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SPECT Ventilation Imaging in Asthma

Catherine Farrow, PhD, BSpSc, CRFS,^{*†} and Gregory King, MBChB, FRACP, PhD^{*‡}

Uneven distribution of ventilation, or ventilation heterogeneity, has been observed in asthma for over 60 years using multiple breath nitrogen washout (MBNW) studies. Ventilation heterogeneity has been known to predict airway hyperresponsiveness (the ability of the airways to constrict too easily and by too much) in asthma, which is a core physiological characteristic of this disease. SPECT ventilation imaging allows topographical analysis of changes in ventilation distribution. Technegas as a SPECT ventilation agent has a key advantage as it remains fixed after inhalation, which allows imaging of upright ventilation distribution, analogous of pulmonary function tests. Recent studies using Technegas ventilation SPECT have shown spatial imaging markers also relate to airway hyperresponsiveness in asthma, and are predicted by a MBNW index of peripheral ventilation heterogeneity. It has also been shown that low-ventilation regions induced by bronchoconstriction were also related to peripheral ventilation heterogeneity. Furthermore, this suggests that the function of peripheral airways may determine the topographical pattern of airway narrowing with a more widespread distribution of narrowing. SPECT ventilation adds spatial characterisation information and it should be included in research protocols to enhance the understanding of complex physiological mechanisms in asthma.

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Why do we need SPECT ventilation imaging in asthma?

Asthma is a condition of unknown cause and incompletely understood pathophysiology. It is the commonest chronic illness of childhood and affects 5-10% of adults in western countries. It has been suggested that asthma is not a single disease entity but a collection of different diseases, manifest as intermittent airway narrowing that may be triggered by environmental stimuli, which causes typical respiratory symptoms. It is associated with inflammation, which is variable in type and severity; changes in the structure of the airway walls and lung parenchyma (called remodelling); and a characteristic physiologic abnormality – airway hyper-responsiveness (airways which narrow too easily and by too much) (1). Whether ‘asthma’ as a diagnostic

label will change or disappear by defining “the group of conditions” that is asthma,; or asthma is broken down into different subtypes (phenotypes or endotypes), the route to achieving this is to better characterise the lungs’ behaviour physiologically in individuals with asthma. It is in this domain that SPECT (single photon emission computed tomography) of the airways can provide unique information.

The lack of physiological characterisation of asthma is obvious, in contrast to the impressive body of cellular and inflammatory mechanistic work. It may be that the reliance placed on spirometry in asthma studies had led to the belief that the forced expiratory volume in one second (FEV1) is all that is needed to measure what is going on in asthmatic lungs. Drug registration studies always include response in FEV1, as is mandated by the US FDA, which reinforces the importance of the FEV1, which undoubtedly is a vitally important indicator ventilator impairment in asthma (2). However, the FEV1 being a global and a maximal forced expiratory manoeuvre cannot describe the complex nature and variations of physiologic abnormalities in asthma. Functional tests such as inert gas washouts and forced oscillatory impedance have allowed investigators to probe the lungs of asthmatic individuals, using a variety of innovative testing protocols to extract physiologic information that is relevant to disease mechanisms and behaviour. For example, the heterogeneity of ventilation in asthmatic

*Airway Imaging and Physiology Group, The Woolcock Institute of Medical Research, Glebe NSW 2037.

†Northern Clinical School, Faculty of Medicine & Health, University of Sydney NSW 2006.

‡Department of Respiratory Medicine, Royal North Shore Hospital, Pacific Highway, St Leonards NSW 2065.

Address reprint requests to Catherine Farrow PhD Respiratory Investigation Unit Royal North Shore Hospital St Leonards NSW 2065. E-mail: catherine.farrow@sydney.edu.au

lungs that is measured by inert gas washout studies, is strongly related to airway hyperresponsiveness (3, 4), clinical symptoms (5) and medication requirement (6). But none of these measures provides *regional* information, as SPECT can.

The evolution of SPECT Imaging of asthma

Ventilation distribution has been shown to be markedly heterogeneous and, in some instances, absent in asthmatics using imaging for many decades. It was seen with planar scintigraphy of inhaled ^{133}Xe in 1970 (2, 7) and in 1986 ventilation in asthmatic lungs was imaged 3-dimensionally using Single Photon Emission Computed Tomography (SPECT) using $^{81\text{m}}\text{Kr}$ (8). The half-life of $^{81\text{m}}\text{Kr}$ being 13 seconds meant that SPECT data could be acquired after the distribution of radioactivity reached steady state, with the regional activity reflecting regional ventilation. Inhaled gas radionuclides with longer half-lives would be unsuitable for measuring ventilation distribution as, during a SPECT acquisition, slowly ventilating spaces would continue to accumulate the radiotracer slowly, after faster ventilating spaces had reached steady-state. True steady-state would be reached at some point in time, after which regional concentrations in all regions would be equal, whereas for shorter half-life radionuclides, regional differences in radioactivity concentration would remain since the inflow of fresh radiotracer would be balanced by disappearance (outflow) but at a lower level of radioactivity. In the early study by Orphanidou *et al*, the gravitational gradient of ventilation was reversed in three asthmatic subjects. Areas of totally absent ventilation, presumably due to airway closure or mucous plugging, were seen in their figure but not commented on (8).

