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Issue 4, May 2008

## Introduction

Cyclopharm Limited (CYC) has now completed agreements with the Macquarie University Private Hospital (MUPH) to establish our first commercial production site in NSW for Positron Emission Tomography (PET) radioisotopes and Molecular Imaging targeting molecules on the new MUPH campus and the Dalcross Private Hospital. The achievement of this strategic goal represents a seven million dollar investment by CYC. Site construction is in progress and our facility will become the first commercial radiopharmaceutical production company in the state of NSW with a planned range of radiopharmaceutical products to service the nuclear medicine community.

CYC selected the Macquarie University and Dalcross Private Hospital affiliation for this endeavour to enhance the Australian Nuclear Medicine/Radiopharmaceutical scene. CYC will support Molecular Imaging Research at the Macquarie University. Non-production time of the cyclotron will be available to conduct cutting edge research in the development of PET diagnostic targeting molecules in collaboration with the University and the Pharmaceutical Industry using state of the art technology incorporating biologically compatible positron emitting radioisotopes such as carbon-11. In addition, world-renowned CYC research staff together with company-supported University staff will collaborate on research and educational programs to develop the future scientific work force. This will establish at Macquarie University and NSW a premier Radiopharmaceutical Science educational program necessary to advance Molecular Imaging in Australia.

The MUPH radiopharmaceutical production site will be compliant with the related Therapeutic Goods Administration (TGA) requirements for Good Manufacturing Practice (GMP) and will also house a GE PETTrace cyclotron. The first planned product will be the widely used PET diagnostic molecule: Fluoro-Deoxy-Glucose (FDG) to mitigate the pressure for its demand in NSW.

Cyclopharm believes that the establishment of commercial FDG production capacity in NSW by the private sector will foster PET imaging. This will also alleviate demands on the government to fund the required infrastructure in hospitals such as costly cyclotrons and FDG production facilities.

PET is the fastest growing nuclear medicine diagnostic imaging modality in the world and was recently recognised by the Federal government as the best option for the diagnosis and staging cancer-patients treatment in Australia. In fact, this imaging technique has experienced a 200 percent global growth in the last two years and CYC is committed to enhance the Australian scene by making this imaging technique equally available here. Thousands of patients in NSW could not access this diagnostic capability last year because of the FDG supply shortfall.

## BACKGROUND

PET imaging is a nuclear medicine diagnostic modality useful for imaging various major diseases inflicting society including cancer, cardiac, neurologic, nephralgic, hepatobiliary and gastroenterological disorders. Advances in the technology also provide for the prognostication and assessment of therapy for these diseases in patients.

PET imaging is based on a paradigm shift in diagnosis from the conventional structural and



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# Major boost to V/Q SPECT with Technegas

Exactly 21 years after the first publication of Technegas in the same journal foreshadowing the potential value of tomographic imaging, there is a seminal report from a Canadian group clearly demonstrating the truth of that prediction. Michel Leblanc and his team (Prospective evaluation of the negative predictive value of V/Q SPECT using <sup>99m</sup>Tc-Technegas. Leblanc M, Leveillé F, Turcotte E. Nucl Med Commun 2007, 28:667-672) have performed a detailed analysis on 584 consecutive patients. And this itself is a significant point. There was no filtering out of patients to give the best chance of a favourable result, which was measured as the outcome after at least 3 months from diagnosis. In fact the mean outcome review time was over 5 months, giving solid credibility to their claim of a negative predictive value of 98.5%.

Another important side result was that there was an extremely good inter-observer agreement (0.94-0.97) between the initial report from the attending Physician who happened to be on duty at the time of the study, and the blinded review of the first 100 cases, highlighting the objective nature of the test. There was no need for probabilities, Gestalt, or any form of numerical gymnastics to produce their figures. Importantly too,

the patients had a wide variety of clinical characteristics, as you would expect from a consecutive cohort. There was only 24% of patients with normal perfusion images, and a significant proportion of the whole study group had abnormal chest x-rays. "It is noteworthy that only one of the false negative patients had an abnormal chest x-ray. There were 134 patients with abnormal X-rays in the 'no PTE' group, 86 with major anomalies (frank effusion, consolidation, infiltrate, atelectasis). Also, many cases with an X-ray abnormality will show sub-segmental vascular mismatches away from the anomaly, helping to make the diagnosis of embolism, another advantage over planar imaging."

