

Measurements of Blood Flow and Exchanging Water Space in Breast Tumors Using Positron Emission Tomography: A Rapid and Noninvasive Dynamic Method

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ABSTRACT

A noninvasive dynamic method for the measurement of blood flow, using ¹⁵O-labeled water and positron emission tomography, has been developed and used to study 20 patients with breast carcinoma. The mean tumor flow was 29.8 ± 17.0 (SE) ml/dl/min of tissue, while normal breast flow was 5.6 ± 1.4 ml/dl/min of tissue.

The exchanging water space of tissue known as the volume of distribution of the tracer (V_d) was also derived. This is defined as the volume of water in tissue that exchanges with a unit volume of water in arterial blood during the period of the study (7 min). The mean tumor V_d was 0.56 ± 0.15 ml/ml while normal breast V_d was 0.14 ± 0.05 ml/ml. The low value in normal breast is partly due to the high fat content of the tissue. The mean flow per unit of exchangeable volume was similar in tumor (52.8 ± 22.0) and normal breast tissue (45.2 ± 20.0). This suggests that the major discrepancy seen in measured values of flow between breast tumors and normal breast principally reflects the different composition of the two tissues. This method is rapid and suited for studying the reactivity of human tumor vasculature, so extending studies are being performed on animal tumors.

INTRODUCTION

Tumor blood flow is an important biological parameter. Its measurement not only gives an indication of a tumor's general metabolic activity, but is a means for assessing the delivery of chemotherapeutic agents, monoclonal antibodies, or other targeted therapies.

There are relatively few data on the quantitative measurements of blood flow in human breast tumors. The techniques used have included xenon washout (1), a thermodynamic method (2), and ¹⁵O-labeled water and positron emission tomography using the steady-state inhalation technique (3). Tumors were found to have a much higher average flow than normal breast tissue. The xenon washout method is suitable for superficial nodules but requires an assumption on the partition coefficient of xenon between the nodule tissue and blood. This is strongly dependent on the fat content of the tissue, since xenon is highly lipophilic and may cause errors in absolute results (1). The thermodynamic clearance technique is also limited to superficial tumors, and only approximate results are obtained (2).

PET³ allows the study of deep-seated and primary tumors. The "standard" steady-state method (3) requires an assumption of the volume of distribution (V_d) of the tracer. This is the fraction of the tissue's physical volume within which the radioactive water is distributed as compared with arterial blood. This

creates potential errors if the true V_d is very different from the assumed value. Furthermore this method is sensitive to the effects of tissue heterogeneity and will tend to underestimate tissue blood flow (4). The sensitivity of the ¹⁵O steady-state technique has been the stimulus for developing less sensitive alternatives. With the introduction of the multiring PET scanners, dynamic blood flow methods have been developed and validated for brain and cardiac studies (5, 6). A modification of these techniques has been used to study 20 patients with breast tumors. For studies in which the heart is included within the field of view, arterial input curves may be derived from the left atrium (6). This negates the need for arterial cannulation, and thus the method becomes completely noninvasive. Using tracer kinetic models, absolute values for blood flow and the volume of distribution of water during the study are obtained.

The short duration of this technique (7 min) makes it suitable for repeated measurements and for combination with other measurements of tissue function using PET.

PATIENTS AND METHODS

Details of the patients' age and tumor (TNM) stage are given in Table 1. There were 3 premenopausal patients, 16 postmenopausal patients, and one male breast cancer patient. Five patients with T₂ (2 to 5 cm), 6 with T₃ (>5 cm), and 7 with T₄ (ulcerating or fixed) tumors were studied. Only one T₁ (<2 cm) lesion was included. Patient 11 had undergone a contralateral mastectomy, while Patient 7 had previously received radical radiotherapy to the opposite breast.

The histology for all patients was invasive ductal carcinoma apart from the one male patient who had a lobular carcinoma.

Permission to carry out this research was obtained from the Ethics Committee of Hammersmith Hospital. Authorization for the use of radionuclides was given by the Administration of Radioactive Substances Advisory Committee. All patients gave informed consent.

