



Cyclopharm *Limited*

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Overview

Many competing modalities claim to be useful in the diagnosis of Pulmonary Embolism. What does the casualty physician do when faced with the patient complaining of shortness of breath, chest pain and other non-specific symptoms? The consequences of missing the diagnosis, either way, can be dire.

This brochure, whilst not claiming to be exhaustive, is the first in a number of coordinated leaflets, which when complete, will provide a logical rationale for considering Technegas as the most appropriate scanning tool in the diagnosis of P.E.

In this offering, the extent of the problem is identified and the supporting evidence for considering the Ventilation/Perfusion scan, specifically with Technegas, as the optimal test, is outlined.

Defining The Problem

"VTE [venous thrombo-embolism] is an uncompromising predator that can gnaw at the very strands of life itself. Yet it develops slowly, usually unseen and unheralded, to burst upon clinical consciousness with frightening rapidity". So wrote Henry W Gray as part of a dramatic personalised introduction to his excellent review 'The Natural History of Venous Thromboembolism: Impact on Ventilation / Perfusion Scan Reporting' published in 2002 (1). It is in this context of a stealthy, potentially fatal condition, where the statistics of clinical examinations alone to make a diagnosis generally point to about a 65% accuracy, that there is such an ongoing need for a reliable, non-invasive screening test that is available at any time. And there is no place for error: false positives and false negatives both carry severe risks for the patient.

Pulmonary Embolism (P.E.) is a major health problem which is more common than might be thought and more lethal than usually appreciated. The incidence of venous thromboembolic diseases in the U.S. is increasing as the population increases and ages. Morbidity is generally determined by early and accurate diagnosis and immediate treatment. Unfortunately, the diagnosis is frequently missed because the symptoms of P.E. are vague and non-specific.

The embolus is usually a thrombus but bone marrow, fat and air may be involved. In 60% of cases the source of the thrombus is the venous system of the lower legs highlighting the importance of Deep Vein Thrombosis (DVT) in the equation.

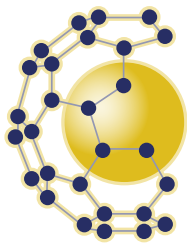
In the U.S. about 600,000 patients per year have clinically P.E. and 120,000 (20%) of them die annually without being diagnosed. P.E. is present in about 80% of patients with DVT and more than half are asymptomatic.

Making The Diagnosis

Attempt to diagnose P.E. using the traditional "gatekeeper" of emergency medicine imaging, Radiology, with the latest tomographic x-ray contrast equipment and procedures, generally known as CTPA, have been supported by an extensive literature and a growing referral rate. But apart from the high radiation dose especially to the female breast, there seems to be minimal recognition that up to 15% of the potential patients are unable to have the test for various reasons. By definition, this should eliminate its status as a screening test.

Other interpretive pitfalls include high interpreter variability, questionable sensitivity at the subsegmental level, breathhold and high false negatives.

In practice what usually happens is that the Nuclear Medicine V/Q procedure is then called upon as a second best option. Yet from its inception in 1963 (2), the sensitivity of the perfusion imaging test, whereby up to half a million radio-labelled micro-emboli, usually aggregates of human serum albumin, are injected, has never been surpassed. The clinical problem has always been vascular obstructions of non embolic origin which may confound the diagnosis, and in our urbanised industrialised societies, at least 40% of all adult lung imaging show such perfusion defects. Physiologically, the body's attempts to maintain high oxygen saturation in the blood leads to an extremely rapid closure (milliseconds) in localised perfusion (Q) if the congruent region of airways is obstructed. But the converse does not occur, and it can take days for airways patency to be affected by perfusion defects. Hence the potential value of a test for P.E. that is both highly sensitive and specific when a perfusion defect is shown still to have ventilation patency-the V/Q mismatch.



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The Role Of Technegas

Throughout the 43 year history of the V/Q procedure, the biggest variable has been the quality of the ventilation agent. Until Technegas was discovered, these agents had universally been an aqueous aerosol of one kind or another. All such aerosols, however generated and initially polydispersed, once they reach the supersaturated vapour of the lung at about the 3rd division of the bronchial tree, grow almost instantly to a larger uniform sized particle, a process named "isothermal distillation" (3). Thus for these aerosols, the specific delivery size at the mouth bears little relationship to the ultimate equilibrium size. Note that a doubling in size effectively multiplies the momentum by 8, leading to impaction at the branches deeper into the lungs. Evolution has helped prevent too deep a penetration of airborne particles, by creating increasing branch angles with depth into the lung. As a consequence, it is possible that ventilations performed with aqueous aerosols could lead to false positive diagnosis of P.E., since the combination of deposition at or above the respiratory bronchioles, combined with lung movement during image acquisition can create an apparently uniform ventilation image.

The long search for Technegas was driven primarily by the meta-analysis graph by Friedlander (4). It was clear that to get an aerosol deep into the lungs, it had to be as small as possible and mimic a gas. Technegas satisfied not only this criterion ($<< 0.1 \mu\text{m}$), but also being hydrophobic, did not grow during its transport into the lung. Several workers attested to its gas-like quality in comparative studies with Xenon-133, for example Amis et al (5). In fact, the 5 second breath-hold at the end of inhalation is important to allow diffusion kinetics to propel the particles to the alveolar walls where they lodge in the surfactant. If the inspiratory pause is not performed, efficiency of retention drops from around 80% to 50% providing proof of its gas-like behaviour (6).

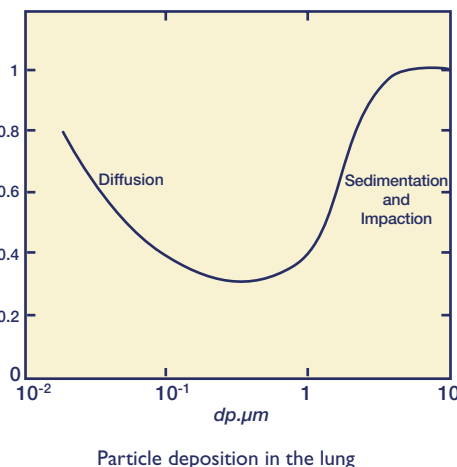
Results

The V/Q test using Technegas as the ventilation agent of choice can generate diagnostic results at the very least equivalent to radiological procedures without any limitations on patients to be examined, whether they are babies, frail-aged or comatose. An extensive study by Howarth et al (7) in 924 patients just published, has demonstrated a simplified criterion of >0.5 segment of V/Q mismatch for P.E. diagnosis. This protocol returns an indeterminate rate of $<5\%$ from a three months outcome follow up. The work was conducted with planar imaging by a highly skilled practitioner. SPECT imaging using the same criterion should be shown to make the data more independent of interpretive skill base leading to wider adoption. More than anything else, SPECT offers the opportunity to share problematic diagnoses like P.E. with the referring physician, a point underlined recently by Ell (8).

Broadly speaking, sensitivity, specificity and accuracy of V/Q SPECT are above 95% (9) making this easily comparable to the results with multi-slice CT. However, CT is less sensitive at the subsegmental level, more susceptible to interpreter variability and results in the reporting of 17% false negatives in some studies.

Future Issues

In the next brochure the issue of tissue dose with CTPA will be highlighted. Many departments are already implementing guidelines designed to regulate the appropriate use of CTPA. Such is the concern regarding the radiation dose to tissue, viz. breast tissue in young females, that recommendations restricting the delivered dose are now being imposed.



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