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Review

# Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis of the literature, and cost and dose comparison

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ABSTRACT

Diagnosing acute pulmonary embolism (PE) is an indication for scintillation V/Q imaging (planar and SPECT) and/or CTPA. This study reviews, compares and aggregates the published diagnostic performance of each modality and assesses the short-term consequences in terms of diagnostic outcomes, monetary cost, and radiation burden.

We performed a formal literature review of available data and aggregated the finding using a summary receiver operating characteristic. A decision tree approach was used to estimate cost and dose per correct diagnosis.

The review found 19 studies, which comprised 27 data sets (6393 examinations, from 5923 patients). The results showed that planar V/Q was significantly inferior to both V/Q SPECT and CTPA with no difference between the latter two. CTPA represents best value; £129 per correct diagnosis compared to £243 (SPECT) and £226 (planar). In terms of radiation burden V/Q SPECT was the most effective with a dose of 2.12 mSv per correct diagnosis compared with 3.46 mSv (planar) and 4.96 (CTPA) mSv.

These findings show no performance difference between V/Q SPECT and CTPA; planar V/Q is inferior. CTPA is clearly the most cost effective technique. V/Q SPECT should be considered in situations where radiation dose is of concern or CTPA is inappropriate.



## 1. Introduction

Managing the suspicion of pulmonary embolism (PE) is a common clinical practice problem. PE, deep-vein thrombosis, and venous thromboembolism are common cardiovascular disorders and are potentially fatal. Presentation of PE is varied and may include dyspnoea or pleuritic chest pain. An incidence of 0.6–1.2 per 1000 persons per year has been reported [1] and consequently the management of PE is a significant component of any acute medical workload. Imaging plays an essential role in diagnosis; the aim of imaging is to accurately confirm or rule out the diagnosis of PE, after which, if indicated, anticoagulant treatment can be initiated, with its associated costs and hazards. Over the last decade, different imaging modalities have been established as useful diagnostic tools, with various ranges of diagnostic performance being reported. Choice of modality varies by location with usage of a particular modality influenced by a combination of site history, availability of equipment, physician personal preference, and patient suitability.

Guidance on which modality to use varies. Currently in the UK, the National Institute of Health & Clinical Excellence (NICE) [2] recommends immediate computed tomography pulmonary angiography (CTPA) or immediate interim anticoagulant therapy followed by a CTPA, if a CTPA cannot be performed immediately. Similarly, the European Society of Cardiology [3] describes

*Abbreviations:* ARSAC, Administration of Radioactive Substances Advisory Committee; AUC, area under curve; CI, confidence interval; CT, computed tomography; CTPA, computed tomography pulmonary angiography; ImPACT, Imaging Performance Assessment of CT scanners; NICE, National Institute for Health & Care Excellence; PE, pulmonary embolism; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; PISA-PED, Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; Q*, point on SROC curve where sensitivity = specificity; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; ROC, receiver operator characteristic; SPECT, single photon emission computed tomography; SROC, summary receiver operator characteristic; V/Q, ventilation/perfusion.

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CTPA as the method of choice for the investigation of PE. Conversely, the European Association of Nuclear Medicine broadly recommends ventilation/perfusion single-photon emission computed tomography (V/Q SPECT) over CTPA, where available [4]. This recommendation is based on claimed advantages of V/Q SPECT including absence of contrast agent injection; lower radiation burden; lower rate of non-diagnostic reports; higher sensitivity at similar specificity; and better estimation of PE extent based upon the functional impact.

These and other recommendations are based on extensive literature reviews justifying the advice given. However, little attempt is given to aggregate and compare the performance of two modalities in a quantitative manner, assess quality of studies used to justify advice given, or examine the potential cost advantage of each modality. Previous work in this vein has been performed including ROC analysis of planar V/Q and CTPA [5] – this work is over a decade old, however, and does not include consideration of V/Q SPECT.

Aggregating findings from imaging studies with and without quantitation is not a simple process due to lack of homogeneity in technique and diagnostic significance threshold used. A summary receiver operating characteristics (SROC) analysis is a statistical technique that can be applied to meta-analysis of imaging tests; the technique overcomes the limitations associated with simple pooling of sensitivities and specificities of published studies [6]. In this study, we apply this approach to summarise published data describing performance using the area under the ROC curve (AUC) and the point where the sensitivity equals the specificity on the ROC curve ($Q^*$), which are common figures of merit for evaluating performance [7]. For completeness this study also includes an assessment of planar scintigraphy for comparison.