Scanning Procedure. The patients were scanned with an ECAT 931-08/12 PET scanner (7). Fifteen contiguous planes of data were recorded simultaneously over a transaxial length of 10.8 cm. Images were reconstructed using a 0.5 Hanning filter resulting in a spatial resolution of 8.4 x 8.3 x 6.6 mm (full width at half maximum) at the center of the field of view (7). The patient was usually positioned with laser cross-wires so that the tumor lay in the field of view of the central ring of detectors. Patient movement was monitored using a closed circuit television and was immediately corrected for.

Prior to the study, a transmission scan of 15 to 20 min was performed using an external ring source of ⁶⁸Ge. This transmission scan was used for subsequent attenuation correction of all emission scans.

C¹⁵O₂ at an activity of 6 MBq/ml was supplied at a constant rate (500 ml/min) via a standard oxygen face mask for a period of 3.5 min. In the lungs the ¹⁵O label is rapidly transferred to the pulmonary water pool by carbonic anhydrase to produce a constant infusion of water (H₂¹⁵O) into the arterial tree (8).

Patients were scanned during both the inhalation phase and the subsequent washout period of 3 min. The scanning protocol consisted of a background frame of 30 s collected immediately prior to the gas delivery, followed by 6 frames of 5 s, 6 x 10 s, 6 x 20 s, and 6 x 30 s in duration, providing a total of 25 frames over 7 min.

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³ The abbreviations used are: PET, positron emission tomography; TNM, tumors-nodes-metastases; ROI, region(s) of interest; V_d , volume of distribution; F/V_d , flow/unit of exchangeable volume; CT, computed tomography.

Table 1 Patient characteristics

Patient	Age (yr)	TNM stage	Treatment (at time of study)	Survival
1	77	rT _{4c} N ₀ M ₀	No	Died 6 mo
2	60	T ₃ N ₀ M ₀	No	Died 20 mo
3 ^a	44	T ₃ N ₂ MX	No	Died 3 mo
4	50	T ₂ N ₀ M ₀	Hormonal	>14 mo
5	57	T ₄ N ₀ M ₀	No	Died 2 mo
6 ^a	35	T ₁ N ₀ M ₀	No	>24 mo
7 ^b	38	T ₂ N ₁ M ₁	Chemotherapy	Died 8 mo
8 ^a	42	T ₂ N ₂ MX	Chemotherapy	Died 8 mo
9 ^c	69	T ₃ N ₂ M ₁	Hormonal	Died 2 mo
10	71	T ₂ N ₀ M ₀	Hormonal	>18 mo
11 ^d	40	rT _{4c} N ₂ M ₁	Chemotherapy	Died 9 mo
12	54	T ₃ N ₀ M ₀	No	>14 mo
13	75	T ₃ N ₀ M ₀	Hormonal	Died 6 mo
14	61	T ₀ N ₂ M ₀	Hormonal	>14 mo
15	67	rT _{4c} N ₀ M ₀	Hormonal	Died 4 mo
16	56	T _{4c} N ₂ M ₀	No	>12 mo
17	51	T ₂ N ₁ M ₀	No	>12 mo
18	56	T _{4c} N ₂ M ₀	Radiotherapy	Died 3 mo
19	64	T ₂ N ₀ M ₀	Hormonal	>8 mo
20	66	T ₃ N ₁ M ₀	No	Died 5 mo

^a Premenopausal.^b Previous contralateral tumor.^c Male cancer.^d Contralateral mastectomy.

The reproducibility of the method was assessed in 5 patients with repeated measurements in which the time interval between studies was about 30 min. In 3 patients, further measurements were obtained after an interval of 1 to 2 wk.

Analysis. The scans were analyzed using image analysis software (Analyze Version 2.0; BRU Mayo Foundation, Rochester, MN) and a mathematical software package (Pro-Matlab; The Mathworks, Inc.) on a SUN 3/60 workstation.

To define the arterial input curve, the scans collected over the first 1.5 min were added to provide composite images from which ROI could be defined in the left atrium. This chamber was chosen in preference to the left ventricle because it experiences less movement and spillover of activity from the atrial wall (6). The atrium was defined in three planes. The average ROI size per plane was 28 pixels (8 cm²) (range, 20 to 32 pixels). The ROIs were subsequently projected onto the 25 dynamic frames, and the pixel count therein was measured in each frame and averaged over the three planes to generate an arterial time-activity curve.