Short half-life, inert gas radionuclides allow SPECT acquisitions. The radiotracer has to be administered continuously during SPECT acquisition and so is representative of ventilation distributions in supine, prone or decubitus positions. This may have severely limited its use in research studies. Technegas, in contrast, is an ultra-fine, carbon particle aerosol labelled with $^{99\text{m}}\text{Tc}$ that was invented in Australia and first described in the literature in 1986 (9). The role of Technegas was to deliver $^{99\text{m}}\text{Tc}$ to the lungs in one or more inhalations, for ventilation scans, done in conjunction with perfusion scans for investigation of suspected pulmonary embolism (PE). At that time, ventilation/perfusion scans were performed using planar acquisitions. In 1997, Technegas was used to image the pattern of ventilation in asthma using SPECT (10) in healthy subjects by delivering a small-volume bolus from low lung volume, at which airways were closed. The strong correlation with airway closure measured using 'traditional' lung function (single breath nitrogen washout), suggested that timed delivery with control of pre-inhalation lung volumes and simple measurements from the SPECT images was a valid method of measuring ventilated (and non-ventilated) lung volumes. Furthermore, since Technegas appeared to be "fixed" to the airways and alveoli after inhalation and remained static for at least 20 minutes (11), the

distribution of Technegas, which could represent ventilation in the upright posture during inhalation, could be measured, albeit with some distortion from regional lung changes, when positioned supine for the SPECT scan.

The pattern of ventilation in asthmatic subjects measured using Technegas SPECT imaging showed that the gravitational gradient of ventilation was altered with diversion of ventilation to non-dependent (apical lung) regions compared with non-asthmatic subjects. This was consistent with the findings from studies in 1970 (2, 7). Small peripheral regions of non-ventilation were described and these regions occurred predominantly in the lung bases, presumably where airway closure is mostly likely to occur because elastic recoil pressure is lower in dependent zones.

What are the technical characteristics of Technegas SPECT ventilation imaging — what are we imaging?

Imaging using Technegas SPECT has the unique ability to examine functional ventilation distribution which reflects airways that communicate with the oral cavity. Other functional imaging modalities are limited as they are only able to observe indirect and/or supine-only ventilation (PET with radioactive gases and MRI) (12, 13). Nitrogen-13 PET gives an overview of the function of ventilation and perfusion as the radiotracer is injected intravenously ($^{13}\text{N}]\text{N}_2$ in saline) and then must perfuse in the lungs before being removed or "washed-out" by ventilation. The remaining radiotracer in so-called "hot zones" represent perfused but unventilated areas of lung (14). Due to the high flow rate of pulmonary perfusion the injection must be performed during a breath-hold manoeuvre whilst the subject is supine in the scanner, resulting in a reflection of supine perfusion and ventilation. This technique has also been used to develop sophisticated lung models providing experimental evidence that bronchoconstriction leads to patchiness in lung ventilation (15). Similarly, MRI using hyperpolarised helium-3 (HP ^3He) must also be performed whilst the subject performs a breath-hold, supine in the scanner, as the images are recorded immediately after inhalation of the gas (16). The HP ^3He is exhaled immediately, and due to scarcity of this resource, must be carefully collected for reuse. The ability to breath-hold whilst supine is key for these functional PET and MRI techniques to work, and this would preclude sicker patients from being involved, potentially limiting the range of disease that could be studied.

The advantage of using [$^{99\text{m}}\text{Tc}$]Technegas is that it can be administered in the upright position, as the subject is not required to be lying in the scanner during inhalation¹, unlike MRI and PET. Furthermore, due to the properties of Technegas, the images can be captured supine with the Technegas remaining in the deposition pattern when it was inhaled

¹For more information of lung function in supine vs upright positions, see accompanying article by Bailey *et al* in this same issue of the journal.

upright (11). As it is an inhaled radiotracer, it gives a true representation of ventilation via airways that communicate with the nasopharyngeal space (*i.e.*, the images represent how an individual actually ventilates during normal upright breathing). Finally, when Technegas is inhaled it remains where it deposits in the lungs and it is not moved by mucociliary clearance. The 6 hour half-life of ^{99m}Tc allows for a delay between inhalation and imaging, and does not require the subject to be inside the scanner for inhalation. These advantages have allowed the asthmatic lung to be studied before and after induced bronchoconstriction and compared with lung function which is performed upright.

