Measurement of Perfusion in Stage IIIA-N2 Non-Small Cell Lung Cancer Using $\text{H}_2^{15}\text{O}$ and Positron Emission Tomography

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ABSTRACT

Purpose: As the interest in antiangiogenesis therapy in oncology is rising, the need for in vivo techniques to monitor such therapy is obvious. Measurement of tumor perfusion using positron emission tomography and $\text{H}_2^{15}\text{O}$ potentially is such a technique. The objective of the present study was to assess whether it is feasible to measure perfusion in vivo in non-small cell lung cancer (NSCLC) using $\text{H}_2^{15}\text{O}$ and positron emission tomography.

Experimental Design: Fifteen dynamic $\text{H}_2^{15}\text{O}$ and $[^{18}\text{F}]\text{2-fluoro-2-deoxy-D-glucose}$ ($^{18}\text{FDG}$) studies were performed in 10 patients with stage IIIA-N2 NSCLC. Blood flow (BF) data were correlated with simplified methods of analysis (tumor:normal tissue ratio and standardized uptake value) and with glucose metabolism ($MR_{\text{glu}}$).

Results: $^{18}\text{FDG}$ data were required for accurate definition of tumor and mediastinal lymph node metastases. There was large intertumor variation in BF. Correlation of simplified methods of analysis with quantitative BF was poor. In addition, BF and $MR_{\text{glu}}$ were not correlated.

Conclusion: Measurement of BF in NSCLC using $\text{H}_2^{15}\text{O}$ and $^{18}\text{FDG}$ is feasible. Simple uptake analysis, however, cannot be used as an indicator of perfusion. Whether BF can be used for response monitoring needs to be evaluated in a large patient study, where results can be compared with outcome.

INTRODUCTION

For the development of novel cancer treatment strategies, knowledge of tumor biology is essential. Heterogeneity of tumor perfusion has therapeutic consequences for both drug delivery and distribution and for oxygenation status. If tumor blood flow could be monitored noninvasively, more insight in the efficacy of therapy could be obtained. For example, in a tumor with very poor perfusion, it could be predicted that chemotherapeutics would not reach the tumor and thus not affect it, and other therapy options would have to be considered.

Presently, the interest in inhibition of vascular growth of tumors (antiangiogenesis) as a possible therapeutic strategy increases. Monitoring the effects of angiogenesis inhibitors requires a noninvasive technique to assess the perfusion status of the tumor.

Using PET$^2$, it is possible to perform physiological measurements in vivo. Most oncology studies are performed using $^{18}\text{FDG}$, which is a tracer of glucose metabolism. However, in those studies where information of the perfusion status of the tumor is needed, water labeled with oxygen-15 ($\text{H}_2^{15}\text{O}$) may be used. Initial PET oncology studies using $\text{H}_2^{15}\text{O}$ were performed in brain tumors (1–7). In tumors outside the central nervous system, only a few studies have been reported (8–19), using a variety of different techniques. To the best of our knowledge, no studies have been reported on the use of $\text{H}_2^{15}\text{O}$ in lung tumors.

The aim of the present study was to develop a method for the measurement of blood flow in lung tumors. After a brief overview of background and theory, initial results of measuring perfusion in stage IIIA-N2 NSCLC patients are presented.

Background. BF can be measured using different tracers and techniques. Of the various tracers, $\text{H}_2^{15}\text{O}$ has the advantage that it is freely diffusible and metabolically inert. In addition, because of the very short half-life of $^{15}\text{O}$, repeat or combined measurements within a single scanning session can be made. Although several techniques to measure BF using $\text{H}_2^{15}\text{O}$ have been described, they are all based on the original tracer kinetic model proposed by Kety (20).

The steady-state technique, a noninvasive inhalation technique using the steady-state principle, was first described by Jones et al. (21) and later implemented for PET by Frackowiak et al. (22). In this technique, a static PET scan is performed during continuous inhalation of $^{15}\text{O}$-labeled carbon dioxide ($\text{C}^{15}\text{O}_2$). $\text{C}^{15}\text{O}_2$ is rapidly transferred in the lungs to the water-pool under the influence of carbon anhydrase (23). After an inhalation period of $\sim 10$ min and because of the short half-life of $^{15}\text{O}$, tissue $\text{H}_2^{15}\text{O}$ will reach a dynamic equilibrium in which the diffusion rate from arterial blood into the tissue is balanced by the diffusion rate out of tissue into venous blood and the rate...
of radioactive decay. The actual scan is started after this equilibration period. Within oncology, the technique has been applied mainly in brain tumor studies (1, 2, 4, 24), in a study in patients with breast carcinoma by Beaney et al. (8), and in 2 patients with hepatic tumors by Taniguchi et al. (19).