Camera acquisition time for the complete study was 18 minutes, a very tolerable time for such a screening test demanding little active co-operation from the patient. The authors also make the point of a lower radiation exposure for the patient compared with X-ray tomography. They conclude: "This prospective series of SPECT pulmonary scintigraphy using <sup>99m</sup>Tc-Technegas demonstrates that this technique can be safely used to rule out pulmonary thromboembolism while giving a small number of indeterminate studies".

## Abstract:

**Objective:** To verify the negative predictive value (NPV) of Pulmonary ventilation/perfusion scintigraphy with single photon emission computed tomography (V/Q SPECT) in ruling out pulmonary thromboembolism (PTE). **Methods:** V/Q SPECT using <sup>99m</sup>Tc-Technegas was performed on 584 patients to rule out PTE between October 2004 and July 2005. PTE was defined as any clear cut vascular mismatch, regardless of size. Indeterminate scans were defined as cases having matching vascular type defects with a corresponding X-ray abnormality, or cases with equivocal mismatches. Other patterns were considered negative for PTE. Outcome data was gathered > 3 months after the scan. Absence of PTE was defined as any patient still alive at least 3 months after the scan, with no anticoagulation

treatment and no proof of PTE by other techniques, either at the time of the scan or during follow up, or death by other causes. **Results:** 108 patients (19%) had a positive PTE reading, 18 (3%) an indeterminate study, and 458 (78%) patients a negative reading for PTE. There were 189 patients with an abnormal chest X-ray. The mean follow up time was 165 days. Of the 458 patients classified as negative for PTE, patients receiving chronic anticoagulation for other causes were excluded from follow up (n=53), which left 405 patients for final analysis. There were no PTE related deaths in the negative group. 6 patients were identified as false negatives. NPV is estimated at 98.5%. **Conclusion:** SPECT pulmonary scintigraphy using <sup>99m</sup>Tc-Technegas demonstrates has a high negative predictive value and a low indeterminate rate.



Bill Burch has retained an Honorary Visiting Fellowship at the John Curtin School of Medical Research within Australian National University since 1976.

His background includes stints in Antarctica in geophysics, radiotherapy, and nuclear medicine in Melbourne, the U.K. and Canberra where from 1976 to 1984 he began his quest to find good ventilation agent. He "stumbled" upon Technegas and has been its champion ever since.

# Diagnosing Pulmonary Embolus

Douglas Howarth FRACP

## Background.

Pulmonary embolus (PE) has always been an anathema with regard to clinical diagnosis. PE cannot be reliably diagnosed at the bedside. Regardless of any particular physician's clinical skill, PE will often be misdiagnosed without the aid of imaging investigations. Basic tests such as chest x-ray, arterial blood gases and electrocardiography are also of limited diagnostic use in this setting other than helping to establish an alternative diagnosis to PE. For many years pulmonary angiography was regarded as the "gold standard" for the diagnosis of PE, despite a glaring lack of outcome data to support this claim. This invasive test has been progressively replaced over the past 35 years with ventilation/perfusion scintigraphy (V/Q scan). The V/Q scan relies on demonstrating a difference in radiotracer distribution in the lungs of the ventilation (V) and perfusion (Q) phases. So-called V/Q mismatch is where perfusion is significantly less than ventilation. This is diagnostic of PE. Controversy has, however, been associated with the optimal diagnostic criterion to determine what represents significant V/Q mismatch. Controversy has also existed with regard to the best ventilation agent, as several are readily available for widespread use, but some may be cost prohibitive and others have physical limitations potentially reducing diagnostic utility. More recently, technical advances in computed tomography (CT) have allowed this modality to be used for the diagnosis of PE with some success. Non-imaging techniques measuring activation of thrombolytic pathways in blood specimens have also been refined over the past 10 years and have been used to help exclude the diagnosis of PE.