Similarly ROIs were defined over the tumor and breast tissue on an added image of the whole study (Fig. 1). Tumors were easily located in all cases because of the increased radioactive signal over surrounding breast tissue. An ROI (average size, 60 pixels or 18 cm²) (range, 24 to 128 pixels) was traced around the whole tumor (including central areas) to measure average tumor flow. Large ROIs (average size, 140 pixels or 43 cm²) (range, 80 to 146 pixels) were placed over the normal breast using the added image and checked with the transmission scan to ensure that they encompassed only breast tissue. These regions were also projected onto the dynamic frames, and time-activity curves were generated for tumor and normal breast. Several axial planes of data (usually >5) were added to improve statistical quality. Using a standard nonlinear least-square regression analysis to best fit the curves (9), blood flow and volume of distribution V_d were obtained using the model equations given in the "Appendix."

The data was also fitted with and without an arterial blood volume component. The quality of the fits was not improved significantly using this component and has subsequently been ignored.

RESULTS

Typical time-activity curves for the atrium and for tumorous and normal tissue as well as fitted curves are given in Fig. 2.

The values for blood flow and V_d are given in Table 2 and plotted in Fig. 3.

The contralateral normal breast data were not recorded in 3

patients: Patient 7 had a contralateral tumor treated with surgery and radiotherapy 3 yr previously; Patient 9 was a male subject with insufficient breast tissue; and Patient 11 had a contralateral mastectomy.

The mean tumor blood flow was 29.8 ± 17.2 (SE) ml/dl/min in comparison with a normal breast tissue blood flow of 5.6 ± 1.4 ml/dl/min. The mean V_d was 0.56 ± 0.15 for tumors as compared with 0.14 ± 0.05 for normal breast.

The differences between tumor and normal breast blood flow and volume of distribution were highly significant using the paired *t* test ($P < 0.001$). Patients 1 to 5 underwent repeat studies. These are plotted in Fig. 4 and illustrate the reproducibility of the method in calculating tumor flow. In some patients, flow heterogeneity was observed with areas of high flow and occasionally areas of apparent lower flows. The regions of interest for the low-perfusion areas tended to be small and were consequently statistically "noiser."

A wide range of flow values was obtained (11 to 77 ml/dl/min). There was no association between tumor size, as determined by TNM staging, and flow in this group of patient. No apparent correlation could be drawn between flow and prognosis, as the majority of patients had advanced or recurrent disease. The three patients with the highest flows developed rapid progressive and metastatic disease and died within 3 mo of the study. Blood flow values were found to be similar for metastatic axillary nodes and breast primaries.

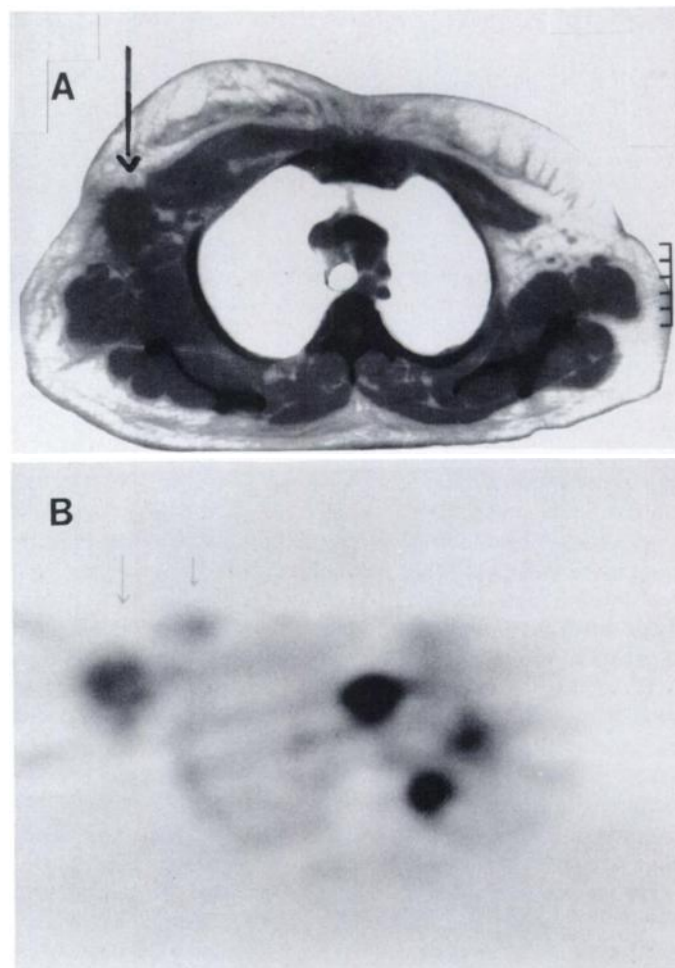


Fig. 1. CT (A) and flow scan (B) through the plane of tumor. The right axillary nodal mass is clearly visible on the CT image, and the primary and mass axillary nodal mass are shown by arrows on the emission scan.