The aerodynamic properties of Technegas are such that it is a fine particle aerosol, and not a true gas, and so there may be differences in the distribution properties of Technegas versus a gas. However, to date, Technegas ventilation imaging has reported valid distribution patterns that match volumes measured by traditional lung function (17). “Hot spots”, which result from impaction of particles at turbulent flow areas in the airways and not true ventilation, are a limitation to ventilation imaging using Technegas. Turbulent flow areas are seen in ventilation images of subjects with airways disease. Whilst this may pose a challenge for interpreting these images, there may also be a physiological significance to the hot spots that could be used in analysis. Alternatively, the hotspots could be accounted for in the analysis, or neutralised by exclusion, so that they do not bias the analysis (17, 18).

What are the recent findings from ventilation SPECT studies of asthma?

Recently, ventilation SPECT (V-SPECT) has been used to examine ventilation distribution in asthma at baseline and after induced bronchoconstriction compared with traditional lung function and inert gas washout. Whilst it has been known for many years that asthma causes heterogeneous ventilation distribution (10), this is the first attempt to quantify these ventilation changes using V-SPECT and compare them with other physiological measures.

A study of asthmatic subjects found that the extent of airway closure induced by methacholine challenge was related to the severity of ventilation heterogeneity at baseline (17). Furthermore, the subjects with more severe airway hyperresponsiveness (AHR) had the greatest volume of airway closure, despite a similar level of bronchoconstriction to those subjects with mild or no AHR. Additionally, there was greater loss of ventilation in the lower third of the lung but its distribution, in relation to middle third or lower third predominance, was not associated with AHR, ventilation heterogeneity or asthma severity. The significant relationship demonstrated between induced airway closure measured by V-SPECT/CT and AHR extends the observations of Chapman *et al* (19) who saw a reduction in forced vital capacity (FVC) which was related to AHR. Known associations between airway closure and severe asthma (20, 21) are also supported

by this topographical observation. Importantly, the correlation between airway closure on V-SPECT and conductive airway heterogeneity (ventilation heterogeneity in convection-dependent airways – “Scond”) measured by multiple breath nitrogen washout (MBNW) suggests that peripheral airways dysfunction may predispose to severe airway narrowing and closure during bronchoconstriction. Notably in this study all subjects had the same decrease in lung function with methacholine (MCh) challenge (20% fall in FEV1 from baseline), yet there was a variable airway closure response. Therefore this airway closure can be explained by small airways that are more sensitive and reactive compared those that do not exhibit airway closure.

Another recent study using ventilation SPECT/CT imaging examined low-ventilation lung regions and showed that regional ventilation was reduced by bronchoconstriction, and that the magnitude of the reduction in ventilation was predicted by peripheral acinar airway heterogeneity (ventilation heterogeneity in diffusion-dependent airways - “Sacin”) measured by multiple breath nitrogen washout (18). The increase in these low-ventilation lung regions varied greatly between subjects despite similar changes in FEV1, and was also related to the loss of total ventilation, thus greater airway narrowing was associated with greater airway closure. The increase in low-ventilation was not related to baseline spirometry, respiratory impedance, airway hyperresponsiveness or baseline V-SPECT ventilation distribution. This suggests that the function of peripheral, diffusion dependent airways as measured by MBNW, may determine the topographical pattern of airway narrowing with a more widespread distribution of narrowing.

A small study of healthy subjects has also shown the development of large areas of airway closure after induced bronchoconstriction (22), as seen in Figure 1. This correlated with the magnitude of reduction in FEV1 that is induced by methacholine, but was not predicted by baseline ventilation heterogeneity measured by MBNW. Whilst this study contains small numbers, it provides evidence that the normal lung has the ability to produce a response similar to what has been observed in an asthmatic lung (17, 18), albeit using a much larger amount of agonist. Furthermore, there are little data in this area as healthy controls are rarely challenged with methacholine. A study by Harris *et al* using PET [^{13}N]N₂ has demonstrated defects in healthy controls after methacholine challenge, but this study did not measure the volume of the defects or compare the results with complex lung function (23). Investigation of healthy normal subjects adds to the utility of SPECT imaging in investigating mechanisms of disease.

How have SPECT data contributed to understanding asthma?