## Commonly Used Diagnostic Modalities.

**1. Pulmonary angiography.** This fluoroscopic guided test is usually only available in larger hospitals and in some settings is not available after hours for emergency diagnosis. It requires a skilled specialist to both administer radio-contrast via a percutaneous catheter into the pulmonary arteries, and to interpret the radiographic images. This test has a 1% major complication rate due to its invasive nature and use of high dose radio-contrast (1). Its true diagnostic accuracy is unknown due to a paucity of non-negative angiogram outcome study data. However, it is purported to have a diagnostic accuracy of >95% (2).

**2. Computed tomography pulmonary angiography (CTPA).** This test has evolved following use of continuous rotating CT x-ray tubes and more recently, improved multi-detector technology that allow rapid imaging of the lungs during breath hold. The test requires a well-timed bolus of intravenous radio-contrast, and an experienced reporter to distinguish what represents true "defect" from partial-volume artifact. The test is limited for use in those patients who can comply with the breath hold and are cooperative within a CT tunnel. Those patients with known radio-contrast allergy, known iodine allergy and those with moderately-severe to severe renal impairment are excluded from testing. This test, like pulmonary angiography delivers a relatively high radiation dose to critical regions such as breast tissue. Although published outcome data indicates that when performed at the highest standards, this test has a high negative predictive value that is the equivalent to that of pulmonary angiography, its true diagnostic sensitivity has not been adequately established (3).

**3. D-Dimer Test.** This test has been available for many years but the use of more advanced bedside latex agglutination tests have resulted in a rapid test of high sensitivity, similar to that of the enzyme-linked immunosorbent assays (ELISA). Like the more time consuming

ELISA test, these tests have a high false positive rate and relatively low false negative rate. Consequently, the most modern rapid latex agglutination tests are of most use in excluding activation of the thrombolytic biochemical pathways in patients regarded as being of low pre-test risk of PE (4). These tests do not, however, have a 100% negative predictive value. Consequently, when used in isolation, the test is of relatively limited clinical utility. Its role is in combination with a clinical scoring test or other imaging.

**4. Simplified Wells Scoring System.** This system is designed for risk stratification in order to assign pre-test probability (low, intermediate or high) for PE (5). It incorporates the use of the D-dimer test, bedside investigations, clinical features and risk factor assessment. The basis of this scoring system in itself is sound enough, but its use is based upon a premise that V/Q scanning is a markedly imperfect test. The authors did not specify how V/Q imaging was performed but it is likely that less than optimal ventilation agents were used in some, if not all of the 4 participating Canadian centres. They used a positive diagnostic criterion of >1-1.5 segment of V/Q mismatch and found more than 47% of scans were classified indeterminate. Had they used the appropriate diagnostic cut-off point (>0.5 segment V/Q mismatch) the V/Q scan's true diagnostic utility would have been apparent. Although this scoring system was originally intended to reduce the use of investigations for PE, the true value of this method, and other similar scoring systems, lies in the assessment of likelihood ratios following a diagnostic imaging test such as V/Q lung scintigraphy. The role of this scoring system, and its heavy reliance on the rapid D-dimer test in excluding PE at the bedside, remains unproven.

