* value comparing the results obtained at 1 year with those at CTPA

Table 4. Number of cases with recurrent PE and those who died

	Group 1 (n=45)	Group 2 (n=95)	*P* value
Recurrent PE	1	3	› 0.999
Mortality	3	7	0.9124

DISCUSSION

The PPV of high probability results of V/Q scanning studies for PE in all group 1 patients was very low (30%, 3/10). This means that 70% of the patients with impaired renal function and high probability for PE according to V/Q scanning might have been subjected to unnecessary anticoagulant treatment in the absence of CTPA evaluation. In fact, all the patients with impaired renal function who did not have CTPA studies but only V/Q scanning (group 2) with high probability for PE were treated with anticoagulants. This demonstrates that V/Q scanning results were given serious consideration by the medical team in our hospital regardless of the results of other studies and clinical or pretest scores.

Restricting the results (high probability results of V/Q scanning studies for PE) to those with elevated D-dimer levels (> 1000 ng/ml) contributed very little to the PPV (~40%) compared to those with levels > 500 ng/ml (30%). Ironically, restricting the results also to those with positive ultrasonogra-

phy of the lower extremity for deep vein thrombosis reduced the PPV. This could be attributed to the small number of patients and/or to the fact that elevated D-dimer levels could be due to a DVT of the lower extremity without the coexistence of PE. However, restricting the results to those patients with Wells' score ≥ 7 and D-dimer levels ≥ 1000 ng/ml increased the PPV to ~72%.

Patients with moderate probability on V/Q scanning comprise the largest bulk (~47%) of group 1 patients. The PPV of moderate probability of V/Q scanning for all patients was also low (~29%). Restricting the results (of moderate probability on V/Q scanning) to those with D-dimer levels > 500 ng/ml increased it slightly (40%) and to those with D-dimer levels > 1000 ng/ml raised it slightly further to 50%. The implementation of Wells' score here resulted in a modest contribution (increased the PPV to ~62% only). The NPV of moderate probability results on V/Q scanning in group 1 represents a different story. When adhering to the old rule of < 500 ng/ml of D-dimer levels, the NPV is 100%, a much better result than the ~70% obtained with D-dimer levels < 1000 ng/ml.

As expected, a high level of NPV was obtained with low probability on V/Q scanning for PE in all patients (~79%). However, in contrast to moderate probability, restricting to D-dimer levels of either < 500 or < 1000 ng/ml raises the NPV equally to 100%. So, similar to other studies in patients with normal kidney function, V/Q scanning is very reliable in ruling out PE once a low probability result on V/Q scanning is obtained in patients with impaired renal function.

Twenty patients in group 1 had normal chest X-ray as compared to 25 patients with abnormal findings, yet only 12 patients from all the categories of probabilities had a positive CTPA. Positive CTPA results were seen in patients with normal and abnormal X-rays in each category. With the range of abnormal findings on chest X-ray, stratification of positive CTPA results in each category of probability with chest X-ray finding will result in very few patients, if any, in each stratum. Normal lung fields or mild pleural effusion on chest X-ray is not necessarily associated with higher probability of positive CTPA results. It could make interpretation easier once ventilation is not available. However, the mismatch needed for the classification of high or moderate probability on V/Q scanning is between perfusion and ventilation rather than between perfusion and chest X-ray findings. Yet chest X-rays are frequently reviewed by the nuclear medicine team when findings on V/Q scanning are questionable.

There was no worsening of renal function following the CTPA studies in our patients. On the contrary, there was an improvement in mean creatinine levels after 2-4 weeks, although this was not significant. There was also no significant change in renal function after 1 year. Hydration and N-acetyl cysteine administration before and after the CTPA studies in patients with impaired renal function are standard measures in our institution, in addition to the withdrawal of other potential harmful medications prior to the CTPA study. Such measures are known to prevent worsening of kidney function in these patients [13].