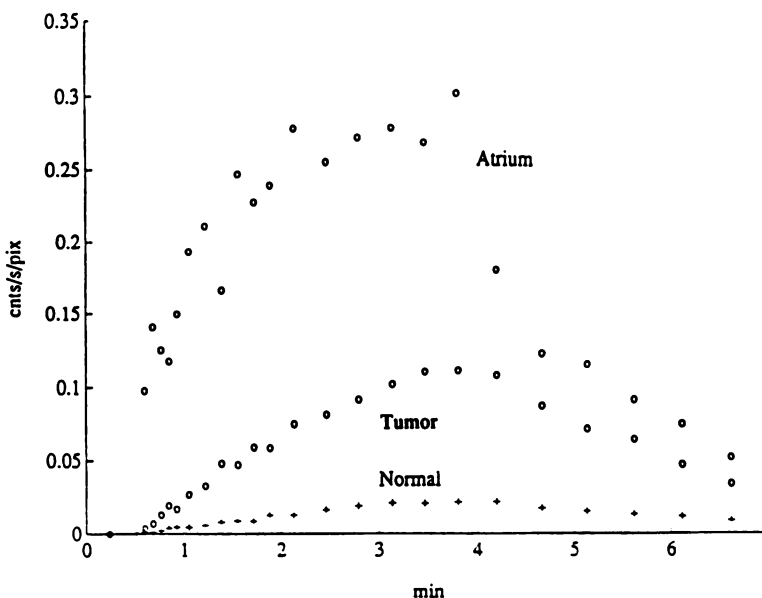
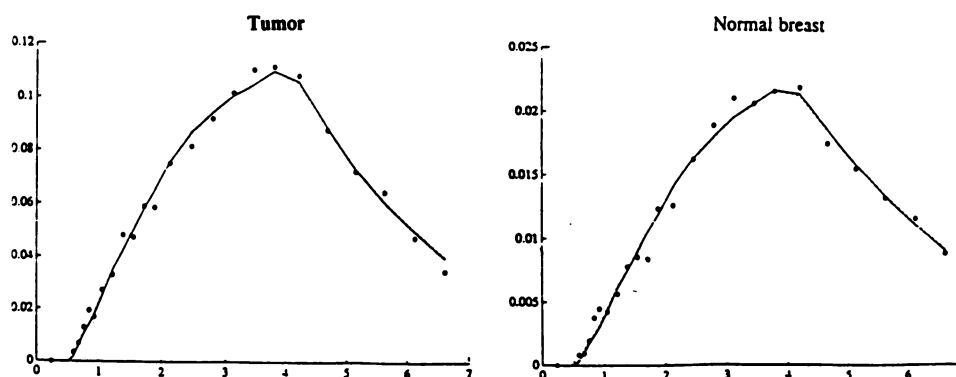


Fig. 2. The top diagram shows time-activity curves for the atrium, tumor, and normal breast tissue. The fits obtained for the tumor and normal breast are shown below.



Breast flows and volumes of distribution were consistently low in undiseased tissue irrespective of whether the patient was pre- or postmenopausal.

Calculation of the F/V_d is also shown in Table 2. Although a wide scatter is obtained, the values for normal breast and tumorous tissue are of a similar order of magnitude.