**5. V/Q lung scintigraphy.** As a consequence of 2 important factors, this test has been undervalued as the imaging diagnostic test of choice for PE: (i) a major source of published medical data pertaining to V/Q imaging has come from the USA, or been unduly influenced by other data derived from the USA, (ii) V/Q imaging quality in the USA is largely inferior to that in Australia, Europe, other regions of North America and an increasing number of Asian countries due to the widespread use of inferior ventilation imaging agents. With the use of good quality ventilation agents such as Technegas, Krypton-81m or, in selected patients, appropriately administered nebulized Tc-99m diethylene triamine penta-acetic acid (DTPA) particles, V/Q lung scintigraphy has a very high diagnostic accuracy for PE. SPECT imaging using Technegas ventilation/perfusion has also been shown to enhance the diagnostic ability of this test (6). However, with a diagnostic accuracy of 97% for standard planar imaging, there is little room for improved accuracy (7). The key to understanding the true diagnostic accuracy of this test lies in the use of an appropriate diagnostic criterion. A simple and proven criterion uses  $\geq 0.5$  segments or total equivalents of V/Q mismatch as diagnostic for PE and  $< 0.5$  segments as negative (7). Using this criterion <5%, and more likely, only about 1% of studies are indeterminate.

## Recommendations.

Many very elaborate diagnostic algorithms have been proposed for the diagnosis of PE. Generally, the more complicated the algorithm, the greater the uncertainty expressed in all the currently available diagnostic tools. Although no one test is always correct, on occasion a test is falsely vilified due to either the test being incorrectly performed or incorrectly interpreted. Both of these have occurred in the case of V/Q lung scintigraphy. V/Q lung scintigraphy has been around a long

## Diagnosing Pulmonary Embolus (continued)

Douglas Howarth FRACP

time, and has not been replaced because of an inherent understanding of the value of the test, despite widespread use of inappropriate ventilation agents and inappropriate diagnostic criterion. Used correctly it has the potential to offer a diagnostic accuracy of around 97% in more than 95% of cases.

For a systematic and reliable approach for the diagnosis of PE the clinician should use the simplified Wells score system, or its equivalent, to determine the pre-test risk/probability for PE. Those patients in a low probability group should also have a negative d-dimer test and can then be investigated for another diagnosis. Those in the intermediate

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and high probability groups should undergo V/Q lung scintigraphy using a reliable ventilation agent such as Technegas. Where using a criterion of  $\geq 0.5$  segment of V/Q mismatch as diagnostic, a definite diagnosis will be established in all but the small minority of cases. In the rare case of a non-diagnostic V/Q scan, where appropriate, the patient can undergo CTPA to help exclude PE or seek another diagnosis. It should be remembered that a false positive diagnosis for PE is just as life-threatening as a false negative test result. Outcome data confirms a high risk of bleeding complication in patients receiving anticoagulation therapy (8).

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## New report into the carcinogenic consequences of radiation from CT imaging

Radiation exposure to patients from CT procedures has been of relatively low level interest within the medical community, as it is generally presumed that those ordering the tests make informed risk-benefit judgements. But a review just published in the prestigious *New England Journal of Medicine*, should shake any complacency among referring clinicians to its core.

The review, written by two of the world's most eminent Radiobiologists, David Brenner and Eric Hall and titled "Computed Tomography — An Increasing Source of Radiation Exposure"\* presented hard data links between the kinds of exposure common in modern CT to the long term documented cancer incidences from A-bomb survivors and a recent large-scale study of 400,000 radiation workers in the nuclear industry. The latter were exposed to an average dose of approximately 20 mSv (a typical organ dose from a single CT scan for an adult).

The review focused mostly on doses to children, where the major growth area in CT use has been 'pre-surgical diagnosis of appendicitis, for which CT appears to be both accurate and cost-effective — though arguably no more so than ultrasonography in most cases. Estimates of the proportion of CT studies that are currently performed in children range between 6% and 11%.' The review goes on to state 'A large part of the projected increase in CT scanning for adults will probably come from new CT-based screening programs for asymptomatic patients. The four areas attracting the most interest are CT colonography (virtual colonoscopy), CT lung screening for current and former smokers, CT cardiac screening, and CT whole body screening', citing references for each of these points. Although not stated explicitly, it may well be the use of CT for PE diagnosis, particularly in the USA where V/Q plays such a minor role, is built in

to the 'screening' figures for the lung.