Advantages of the steady-state technique are its simple implementation, even for obtaining functional blood flow images, and the possibility to improve the statistical quality of the data simply by increasing the duration of the scan. An important disadvantage of the steady-state technique is the underestimation of BF in heterogeneous tissue (25, 26). Tumor is known to be nonhomogeneous, being an admixture of clusters of tumor and normal cells, vascular structures, and necrotic tissue. The steady-state technique assumes that the partition coefficient of water equals 1, which might not be valid in tumors (25), and because of the equilibration period prior to scanning, rather inefficient use is made of the administered radiation dose.

As an alternative to the steady-state technique, the so-called autoradiographic method was developed for the first (slow) generation of PET scanners (27–29). In this method, the integral counts over the first period after H$_2^{15}$O injection (i.e., single frame study) are collected. BF is calculated using the measured arterial input function (multiple samples), assuming a fixed partition coefficient of water. The method was validated for the brain using a 40-s integration period after arrival of H$_2^{15}$O in the brain. An advantage over the steady-state method is the much shorter acquisition time, however, at the cost of decreased statistical quality. In addition, there is a more linear relationship between counts and BF than in the steady-state technique. A disadvantage over the steady-state technique is the increased sensitivity to the presence of arterial blood. In addition, results were found to be dependent on the integration (acquisition) time, possibly because of delay and dispersion of the arterial input function. The method shares an important disadvantage with the steady-state technique, at least in onco-logical applications, in that a value for the partition coefficient of water has to be assumed. To the best of our knowledge, the method has not been applied to tumors outside of the brain.

With the introduction of fast multiring PET scanners, dynamic blood flow methods were developed and validated for the brain (30), myocardium (31–34), and tumors (12) outside the central nervous system. Reproducibility in the brain was found to be better than 10% (33). The main advantage of this dynamic technique is that no value for the partition coefficient or volume of distribution of water ($V_d$) has to be assumed, thereby significantly increasing the accuracy of the BF measurements. In addition, it has been demonstrated that the sensitivity to tissue heterogeneity is low (26), and that the flow estimates are independent of scan duration. Finally, when necessary, it is possible to account for contamination of the tissue signal within arterial blood activity.

To quantify BF an arterial input function is required. The most accurate method to determine this input function is continuous on-line arterial blood sampling. In patients for whom repetitive scans are needed, however, arterial cannulation should, whenever possible, be avoided. For studies of the myocardium and in breast tumor patients, input curves obtained from both the left atrium and left ventricle have been used and validated (34–36).

Several studies have been performed using a H$_2^{15}$O bolus injection and PET to assess blood flow in different tumor types (9–16, 18). Some of these studies used the SUV or differential absorption ratio (9, 13, 15, 16, 18) as a measure of tumor BF. Although SUV is used extensively as a measure of glucose metabolism in 18FDG studies, its use is controversial (37). Criticism of the use of SUV would be even more relevant to H$_2^{15}$O studies (e.g., dependence on scan duration and measurement time), and no comparison with measured BF values has been made.

**MATERIALS AND METHODS**

As part of an ongoing response monitoring study, 15 dynamic H$_2^{15}$O scans were performed in 10 patients using dedicated PET scanners ECAT EXACT HR+ (Siemens/CTI). All patients (7 men, 3 women; mean age, 66.5 years) were clinically staged as having stage IIIA-N2 NSCLC. Patient characteristics are listed in Table 1. The study protocol was approved by the medical ethics committee of both hospitals participating in this study. All patients gave written informed consent.

First, a 10-min transmission scan over the tumor area was performed, followed by injection of H$_2^{15}$O using an automated injector (Med-Rad multilevel CT injector), simultaneously starting a 10-min dynamic emission scan (12 × 5 min, 12 × 10 min, 6 × 20 min, and 10 × 30 min). Injection (1000 MBq dissolved in 2.5 ml) was given as a bolus (15 s; 10 ml/min), followed by a flush of 2 min. Ten min after the H$_2^{15}$O scan (to allow for radioactive decay of $^{15}$O), 370 MBq of $^{18}$FDG were injected, and a second (60-min) dynamic emission scan with progressive frame lengths was started.