Although there was no significant difference between group 1 and 2 in terms of number of cases with recurrent PE or death, group 2 had relatively more such cases, including one fatality who presented with anemia-related myocardial infarction with evidence of gastrointestinal bleeding under anticoagulant treatment due to "PE." This case highlights the potential of severe adverse effects of unnecessary anticoagulant treatment, mainly in elderly patients.

We cannot fully explain the low PPV of high probability results on V/Q scanning for PE among patients with impaired renal function. The literature lacks supportive data. The results of our study could be coincidental. Yet such results could not be dismissed, especially at the time that the NPV of at least the low probability results was similar to those levels already known in the literature. CTPA and V/Q scanning studies were not performed on the same day and embolic resolution could have occurred; however, it usually takes much longer for pulmonary emboli to resolve [14]. Ventilation-perfusion mismatch could be seen in various conditions other than PE. Such conditions could be common or less common. Common conditions include bronchogenic carcinoma and previous radiation therapy [15,16]. None of our patients with high probability on V/Q scanning belonged to these categories. On the other hand, less common conditions associated with V/Q mismatch were based on case reports or case series. These conditions include vascular, neoplastic, parenchymal and systemic diseases [17-20]. Pulmonary hypertension is an uncommon cause that could be associated with V/Q mismatch. Pulmonary hypertension could be associated with renal failure, but this association was found among patients with end-stage renal disease and on hemodialysis, but not among patients with mild-moderate impaired renal function [21].

Nonetheless, efforts should be made to proceed with CTPA in those cases with mild to moderate impaired renal function and high or even moderate probability for PE on V/Q scanning. Also, a pretest or clinical probability should be given serious consideration especially if these patients are not candidates for CTPA studies. Otherwise, many of these patients might eventually be treated, incorrectly, with anticoagulants.

Our study had some shortcomings. First was the lack of a control group. There were very few patients (n=4) with normal kidney function at presentation who had undergone both CTPA and V/Q scanning. A controlled prospective study could not be conducted in our hospital due to the lack of ventilation (after 2008). Second, ideally, creatinine clearance would be a

DVT = deep vein thrombosis

better measure of renal function; only a few patients had this test. Actually, elevated creatinine levels in elderly patients (the overwhelming majority of our patients) have a very high predictive value for impaired renal function. Third, the assumption that CTPA results are true is not totally correct. Although the specificity is high, it is not yet 100% and cases of false positive results have been reported [22]. Yet our hospital usually uses the latest models of CT machines. Fourth, repeated V/Q scanning would shed more light on the validity of these studies, but unfortunately such studies were not repeated in a retrospective study. Finally, since CTPAs were performed after V/Q scanning, interpretations of the CTPA results might be biased by the results of the V/Q scanning.

Nonetheless, in view of the total lack of data in the literature on the PPV and NPV of V/Q scanning for the diagnosis of PE in patients with impaired renal function, we feel that our findings merit consideration due to the enormous number of patients with impaired renal function who are evaluated with V/Q scanning. Further prospective controlled studies are needed to refute or support our findings.

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Capsule

Link between the complex phenotype of type 2 diabetes and epigenetic modifications

Methylation is a form of epigenetic regulation that can influence gene expression. Furthermore, methylation has been postulated to underlie some complex traits and diseases, especially those for which genetic factors have been poorly identified or functionally understood. In order to investigate the epigenetics of type 2 diabetes (T2D), Dayeh and team examined the genome-wide DNA methylation patterns in pancreatic islets in both diabetics and non-diabetics. They found that the degree of methylation was correlated with transcription, although overall levels of methylation did not differ between diabetics and non-diabetics. Differentially methylated regions between individuals with and without T2D were identified. Of the more than 800 genes exhibiting differential methylation, 102 showed differential mRNA expression, including 17 candidate T2D genes expressed in islets. Furthermore, functional analyses provided support that these observed methylation differences may underlie differences in gene expression and potentially link the complex phenotype of T2D with epigenetic modifications.

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