One of the most significant points made in relation to cancer risks in the review, again backed up from the bibliography was 'The organ doses for a typical CT study involving two or three scans are in the range in which there is direct evidence of a statistically significant increase in the risk of cancer, and the corresponding CT-related risks can thus be directly assessed from epidemiologic data, without the need to extrapolate measured risks to lower doses. [from that], 0.4% of all cancers in the United States may be attributable to the radiation from CT studies. By adjusting this estimate for current CT use, this estimate [of future cancers] might now be in the range of 1.5 to 2.0%'.  
Although the review did not mention the ALARA principle specifically in its discussion, it referred directly to the need for the best possible and most appropriate technology to be used for each patient's diagnosis. It concluded with an unequivocal rather chilling point: '...the most effective way to reduce the population dose from CT is simply to decrease the number of CT studies that are prescribed. From an individual standpoint, when a CT scan is justified by medical need, the associated risk is small relative to the diagnostic information obtained. However, if it is true that about one third of all CT scans are not justified by medical need, and it appears to be likely, perhaps 20 million adults and, crucially, more than 1 million children per year in the United States are being irradiated unnecessarily'.

Bill Burch  
\* Ref - The New England Journal Of Medicine, Volume 357: 2277-2284, Nov 29, 2007, No 22.

## Introduction (continued)

Professor Nabil Morcos, Cyclopharm Chief Operating Officer and Director of Science.

Cyclopharm will make available its facilities and scientific capabilities to researchers and collaborate in the investigational studies to evaluate new moieties for PET imaging during off-production hours. This will attract the collaboration of an elite group of researchers, foster discovery and publications, and lead to the commercialization of specific disease targeting new products.

Carbon-11 has a half-life of 20.3 minutes. That is, half of the produced radioactivity disappears every 20.3 minutes (1/2 after 20.3 minutes, 1/4 after 40.6 minutes etc...). Its production, incorporation into the moieties under investigation, its injection into patients, and image acquisition must be accomplished within no more than 2 to 3 half lives to obtain useful biodistribution data. This crucial restriction requires that the production center must be within close proximity to the PET imaging facilities and preferably within a hospital setting.

### CONCLUSION

By incorporating PET imaging facilities with a cyclotron, researchers and physicians can extract maximum benefit from this technology which has enormous immediate and future applications.

By partnering with MUPH, the Hospital and Macquarie University will create a synergistic alliance to provide world leading infrastructure and

facilities to the Molecular Imaging community and be in a position to undertake "best practice" oncology. This synergistic association will attract the collaboration of an elite group of researchers, foster discovery and publications, and lead to the commercialization of specific disease targeting new products and ultimately enhance the quality of health care in NSW. In addition, the commercialization of this essential supply of PET radioisotopes and targeting molecules will stimulate employment in the commercial sector, enhance technical and scientific employment, and remove the need for the government to pay for the infrastructure required to make this medically essential commodity available.

Consequently, Cyclopharm is recruiting potential sites to establish its initial FDG production centers so that they are co-located within or in close proximity to teaching hospitals.

We look forward to sharing our vision with you.

Sincerely,

Professor Nabil Morcos,

# Introduction (continued)

Professor Nabil Morcos, Cyclopharm Chief Operating Officer and Director of Science.

anatomic assessment to evaluation of the metabolic activity of cells and tissues and thus differentiates between healthy and disease state of organs and organisms. This new paradigm in identifying disease provides the clinician with a powerful and more accurate capability to diagnose the condition of patients, stage the approach and progress of therapeutic regimes, and has provided a powerful cross-link between the diagnosticians and oncologists with respect to cancer diagnosis, patient staging and assessment of therapy course for a large number of cancer patients.

PET imaging represents the amalgamation of key scientific fields including biology, cellular and molecular biology, physics, electronics and chemistry. The latest advances in cellular and molecular biology have enabled scientists to identify chemical entities and molecules that uniquely target specific biological functions that differentiate between healthy and disease states by honing in on their targets and concentrating therein. Chemistry has enabled the manufacture of these molecules, and provided the capability of attaching specific radioisotopes to these molecules. These attached radioisotopes allow tracking of the fate of the radiolabeled molecules in the body and identifying the location and extent of diseased tissue. Physics has provided the knowledge to produce the radioisotopes, and together with electronic advances have enabled the development and production of the imaging systems used to visualize the distribution of the radiolabeled targeting molecules in the body.