**Data Analysis.** All dynamic scan data were corrected for dead time, decay, scatter, randoms, and photon attenuation and were reconstructed using FBP with a Hanning filter (cutoff, 0.5 cycles/pixel). This resulted in a transaxial spatial resolution of ~7 mm of full width at half maximum.

ROI were defined automatically over both tumor and MLN metastases by applying a threshold of 50% of the maximum $^{18}$FDG pixel value within the lesion. For this purpose, the last three frames (i.e., 45–60 min after injection) of the sinograms of the $^{18}$FDG scan were summed and reconstructed using ordered subset expectation maximization with 2 iterations and 12 sub-
sets. This was followed by postsmoothing of the reconstructed image using a 5-mm full width at half maximum Gaussian filter to obtain the same resolution as the dynamic images reconstructed with FBP. The ordered subset expectation maximization reconstructions were used because of their superior image quality, thus facilitating ROI definition. For quantification, however, the more accurate FBP reconstructed images were used (38), and therefore, tumor ROI were copied to the (FBP reconstructed) dynamic H215O data to create tumor time activity curves. Furthermore, ROI were defined manually over the aortic arch, left ventricle, and left atrium on a summed (FBP) image of the first min of the H215O scan. These data were used to create an image-derived input function.

Time activity curves were analyzed using standard nonlinear regression techniques and the single compartment model, both with and without an arterial blood volume component (see Appendix, Eqs. C and D, respectively), weighting data for acquired counts and frame duration. In addition, to assess the validity of data presented in the literature, T/N ratios from 0 to 5 min and the SUV corrected for body surface area (SUVBSA) from 0 to 5 and from 4 to 5 min were evaluated.

Glucose consumption (MRglu) was obtained from the 18FDG data using nonlinear regression and the standard two-tissue (3k) compartment model (39) with three rate constants and a blood volume component (40) and an image derived input function (41).

Statistics. The presence of an arterial blood volume component in the tumor curves was assessed by comparing the residual sum of squares with and without such a component using the Akaike (42) and Schwarz (43) criteria. The correlation of T/N and SUVBSA values with both BF and Vd values was assessed, using the Pearson bivariate correlation; P < 0.01 was considered to be significant. The correlation of MRglu with BF values was assessed, using Pearson bivariate correlation; again, P < 0.01 was considered to be significant.

RESULTS

In Fig. 1, transaxial images at the level of tumor and MLN metastases are shown for both H215O and 18FDG data. It can be seen that the tumor could have been identified and defined on the H215O scan itself. However, for the definition of MLN metastases, the 18FDG scan was needed. Therefore, all tissue ROI were defined on the 18FDG scan.

ROI to generate the image-derived input function were defined on summed dynamic H215O data. For the input function, as many time-activity curves as possible were averaged (weighted to ROI size) to obtain optimal statistics. In 8 scans, the curves from the aortic arch could be used. ROI defined in both the left ventricle and atrium could be used in 13 scans. An example of an average blood time-activity curve (input function) is given in Fig. 2A.

Examples of fits with and without an arterial blood volume component are given in Fig. 2B. In 14 of 15 scans (93%), incorporating an arterial blood volume component provided significantly better fits according to the Akaike criterion. This was 12 of 15 (80%) according to the Schwarz criterion. Therefore, all results presented here are for the model with arterial blood volume component (i.e., according to Eq. D).

Individual values of T/N, SUVBSA, BF, and Vd are presented in Table 2. The mean ± SD for blood flow in tumor was 0.59 ± 0.37 ml/ml/min, with a range of 0.15–1.29 ml/ml/min. For MLN metastases, this was 0.48 ± 0.23 ml/ml/min with a range of 0.21–0.86 ml/ml/min. The mean ± SD value for Vd was 0.63 ± 0.10 with a range of 0.45–0.78 for tumor and 0.74 ± 0.17 with a range of 0.47–0.99 for MLN metastases, respectively.

The correlation between BF and SUVBSA (0–5 min) was 0.60 (P = 0.02) and 0.32 (P = 0.25) for SUVBSA (4–5 min), which were both not significant. The correlation between BF and T/N ratio was 0.58 (P = 0.02). SUVBSA (0–5 min) was also poorly correlated with Vd (r = 0.49, P = 0.06); for SUVBSA (4–5 min), this was 0.37 (P = 0.18).

Values of MRglu are also given in Table 2. The correlation with BF was poor (r = 0.28, P = 0.31), as illustrated in Fig. 3.