When performing such a comparison it is prudent to use some means of assessing the relative quality of included studies. It is clear from almost any similar literature review that the quality of studies varies greatly when different quality factors are considered. The second version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [8] methodology is a refinement of the original QUADAS tool developed at the University of Bristol. The QUADAS-2 methodology aims to assess quality based on four domains (patient selection, index test, reference standard, flow and timing). For each study, an assessment is made of risk of bias in each domain, and a mark of high, low, or indeterminate is assigned. For the first three domains concerns regarding applicability are also assessed, and a mark of low concern, high concern, or indeterminate concern assigned. The QUADAS-2 guidance suggests several generic signalling questions to aid in this assessment, which we adapted to our review.

Having assessed the diagnostic efficacy of each technique, the next logical question to ask is: 'is it worth it?' A complete downstream analysis of the cost and consequences of inappropriate therapy, brought about by the limitations of the examination, is beyond the scope of this study; an estimate of their short-term costs and consequences are possible given the data available, however. In this context, a false positive result will waste resources spent on intervention with no commensurate increase in health gains, as well as a potential decrease in lifespan caused by unnecessary administration of oral anticoagulation therapy in otherwise healthy patients. The impact of false negatives is more difficult to assess, as a detailed model of downstream consequences of non-diagnosis of PE is required (including patient death). Given the complexity of factoring in the effect of false-negatives, in this paper we limit our analysis to estimation of the cost per correct diagnosis.

As with all examinations involving radiation, cost per exam is not the only factor to consider. Radiation exposure is also to be considered when estimating potential health gains. Similarly, as with the cost analysis we will summarise radiation dose to the patient associated with each method, and relate this to the diagnostic performance of each method.

The aim of this study is therefore: to compare and aggregate the evidence underpinning two widely used imaging techniques for the detection of PE by perform a structured literature review and aggregating available data using a summary ROC analysis. In addition, the study aims to quantify for each technique the diagnostic costs per correct result and to relate the radiation burden per correct diagnosis.

## 2. Method

An online literature search was conducted using Web of Knowledge™, Medline, ScienceDirect, Google Scholar and PubMed using the following search criteria in the topic field: "(PE OR embolism) AND (V/Q OR VP OR perfusion) AND (planar OR SPECT OR scintigraphy) AND (CTPA OR CT)". The search was limited to studies published as full papers, between 1997 and August week 42, 2014, in English. Abstracts were then reviewed by one author (JP) for exclusion. Papers were excluded if they clearly non-relevant reports, non-human studies, full manuscript unavailable and qualitative reviews. All potentially eligible studies identified from this trawl were reviewed (full manuscript) by JP and RS. Studies were excluded if they had no clearly defined gold-standard and/or did not report sensitivity and specificity.

Data extraction was completed by JP and RS independently; discrepancies were settled by consensus. True-positive, true-negative, false-negative and false-positive values were extracted from the data given. When these values were not noted explicitly, they were inferred from the given values for sensitivity, specificity, positive predictive value and negative predictive value. In two studies [9,10] the same patient data were analysed with two or more different sets of diagnostic criteria (i.e. Prospective Investigation of Pulmonary Embolism Diagnosis-II (PIOPED-II) and Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) in planar scintigraphy). To avoid including the same patients more than once in our ROC curve and to simplify our overall analysis, we included only the more contemporary (PISA-PED) results showing the lowest proportion of non-diagnostic tests. Where results were noted as non-diagnostic, inconclusive, or similar, they were recorded but not included in any further analysis.

The data were entered into the metaDisc [11] meta-analysis software. SROC curves were generated for each technique (viz. planar, SPECT, CTPA) using a study-size weighted least-squares fit approach. AUC is a figure of merit for ROC curves, with 1 representing perfect performance and 0.5 indicating random performance. AUC are calculated within the programme using the trapezoidal method. $Q^*$ represents the point on the SROC curve where sensitivity equals specificity. We quote both these results as measures of diagnostic performance.

As a means of quality assessment, we adapted the QUADAS-2 signalling questions [8] to our study pool assigning each study a mark in the four *risk of bias* domains and the three *applicability concern* sections. These marks were performed by JP and RS independently, with discrepancies again being settled by consensus. For the cost-consequence analysis, costs of the different imaging modalities were obtained from the NICE costing report on the subject [12]; costs (including reporting) for a standard planar V/Q, V/Q SPECT, and CTPA, are £181, £229, and £120 respectively.

For the nuclear medicine modalities, mean administered radiopharmaceutical activity was calculated using the figures provided by each study (where stated) and weighting this by patient sample size. To estimate dose we related mean values to the dose/activity figures found in the Administration of Radioactive Substances Advisory Committee (ARSAC) notes for guidance, and simply multiplied