The current major market application for PET is in the diagnosis and staging of cancer patients. In particular, lung, colon, breast, cervical, prostate, head and neck, lymphoma, melanoma, and oesophageal cancers are the prime targets. The primary targeting radiopharmaceutical currently used is a radiolabeled glucose called Fluoro-Deoxy Glucose (FDG) and the attached radiolabel is Fluorine-18. There were approximately 1.8 million PET procedures performed in the USA in 2005 with an expected 31% growth in 2006 and a total of 4.4 million anticipated by 2012. Although the dominant focus of PET is still in oncology, applications in cardiology are increasing, particularly rubidium PET studies for myocardial perfusion. FDG sales in the USA were \$259 million in 2005, will increase 31% in 2006 to \$340 million, and reach \$933 million by 2012. These estimates are conservative and are based on present utilization. It is likely that new indications in oncology and cardiology as well as neurology will add further stimulus to the market for PET and FDG.

Although the Australian and Pacific Basin markets are different from the USA market, a relative scale is expected to ensue and Cyclopharm expects to be positioned in a leadership position while anticipating this projected growth. CYC's plan is to commercially provide FDG to the area by establishing centralized radiopharmacies for its production. Consequently, our FDG production centres will include: a Cyclotron, a GMP-compliant production facility, a quality control/quality assurance laboratory for product release and a product distribution network.

The Cyclotron is an electric/electronic device used to manufacture the radiolabel – Fluorine-18. This is achieved by introducing into the device hydrogen atoms that are then accelerated to very high velocity using very high frequency (Radio Frequency) electrical fields along an increasing circular path in a very high vacuum. The accelerated hydrogen atoms

are then extracted from the device and made to impinge on a special target of Oxygen to produce the Fluorine-18. The device itself is non-radioactive and does not produce any Fluorine-18 when switched off but must be shielded properly during production. Placing the device within a concrete enclosure usually provides sufficient shielding to protect the operator.

The Fluorine-18 is then transported to the GMP-compliant production laboratory where it is incorporated into the Deoxy Glucose molecule to make FDG. The finished product is assessed for quality and sterility in the quality control laboratory prior to shipment to the end user.

## STRATEGY FOR THE FUTURE

New PET radiopharmaceuticals and molecular targeting agents that will measure biochemical processes to assess patient response to therapy by measuring cellular response to therapy rather than metabolism are under investigation and in the pipeline. This will aid in treatment monitoring and therapy planning for breast cancer, prostate cancer, brain cancer, bone cancer, and other common cancers. Furthermore, as the availability of PET increases and its capabilities become more visible to referring physicians, it will encourage procedure growth in oncology as well as cardiology and neurology.

Cyclopharm intends to provide the forum and environment for a center of excellence in PET imaging in Australia. Carbon-11 is the PET radioisotope of choice to evaluate targeting molecular entities. It is a radioisotope that is chemically identical to components of biologically active molecules under evaluation as targeting agents. Its production and incorporation into new PET molecules will provide products in the future. It is already widely used by research scientists and clinicians to evaluate the biodistribution of these new targeting agents.

Agent	Images
F-18 fluorodeoxyglucose	Regional glucose metabolism
F-18-fluorodeoxythymidine	Tumor cell proliferation
18-F-fluoro-L-tyrosine	Tumor protein synthesis
18-F-fluoro-DOPA	Neuroendocrine tumors
18-F-fluoromisonidazole	Tumor hypoxia
F-18 sodium fluoride	Bone tumors
C-11 methionine	Amino acid uptake/protein synthesis
C-11 choline	Cell membrane proliferation
C-11 deoxyglucose	Regional brain metabolism
C-11 carbon monoxide	Cerebral blood volume
C-11 butanol	Cerebral blood flow
C-11 N-methylspiperone	Dopamine D2 and Serotonin S2 receptors
F-18 N-methylspiperone	D2 and S2 receptors
C-11 raclopride	D2 receptors
F-18 spiperone	D2 receptors
Br-76 bromospiperone	D2 receptors
C-11 carfentanil	Opiate mu receptors
C-11 flumazenil	Benzodiazepine (GABA) receptors

