

ORIGINAL ARTICLE

First-in-human quantitative [^{15}O]H $_2\text{O}$ PET imaging of tumour blood flow at rest and during exercise in lymphoma patients

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ABSTRACT

Background and purpose: Although exercise is recommended for cancer patients, its acute effects on tumour blood flow (TBF) have not been quantified in humans. As TBF may influence tumour progression and treatment efficacy, we assessed its circulatory responses in malignant lymphoma during exercise using dynamic PET imaging.

Patient/material and methods: Eight patients with Hodgkin or non-Hodgkin lymphoma underwent thoracic [^{15}O]H $_2\text{O}$ positron emission tomography/computed tomography (PET/CT) at rest and during 10 min of supine cycling (Borg RPE 11–16). TBF and its heterogeneity, tumour blood volume (TBV), mean transit time (MTT), and vascular resistance were quantified in eight index and three secondary tumours.

Results: Baseline TBF in index tumours was high (mean 57.6 mL/dL/min; range 30.3–105.0). During exercise, TBF (mean 48.1 ± 16.1 mL/dL/min), its heterogeneity and MTT did not change significantly. However, TBV decreased ($p = 0.038$), and vascular resistance tended to increase ($p = 0.055$). TBF change correlated positively with age ($r = 0.73$, $p = 0.04$) and negatively with tumour volume ($r = -0.67$, $p = 0.02$), but not with heart rate or power output. Secondary tumours showed similar exercise responses, with lower absolute TBF ($p = 0.02$).

Interpretation: This study demonstrates the feasibility of using [^{15}O]H $_2\text{O}$ PET/CT to quantify TBF in lymphoma patients in real time during acute exercise. Baseline TBF is remarkably high in lymphoma tumours, and responses to acute exercise are variable, tending to decline in younger patients and larger tumours, while vascular resistance tended to increase.

ARTICLE HISTORY

Received 25 March 2026
Accepted 30 May 2026
Published 24 June 2026

KEYWORDS

Positron-emission tomography; lymphoma; tumour blood supply; exercise; oncology

Introduction

Cancer is one of the leading causes of death worldwide and a major global public health challenge. Despite advances in screening, prevention, early diagnosis, and treatment, the global burden of cancer continues to rise, with an estimated 20 million new cancer cases and 9.7 million cancer deaths in 2022 [1]. Lymphomas are a heterogeneous group of lymphoid malignancies broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [2].

Lifestyle factors, including physical inactivity, play a significant role in cancer development and progression. Physical inactivity has reached alarming levels globally, with nearly one third of adults worldwide failing to meet the World Health Organization's (WHO) recommendations for physical activity [3]. There is strong evidence that regular physical activity reduces the risk of several major cancer types, including colorectal and breast cancer, and emerging evidence suggests that it is also

associated with improved survival outcomes [4–7]. In addition to its role in primary prevention, physical activity is increasingly recognised as a supportive strategy in cancer care, with growing evidence linking it to improved prognosis across multiple cancer types [8–10]. Exercise is a feasible and effective means of complementary treatment in lymphoma patients [11].

Preclinical studies suggest that physical activity may slow tumour progression and improve outcomes by modulating tumour growth, metastatic potential, metabolism, micro-environment, and immunology [12, 13]. Aerobic exercise training in animal models of prostate cancer has been shown to increase the mean number of perfused tumour vessels and perfused tumour area [14] and reduce tumour hypoxia [15] compared to control animals (from 3.0% of perfused area of total tumour to 7.4% of perfused area) [14]. This effect has been attributed to normalisation of the tortuous, leaky tumour vasculature, which despite strong angiogenic drive results in

poor perfusion [14]; however, exercise training did not alter vessel contractile function [15]. In similar prostate cancer models, acute exercise did not alter blood flow to ectopic (subcutaneous) tumours, but increased the blood flow of orthotopic tumours by approximately 200% when measured with infusion of radiolabelled microspheres, indicating that tumour blood flow (TBF) is dependent on the location of the tumour and host tissue haemodynamics [16], and partly dependent on an attenuation of sympathetic vasoconstriction in preclinical models [14–16]. Moreover, exercise-induced increases in cardiac output and blood pressure likely elevate perfusion pressure within experimental tumours [17], contributing to changes in perfusion dynamics in tumour models. These haemodynamic changes can alter TBF and oxygenation, critical determinants of treatment efficacy, as blood flow of solid tumours is often poor, and together with hypoxia, is known to impair the response to most oncological therapies [18]. Heterogeneous TBF is a major contributor to hypoxia, and preclinical evidence suggests that exercise may reduce TBF heterogeneity and thereby improve tumour oxygenation [13, 14, 19]. In contrast, the direct mechanistic and clinical effects of acute exercise on human tumours remain largely unknown.