The patchy areas of absent ventilation, which are arranged differently to that in non-asthmatic subjects, and which has been reproduced in many different studies since using hyperpolarised ^3He MRI (13, 24-26) and ^{13}N PET (14), suggest that

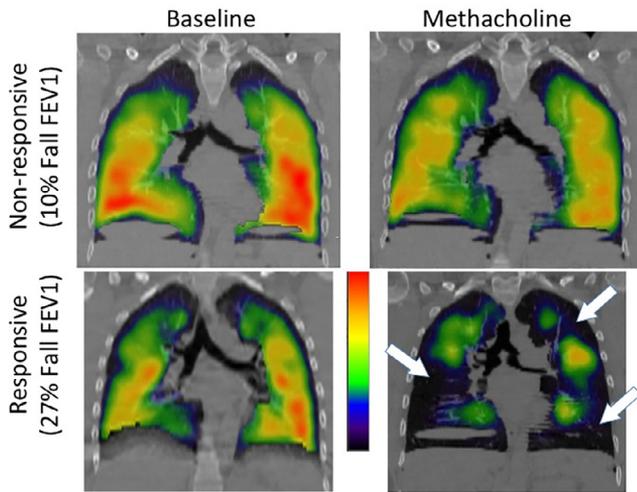


Figure 1 Response to methacholine challenge in healthy normal lungs related to the induced fall in FEV1. Non-responsive subject (10% fall FEV1) vs Responsive subject (27% fall FEV1) imaged at baseline and after challenge, shows clear unventilated areas in the responsive subject after challenge (lower right).

disease causes airway closure and that disease related changes in airway structure that cause this closure are distributed heterogeneously. When bronchoconstriction is induced, for example by a cholinergic agonist, more areas of closure occur. This observation raises the possibility that asthma is 'regional' in nature *i.e.*, that disease is driven by localised regions of responsive airways. Successful treatment of these regions rendering them less responsive, might lead to clinical improvement. Furthermore, severe asthma, as defined by treatment resistance to inhaled corticosteroid / long acting beta-agonist, could be overcome if these regions could be effectively treated.

Ventilation in asthmatic lungs has been shown to be more heterogeneous, at the voxel-length scale, in ^3He MRI (27). That is, ventilation between voxels is more variable in asthma. This analysis could be conducted with SPECT image data as well as other forms of spatial image analysis. The physiologic and clinical significances of ventilation distributions in asthma have never been explored but may prove to be important.

The fact that ventilation heterogeneity measured by nitrogen washout predicts both airway narrowing and airway closure during bronchoconstriction is suggestive that airway behaviour observed in SPECT ventilation scans is probably clinically significant. This is due to the known correlation between nitrogen washout parameters and important clinical indices such as asthma control and treatment requirements (5, 6).

Future use of SPECT ventilation imaging in asthma

It is clear that SPECT has great potential for providing important research information in asthma. SPECT imaging is widely available, relatively low-cost and usually combined with CT imaging, which has many advantages for processing and quantification. $^{99\text{m}}$ -technetium Technegas as the

ventilation agent allows SPECT to be used in a unique way to study asthma. Clinical areas that require urgent study in which SPECT could be applied include: mechanistic studies in severe asthma; determination of what happens when patients improve or are resistant to inhaled-corticosteroid/long-acting beta agonist (ICS/LABA) treatment; characterising asthma/chronic obstructive disease overlap. If newer treatments are to be developed, *i.e.*, going beyond ICS/LABA as standard treatment, there will be a need to measure lung function better, *i.e.*, more than FEV1 and, arguably, ventilation SPECT and other forms of ventilation imaging are a unique way of measuring regional function that complements other complex tests.

In the clinic there are still many clinical challenges. Determining future risk of increasing severity, risk of exacerbations when treatment is decreased or used intermittently, risk of lung function decline, and better characterising function in elderly or obese individuals where disease expression differs can be improved. SPECT ventilation imaging may be regarded as another lung function test that will complement global tests such as inert gas washout and oscillatory impedance measurements and mechanical measurements that will be applied to better characterise a complex condition where, at present, medical assessment simply uses a few symptoms and occasional FEV1 to make an assessment and decisions on treatments.

Conclusions

SPECT ventilation imaging in the asthmatic patient provides regional information about the airways of the lung which has been demonstrated to complement conventional pulmonary function testing. One decided advantage when using a ventilation agent such as Technegas is that the radiotracer remains fixed after inhalation and can therefore be administered in the same upright posture as conventional pulmonary tests are performed in and imaged supine. It is widely available and, apart from the minute risks associated with exposure to low doses of ionising radiation, is readily performed in most tertiary referral environments. It should be considered when designing research protocols for asthma to understand the spatial characterisation of the condition, as well as potentially having a future role clinically in monitoring response to new therapies.

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