DISCUSSION

Inhibition of angiogenesis in tumors is an important therapeutic aim because it might be a means of preventing progression of disease. Presently, many studies are performed to assess the possibilities of such therapy. It is important to be able to monitor the effects of antiangiogenesis therapy in vivo, preferably in a simple and noninvasive manner. A potential means to monitor these effects is the measurement of tumor perfusion. Hence, there is renewed interest in blood flow measurements using PET and H215O.

The most important finding of the present study in lung tumors is the large variation in BF in different tumors, even in the untreated ones. It is likely that this variation has implications for therapy (drug delivery, oxygenation, and others). Therefore, studies are needed to relate perfusion measurements with response to treatment.

In the present study in lung tumors, ROI for tissue time-activity curves and input curves were defined using different datasets. The image-derived input curve was defined using
Measurement of Tumor Perfusion Using $H_2^{15}$O and PET

However, it was not feasible to consistently define an accurate tumor ROI on $H_2^{15}$O data alone, and for this reason, $^{18}$FDG scanning proved to be essential. Very recently, a number of alternative methods for generating parametric images of tumor BF using $H_2^{15}$O have been described (44). In 5 patients with renal cell metastases in the thorax, the lesions could be readily identified in the parametric flow images. Further studies are needed, however, to assess whether those methods would also identify MLN metastases in NSCLC and thus obviate the need for $^{18}$FDG in defining ROI. The same applies for parametric methods, which thus far have only been applied to the brain (45–48) or heart (49). In theory, ROI could also be defined on CT scans. This, however, would require accurate positioning and realignment between CT and PET scans. In practice, this is not possible because patient positioning routinely is different for CT (hands up) and PET (hands down).

In the model used, it is assumed that water is freely diffusible, i.e., that the extraction fraction is 100%. This is likely to be the case for low flow values. For high flow values, however, extraction could be <100%, resulting in an underestimation of flow. This effect is expected to be small because blood vessels supplying a tumor are usually more permeable than normal blood vessels.

In studies performed in brain, the mean volume of distribution of water was found to be 0.86 with a SD of 0.04 (50). For comparison, the mean value of $V_d$ found in breast tumors was 0.56 with a SD of 0.15 (12). In this study, a mean value of 0.63 for NSCLC was found (Table 2), which is very similar to the value found in breast tumors. It should be noted that the estimation of $V_d$ is susceptible to tissue heterogeneity. For example, in the brain, the underestimation attributable to tissue heterogeneity can be as high as 30% (26). In contrast, in the same study, the effect of tissue heterogeneity on flow was <5% (26).

An arterial blood volume component significantly contributes to the counts within the tumor ROI was present in 80–93% of the scans in this study. In addition, for MLN metastases this was 100%. In brain and breast cancer studies (12, 30, 33), the contribution of an arterial blood volume component was found to be negligible. However, in NSCLC, the contribution needs to be taken into account (see, for example, Fig. 2B).

In this study, there was no significant correlation between BF and SUV or T/N ratio. Although the study was limited to a single tumor type, it is likely that the same applies to other tumors. In other words, unless validated for the tumor under investigation, both SUV and T/N ratios cannot be used as indicators of tumor perfusion.

When comparing $MR_{df,bf}$ with BF, a poor correlation was found (Fig. 3). This would indicate that perfusion and glucose consumption are not coupled in NSCLC, and therefore, as expected, $H_2^{15}$O and $^{18}$FDG provide complimentary information on tumor physiology. Whether BF alone, or in combination with $^{18}$FDG, may predict response to therapy will have to be investigated in a larger patient study where results can be compared with outcome.

In conclusion, although the uptake of $H_2^{15}$O in NSCLC is higher than in normal lung tissue (T/N $>1$), it is difficult to determine the exact location. This is especially true for possible MLN metastases because of their position close to vascular structures with high tracer concentration. Therefore at present,
the study needs to be combined with, for example, an 18FDG study for accurate ROI definition.

When performing dynamic blood flow PET using H₂¹⁵O in NSCLC, the influence of an arterial blood volume component has to be taken into account. The volume of distribution of water is similar to reported values for breast tumors.

An important finding is the large intertumor variation in perfusion. This could indicate that perfusion might be an important parameter for predicting therapy efficacy. The actual additional value of PET using H₂¹⁵O for monitoring antiangiogenesis therapy needs to be evaluated further in a larger serial patient study. In addition, the value of combining H₂¹⁵O and 18FDG studies will need further investigation.