DISCUSSION

The values obtained for average tumor blood flow per unit volume of tissue with this technique are of a similar magnitude to those obtained for breast tumors using other methodology (2, 3) and those of human mammary carcinoma xenografts (10). They show the wide variation between tumors of similar stage and histology. The most severe limitation of PET is the spatial resolution, which is in the order of millimeters. As a result, radioactivity measurements represent the average values for larger regions of interest and, therefore, will mask microscopical areas of low flow. Similarly, in order to limit "noise," this method is more suitable for large tumors (>4 cm). The advantage of this dynamic method over the "standard PET" steady-state method is its higher degree of accuracy in determining flow, without any loss of spatial resolution. In the steady-state method, the exchanging water space or volume of distribution of water (V_d) is assumed to be 1, which is unjustified and will lead to errors. In addition, tissue heterogeneity can result in underestimation of flow values of 50% (4). In the dynamic

method, flow (F) and V_d are measured simultaneously throughout the study. The build-up of activity is determined by F , and the washout, by F/V_d . It is therefore more accurate for flow measurements because (a) it includes a measure of V_d , and (b) tissue heterogeneity will not affect the build-up phase determined by flow, although it will affect the washout phase and may lead to an underestimation of V_d .

The reproducibility of the method in calculating tumor flow is illustrated by those patients who had repeat studies. Errors of up to $\pm 10\%$ may occur for single observations. Statistical accuracy increases in high-flow areas owing to improved signal counts. Conversely it is less reliable in areas of low flow where larger error bars are obtained on the fitted values.

A possible source of error lies in the definition of the arterial concentration. An underestimate of this would lead to higher blood flow and V_d values in both tumorous and normal tissue. The most accurate method would involve direct arterial sampling, although this would subsequently require a correction for delay and dispersion of the input function as is required in cerebral blood flow measurement (5). The left atrium is the preferred source of reference, as it is easily definable and of a size that limits partial volume effects. Recovery of the counts is greater than 90% (6). In addition, there are little wall movement and no significant contribution from the atrial wall. The ascending aorta may also be used but, owing to its smaller size, lower total counts are obtained.

ROI definition of the tumor encompassed the whole tumor

Table 2 Individual results

V_d represents exchanging water space.

Patient	Tumor			Normal		
	Flow (ml/dl/min)	V_d (ml/ml)	F/V_d (ml/dl/min)	Flow (ml/dl/min)	V_d (ml/ml)	F/V_d (ml/dl/min)
1	25.7 ± 0.9 ^a	0.66 ± 0.03	38.9 ± 3.4	7.1 ± 0.3	0.14 ± 0.01	49.8 ± 5
2	21.5 ± 0.9	0.44 ± 0.02	48.4 ± 4.5	4.5 ± 0.6	0.09 ± 0.01	49.6 ± 14.6
3 ^b	76.8 ± 2.7	0.76 ± 0.02	100 ± 5.5	6.9 ± 0.9	0.16 ± 0.01	43.9 ± 9.8
4	27.3 ± 4.1	0.43 ± 0.03	63.5 ± 10.7	4.5 ± 1.3	0.26 ± 0.01	17.3 ± 5
5	45.2 ± 2.9	0.64 ± 0.02	67.5 ± 3.8	8.0 ± 0.6	0.16 ± 0.01	50 ± 4.9
6 ^b	42.5 ± 3.5	0.51 ± 0.03	82.8 ± 11.3	6.6 ± 2.2	0.10 ± 0.01	66.7 ± 27
7 ^c	17.3 ± 1	0.32 ± 0.02	53.2 ± 6.3			
8 ^b	25.6 ± 2.9	0.49 ± 0.09	51.5 ± 8.9	7.7 ± 0.4	0.16 ± 0.02	48.9 ± 11.8
9 ^d	64.8 ± 2	0.67 ± 0.02	96.5 ± 4.8			
10	20.4 ± 1	0.80 ± 0.08	25.6 ± 3.8	4.3 ± 0.4	0.12 ± 0.02	37.0 ± 7.7
11 ^e	44.6 ± 0.1	0.81 ± 0.02	55.2 ± 2.1			
12	19.9 ± 2.5	0.48 ± 0.09	41.3 ± 12.0	5.6 ± 0.2	0.15 ± 0.01	36.1 ± 3.6
13	17.9 ± 0.9	0.31 ± 0.02	57.7 ± 5.6	6.2 ± 0.3	0.18 ± 0.01	34.6 ± 4.1
14	20.6 ± 3.1	0.59 ± 0.09	34.9 ± 10.4	3.6 ± 1.0	0.08 ± 0.01	46.0 ± 19.6
15	19.1 ± 0.7	0.65 ± 0.05	29.4 ± 2.5	4.7 ± 0.3	0.10 ± 0.01	47 ± 5.5
16	19.7 ± 0.3	0.66 ± 0.02	29.8 ± 1	5.5 ± 0.6	0.17 ± 0.03	32.4 ± 6.7
17	23.7 ± 1.6	0.57 ± 0.03	41.6 ± 3.8	4.3 ± 0.4	0.23 ± 0.03	18.7 ± 4
18	30.0 ± 0.3	0.53 ± 0.03	56.6 ± 3.2	6.4 ± 0.6	0.14 ± 0.01	45.7 ± 5.4
19	17.2 ± 1.1	0.48 ± 0.05	35.8 ± 4.3	5.7 ± 0.5	0.07 ± 0.01	81.4 ± 13.6
20	11.3 ± 1.3	0.40 ± 0.10	28.2 ± 9.7	3.6 ± 0.4	0.04 ± 0.00	87.6 ± 16.9
Mean	29.8 ± 17	0.56 ± 0.15	52.8 ± 22	5.6 ± 1.4	0.14 ± 0.05	45.2 ± 20