To assess whether these preclinical findings translate to humans – particularly to lymphoma patients – we conducted this study. Specifically, we investigated acute exercise-induced changes in TBF and its heterogeneity using [¹⁵O]H₂O PET/CT imaging in patients with HL or NHL before the onset of oncological treatment. We hypothesised that, consistent with preclinical data, TBF would increase during acute exercise.

Patients/material and methods

This prospective, single-arm clinical study was conducted at the Turku PET Centre, Turku, Finland (ClinicalTrials.gov ID: NCT03987724). The study protocol was approved by the Ethics Committee of the Hospital District of Southwestern Finland. All participants provided written informed consent prior to enrolment. The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient population

Eight patients (six men, two women) with histologically confirmed HL or NHL, referred for oncological treatment at Turku University Hospital, were enrolled. Eligible patients were ≥18 years of age, had newly diagnosed (*n* = 5) or recurrent (*n* = 3) disease, and presented with tumour involvement in the neck and/or thorax. Staging was performed using whole-body CT (*n* = 3) or [¹⁸F]FDG PET/CT (*n* = 5), according to institutional protocols.

Exclusion criteria were abnormal fatigue, anaemia, or disease-related physical impairment; inability to comprehend written Finnish or any chronic condition posing risk or interfering with study procedures. Patients were selected based on physical fitness and favourable tumour locations for thoracic PET imaging. All HL cases (*n* = 3) were of the nodular sclerosis subtype. Among the NHL cases, two patients (Nos. 1 and 2) had diffuse large B-cell lymphoma, two (Nos. 3 and 5) had low-grade follicular lymphoma, and one (No. 8) had small lymphocytic lymphoma. PET imaging was performed prior to the initiation of oncological therapy. The average age of the patients was 54 years (range: 20–69 years), and their mean body mass index (BMI) was 26.6 kg/m² (range: 21.1–34.3 kg/m²). Patients' characteristics are summarised in Table 1.

Exercise imaging protocol and physiological monitoring

To assess the effects of acute exercise on TBF and its heterogeneity, patients performed a 10-min session of supine cycling on a modified ergometer (Tunturi E30R, Tunturi New Fitness B.V., Almere, The Netherlands) during dynamic PET acquisition (Figure 1). The exercise protocol, previously utilised at the Turku PET Centre [20–22], was incorporated into the clinical imaging schedule without delaying the start of treatment or introducing additional interventions. Participants were instructed to abstain from vigorous physical activity, alcohol, and caffeine for ≥ 24 h prior to imaging. Exercise intensity was not standardised to a fixed absolute workload or percentage of maximal capacity to be similar in all patients, but was individually adjusted based on perceived exertion (Borg RPE 11–16) to ensure feasibility and tolerability in this patient population.

Table 1. Clinical and demographic characteristics of the study participants.

No.	Sex	Age	BMI (kg/m ²)	Histologic type	Ann Arbor stage	IPI/IPS score*	Charlson Comorbidity index**	Index tumour volume (cm ³)
1	M	60–64	34	Diffuse large B-cell lymphoma	IA	2	4	6.2
2	M	60–64	27	Diffuse large B-cell lymphoma	IVA	4	6	2.2
3	F	65–69	24	Follicular lymphoma	IIA	1	4	9.2
4	M	20–24	25	Hodgkin's lymphoma	IVB	3	0	1332.7
5	M	65–69	27	Follicular lymphoma	IIIA	3	3	3.1
6	M	50–54	25	Hodgkin's lymphoma	IIB	4	3	29.3
7	M	20–24	21	Hodgkin's lymphoma	IIA	3	0	409.6
8	F	65–69	28	Small lymphocytic lymphoma	IIIA	0	2	2.5

BMI: body mass index; IPI: International Prognostic Index; IPS: International Prognostic Score; CCI: Charlson Comorbidity Index. Patients with histologically confirmed lymphoma (*n* = 8) are described by sex (M, male, F, female), age group, BMI, histologic subtype, Ann Arbor stage, IPI or IPS, CCI and index tumour volume (cm³). Age is presented in 5-year ranges to ensure patient confidentiality.



Figure 1. Supine bicycle exercise setup during [^{15}O]H $_2\text{O}$ PET imaging. To assess the effects of acute exercise on TBF and its heterogeneity, patients performed a 10-min session of supine cycling on a modified ergometer (Tunturi E30R; Tunturi New Fitness B.V., Almere, The Netherlands) during dynamic PET acquisition. Exercise intensity was tailored individually based on pre-study evaluation to ensure a sustainable pedalling rhythm. Heart rate (HR) and perceived exertion were monitored using a pulse oximeter (Palmsat 2500; Nonin, USA) and the Borg scale, respectively. Workload was recorded in watts.