# A seminal report brings new objectivity to PE diagnosis

The ease with which SPECT V/Q can now be performed has at least brought basic image presentation and interpretation for the diagnosis of Pulmonary Embolism (PE) up to an overall par with CTPA from our Radiology colleagues. A by-product has been images easier to share with the referring Physician in difficult cases. But a potentially high number of non-diagnostic patients remain, especially where adherence to long-established, and many would argue inappropriate, probability criteria such as PLOPED is continued.

It is initially somewhat disconcerting then for anyone steeped in Nuclear Medicine to find a significant new paper on V/Q SPECT for PE with only one black and white image of an obvious mismatch – and that purely to illustrate the visual presentation of the data set!

Harris and his colleagues (“Objective analysis of tomographic ventilation-perfusion scintigraphy in pulmonary embolism.” Harris B, Bailey D, Miles S et al. Am J Respir Crit Care Med 2007; 175: 1173-1180) have worked from the physiological principles behind PE as it affects individual functional lung units to derive a mathematical entity “weighted median V/Q value” for the whole lung. They find a clear separation between PE and non PE patients measured against independent consensus review from three experienced Physicians using a battery of clinical and imaging tests, and/or 3 months outcome, for each patient.

The primary goal of the paper was to develop a technique for objectively analyzing V/Q tests for PE using only computer derived numeric analysis, but by no means intending to replace Physician interpretation. One of the obvious questions therefore becomes, with experienced Physician input, can an already impressive diagnostic accuracy be further improved? Only further experience and refinement of the technique will answer that. But even as it now stands, it offers additional input to help resolve indeterminate cases.

Two cohorts of patients were established. A retrospective review of 73 to set up the model, and a prospective group of 50 against which to test it. In the latter cohort, 19 of 26 patients with low or intermediate PLOPED scores had valid weighted median values that led to 100% accurate diagnosis. Whereas in the former, retrospective cohort, 39 of 49 patients with these equivocal PLOPED scores had weighted median values that led to a final accuracy of 90%.

For all this encouraging data, it is nonetheless an issue that 15 of the 73 patients in the first, and 15 of 50 in the second group returned non-diagnostic weighted median values, ie the numbers fell into the zone between the two pre-defined diagnostic bands (+ or – for PE). Now it is clear from the demographics of both cohorts that there was considerable mixed lung pathology other than potential PE present. It would therefore be very instructive to see if these non-diagnostic analyses correlate either with specific diseases or degree of disease in order to refine how and where this numeric technique should be applied.

V/Q Scintigraphy for PE has come a long way in the past 30 years from planar defect identification in a highly heterogenous moving organ to SPECT co-registered, normalized and subtracted (“Quotient”) displays of ‘quasi’ hot spot mismatches. The challenge, partially met in this paper, is to find the threshold for an unequivocal diagnosis. It may well be that numerical analysis might be able to be confined to a suspicious region to enhance its sensitivity. It is not made clear in the paper, for example, whether the single case of PE identified clinically against a “normal” V/Q report was picked up by the weighted median value in this patient. Again, to what extent do the not uncommon emboli, shattered into multiple small fragments by their passage through the heart, and mostly registered as tiny ‘nibbles’ out in the lung periphery, register in this analysis?

For this new, and potentially valuable technique to become part of an essential PE diagnostic screen, it will first have to show at least an equivalence with the best imaging practice, then an ability to reduce the doubt in the remaining few indeterminate cases that currently are referred on to other tests. Then, V/Q with Technegas may fully return to its logical place as the screening test of choice for Pulmonary Embolism.