^a Mean ± SE.
^b Premenopausal.
^c Radiotherapy to normal breast.
^d Male cancer.
^e Mastectomy.

and may have included some reactive surrounding normal tissue. The majority of tumors sampled here were over 6 cm in width, and the flow images correlated well with anatomical definition from CT scans (Fig. 1) or clinical findings. Any error caused by the inclusion of normal reactive tissue might have led to an underestimate of tumor flow, since in no instance was a higher signal noted in the surrounding normal tissue.

Arterial blood volume, if large, may potentially affect the results. The data were fitted both with and without an arterial blood volume component, but the quality of the fits was not improved significantly by including this component.

V_d as measured by this method reflects the amount of tissue that is exchanging water with blood during the study. If complete exchange took place it should average between 0.9 and 0.96 for most tissues. The very low values for the volume of distribution of normal breast (0.14) were surprising but relate

to the high fat and low water content of breast tissue. Using magnetic resonance spectroscopy, the water:fat ratio has been measured to be 0.3 in normal breast as compared with 2.2 (range, 1.2 to 5.0) in tumors (11). This would lead to expected V_d values of 0.23 and 0.69, respectively, if full exchange took place. Similarly proton spectroscopy data from a patient (Fig. 5) show the low water content of normal breast as compared with the contralateral tumor. In this patient expected V_d values of 0.18 and 0.58 for breast and tumor compare well with our obtained values. The higher values found in tumors are in keeping with the fact that they have a higher cellular content than normal breast tissue, and the variation of water content within tumors is dependent on the amount of fibrosis (12) or necrosis present. Hence the two tissues are not directly comparable. In an attempt to correct for this, it is possible to calculate the F/V_d . The values obtained are of a similar order for breast tissue and tumor ($45.2 ± 20$ versus $52.8 ± 22$ ml/dl/

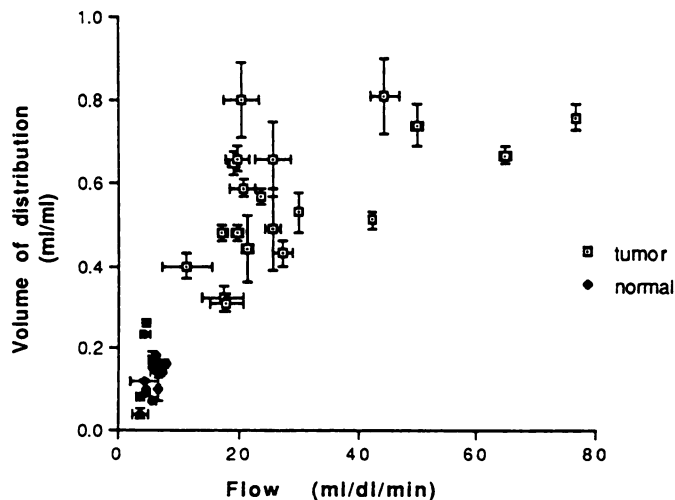


Fig. 3. Blood flow plotted against volume of distribution. A clear distinction exists between values for tumor and normal breast. Points, mean; bars, SE.