**APPENDIX**

For the present study, flow was measured using the dynamic method based on the tracer kinetic model originally described by Kety (20, 51). The single tissue compartment model is illustrated in Fig. 4, where it is assumed that all concentrations are corrected for decay. The rate of change of activity in tissue is the balance between delivery and washout, or in mathematical terms:

\[
dC_t/dt = FC_a - (F/V_d) \cdot C_t
\]

where \(F\) is BF or perfusion (ml blood/ml tissue/min), \(V_d\) is the partition coefficient or volume of distribution of water (unitless), \(C_a\) is the concentration of H₂¹⁵O in arterial blood (kBq/ml), and \(C_t\) is the concentration of H₂¹⁵O in tissue (kBq/ml).

The solution of this differential equation is:

**Table 2 Patient Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time of scanning</th>
<th>Age</th>
<th>Histology tumor</th>
<th>T/N (0–5 min)</th>
<th>SUV₅₀₀₀₀₉₅₀₀₀ (0–5 min)</th>
<th>SUV₅₀₀₀₀₉₅₀₀₀ (4–5 min)</th>
<th>BF (ml/ml/min)</th>
<th>V_d</th>
<th>MR_glu (micromol/ml/min)</th>
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<tbody>
<tr>
<td>1</td>
<td>Prior to start chemotherapy</td>
<td>67</td>
<td>Large cell carcinoma</td>
<td>2</td>
<td>95</td>
<td>112</td>
<td>0.53</td>
<td>0.62</td>
<td>0.119</td>
</tr>
<tr>
<td>2</td>
<td>Prior to start second cycle chemotherapy</td>
<td>76</td>
<td>Planocellular carcinoma</td>
<td>2.7</td>
<td>82</td>
<td>111</td>
<td>1.16</td>
<td>0.78</td>
<td>0.169</td>
</tr>
<tr>
<td>3a</td>
<td>Prior to start chemotherapy</td>
<td>70</td>
<td>Adenocarcinoma</td>
<td>5</td>
<td>106</td>
<td>127</td>
<td>0.95</td>
<td>0.76</td>
<td>0.210</td>
</tr>
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<td>3b</td>
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<td>Adenocarcinoma</td>
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<td>0.141</td>
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<td>69</td>
<td>0.19</td>
<td>0.71</td>
<td>0.165</td>
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<td>5</td>
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<td>76</td>
<td>Large cell carcinoma</td>
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<td>70</td>
<td>76</td>
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<td>7c</td>
<td>Prior to start third (last) cycle chemotherapy</td>
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<td>141</td>
<td>0.73</td>
<td>0.56</td>
<td>0.170</td>
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</table>

**Fig. 3** Scatter diagram of MR_glu versus BF, illustrating poor correlation (\(r = 0.28, P = 0.31\)).

**Fig. 4** Schematic diagram of the single tissue compartment model. For a full description, see the main text.
\[ C_t = F \cdot C_i \cdot e^{-t/V_i} \]  \hspace{1cm} (B)

where \( \otimes \) represents the operation of convolution.

The method is based on the following assumptions: (a) flow (\( F \)) and \( V_i \) are constant during the period of measurement, \( i.e., \) the system is in a physiological steady state; (b) \( H_2^{15}O \) is a freely diffusible tracer, \( i.e., \) the extraction fraction of water is unity, and no binding of water in tissue occurs; (c) \( H_2^{15}O \) that diffuses into tissue equilibrates instantaneously within the tissue, \( i.e., \) there are no concentration gradients in tissue; (d) venous and tissue concentrations do not differ, \( i.e., \) the volume of distribution (\( V_j \)), or the partition coefficient, is close to 1. This means that the venous blood can be considered to be at tissue concentration and, therefore, venous blood and tissue can be considered to be a single compartment; and (e) the contribution of arterial blood activity, \( i.e., \) the signal arising from arterial activity within a ROI is negligible.

The last assumption states that tissue and (measured) ROI concentration are the same, \( i.e., \)

\[ C_{ROI} = C_i \]  \hspace{1cm} (C)

where \( C_i \) is given by Eq. B.

If the signal arising from the arterial blood is not negligible, this can be accounted for by incorporating an additional arterial blood volume (\( V_a \)) term resulting in:

\[ C_{ROI} = (1 - V_j) C_i + V_a C_a \]  \hspace{1cm} (D)

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