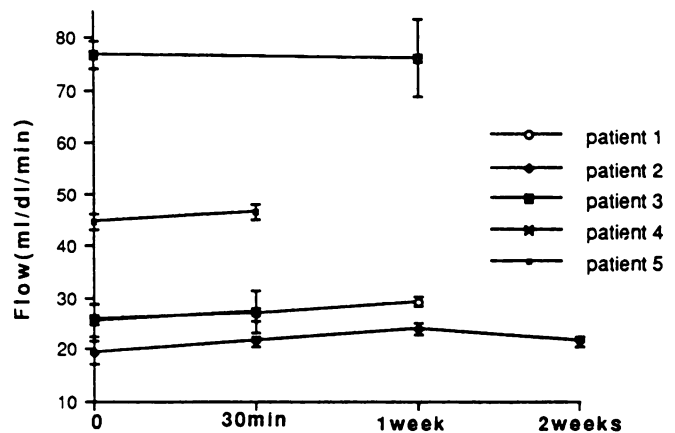


Fig. 4. Result of repeat scans performed in five patients. Studies were repeated at 30 min (Patients 1, 2, 4, and 5) and following 1 wk (Patients 1, 2, and 3) and 2 wk (Patient 2). There is little variability in average tumor flow. Points, mean; bars, SE.

min). This may explain the paradox that, although breast tumors have been shown experimentally and histologically to have a more delicate vasculature than normal tissue and thus would be expected to have a lower perfusion, they are found to have a much higher apparent flow both *in vitro* and *in vivo* (10). The flow per unit perfused of exchangeable water space is similar, although the higher mean value for certain tumors may reflect their increased metabolic demand.

These values are, however, higher than those reported using the xenon washout method (13). For a variety of tumor skin nodules, notably from breast and lung primaries, the flow per

unit volume was 20.0 ± 14.7 ml/min/100 g. This discrepancy may be attributable to the heterogenous group of tumors studied, but also an assumption is made on the partition coefficient of xenon, which may vary considerably according to the lipid content of the tissue. In addition, in this latter technique the isotope is injected locally, which may lead to perturbation of the local microcirculation because of an increase in intratumor pressure (14).

The volume of distribution as described by this method gives an estimate of the volume of tissue being perfused. If V_d is dependent on the cellular mass that contains tumor, this would

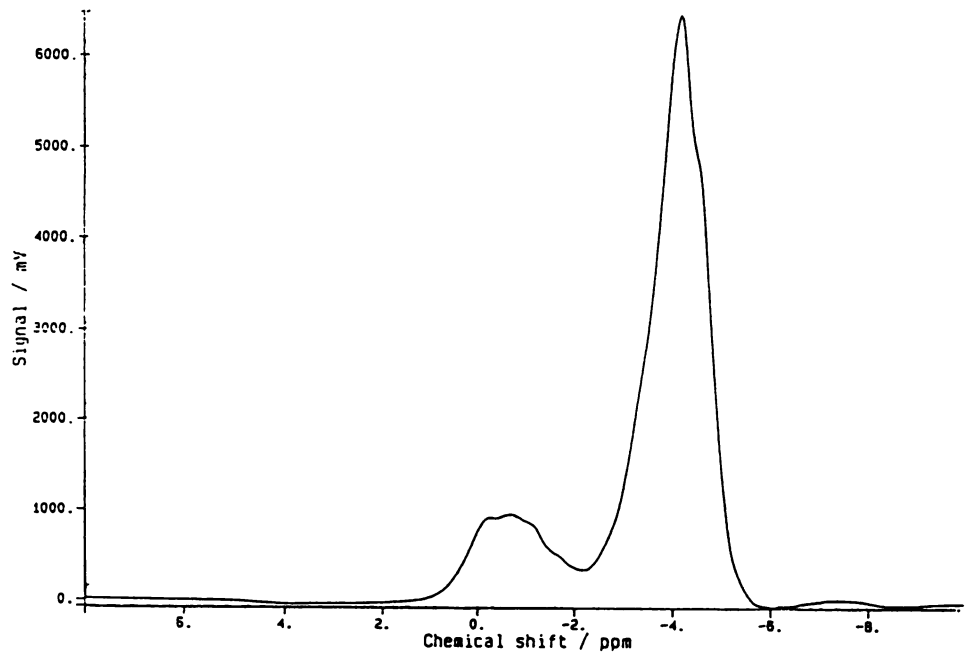
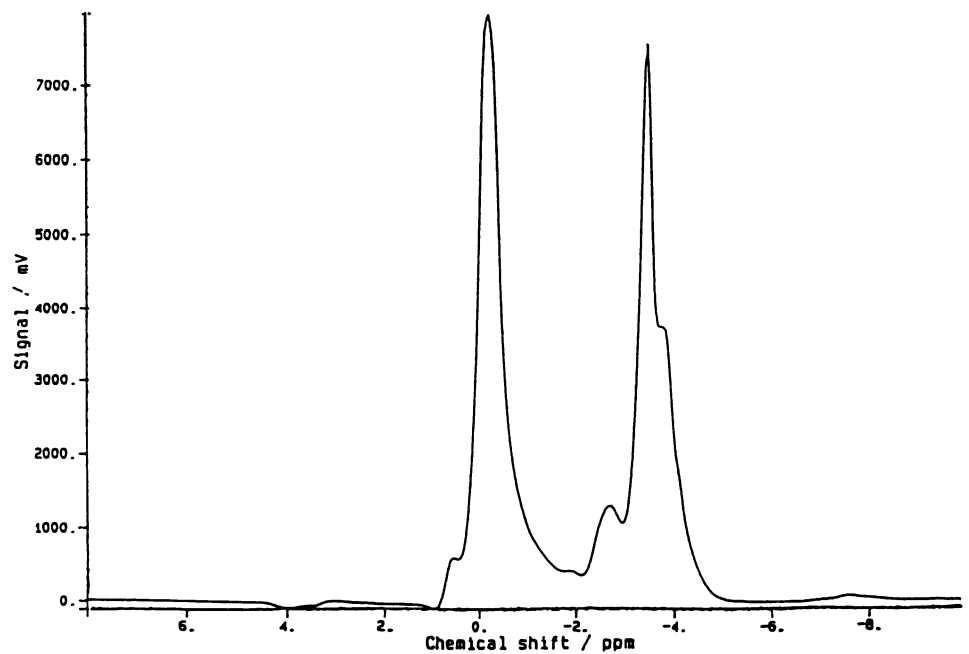


Fig. 5. Proton spectroscopy data from (*upper*) normal breast and (*lower*) contralateral tumor. The *area under the curve* gives a measure of the tissue composition. Normal breast has low water and high fat peaks. In contrast, the tumor has a higher water than fat signal.



be an important parameter to measure. The measurement of F/V_d may prove useful, especially in the assessment of delivery of nutrients, drugs, or targeted therapy.

The main advantage of this dynamic method is that it is quick and, because of the short half-life of ^{15}O (2.05 min), it can easily be combined with other PET studies. It is well suited for the *in vivo* study of tumor blood flow and offers a means for monitoring changes that might prove of therapeutical relevance.

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APPENDIX

^{15}O -labeled water is a metabolically inert, freely diffusible tracer. Its behavior in tissue can be described by the following differential equation for a single-tissue compartment model

$$dC_t(t)/dt = F \cdot C_a(t) - (F/V_d + \lambda) \cdot C_t(t) \quad (\text{A})$$

where $C_t(t)$ is the regional tissue concentration of H_2^{15}O [Bq/ml (tissue)] as a function of time t , $C_a(t)$ is the arterial whole blood concentration of H_2^{15}O [Bq/ml (tissue)] as a function of time t , F is the regional flow in ml (blood)/ml (tissue)/min, V_d is the volume of distribution of water [ml (blood)/ml (tissue)], and, λ is the decay constant of ^{15}O ($= 0.338 \text{ min}^{-1}$).

The solution to this differential equation is given by

$$C_t(t) = F \cdot C_a(t) \star \exp[-(F/V_d + \lambda) \cdot t] \quad (\text{B})$$

where \star denotes the operation of convolution. $C_t(t)$ represents the tissue response to an arterial input function $C_a(t)$. When $C_a(t)$ and $C_t(t)$ are measured over time with dynamic positron emission tomography, best estimates of both F and V_d can be obtained using standard nonlinear

regression analysis. It should be noted that $C_a(t)$ and $C_t(t)$ should not be corrected for decay, since that has already been incorporated in Equation B.

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