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Systemic haemodynamic parameters – HR, systolic and diastolic blood pressure (Apteq AE701f, Rossmax Swiss GmbH, Switzerland), and arterial oxygen saturation – were monitored continuously. The rate–pressure product (RPP) was calculated as $\text{HR} \times \text{systolic blood pressure}$. Mean arterial pressure (MAP) was calculated as $[(2 \times \text{diastolic}) + \text{systolic}] / 3$. The predicted maximal HR (bpm) was calculated as $220 - \text{age}$. TBF-related variables were assessed at rest and during exercise, including tumour blood volume (TBV), mean transit time (MTT, mL/dL-s), and tumour vascular resistance ($\text{mmHg} \cdot \text{dL}^{-1} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$), along with systemic parameters such as HR, MAP, RPP, and oxygen saturation.

Radiotracer production

[^{15}O]H $_2\text{O}$ was synthesised at the Turku PET Centre using established protocol [23]. Good Manufacturing Practice (GMP)

procedures were followed to verify the radiochemical purity, pH, and radioactivity of the [^{15}O]H $_2\text{O}$ bolus.

PET/CT imaging protocol

Imaging was performed using either a GE Discovery 690 or GE Discovery MI PET/CT scanner (General Electric Medical Systems, GEMS, Milwaukee, WI, USA), depending on scanner availability [24]. A venous catheter was inserted into a forearm vein for tracer administration. Patients were positioned supine with feet secured to the ergometer and arms elevated above the head for stability (Figure 1). A low-dose CT scan was acquired for attenuation correction, and standard corrections for attenuation, scatter, and decay were applied. Dynamic PET images acquired with the Discovery 690 scanner were reconstructed using the GE VUEPoint FX SharpIR (VPFXS) algorithm, whereas images acquired with the Discovery MI scanner were reconstructed using the GE VUEPoint HD SharpIR (VPHDS) algorithm, with 6 iterations and 17 subsets, using a 256×256 matrix and a 70 cm display field of view. A bolus of ~ 700 MBq [^{15}O]H $_2\text{O}$ was administered intravenously, followed by a 6-min dynamic PET acquisition of the thorax and lower neck at rest. After a decay period, the patient commenced supine cycling, and a second 6-min dynamic scan was initiated during the exercise session (start time: 4 min after exercise onset, thus steady-state exercise).

Region-of-interest definition

An experienced specialist in diagnostic radiology first reviewed the diagnostic CT or [^{18}F]FDG PET/CT scans in each patient and selected a main lymphoma nodule as the index tumour for TBF measurement. Three patients had an additional secondary tumour conveniently located in the same field-of-view available for analysis. All 11 tumours were identified visually from the experimental [^{15}O]H $_2\text{O}$ scans using low-dose CT guidance, tracer uptake patterns, and prior diagnostic imaging. Differences in patient positioning precluded direct co-registration of diagnostic and experimental CT or PET/CT scans. Regions of interest (ROIs) were then manually delineated and drawn using the Carimas software platform [25] (version 2.10, <https://turkupetcentre.fi/carimas/academic/features/>) in all cross-sectional planes with visible tracer accumulation and automatically summed to create a 3D ROI representing the TBF-activated tumour volume. For exercise images, the resting ROIs were transferred and aligned to ensure anatomical consistency. No respiratory gating was performed, and therefore motion correction was not applied. In cases with large or irregular HL masses, the most representative region was selected for analysis (Figure 2).

Input function and reference tissue

The ascending aorta was used as the source of the input function in seven patients; in one case (No. 6), the right common carotid artery was used due to tumour location. A circular ROI was manually drawn over the vessel lumen and applied

consistently across rest and exercise scans. The same ROI location for input function was used for both rest and exercise measurements within each individual. The right deltoid muscle served as a reference tissue representing resting muscle blood flow.

Blood flow calculation, its heterogeneity and tumour vascular resistance

TBF based on time-activity curves was quantified using a previously validated [^{15}O]H $_2$ O kinetic model (http://www.turkupet-centre.net/petanalysis/model_radiowater.html).

Due to the limited spatial resolution of PET-[^{15}O]H $_2$ O for assessment of spatial blood flow heterogeneity, summed radioactivity images (0–90 s) were used to assess spatial heterogeneity, assuming a linear correlation between tracer activity and blood flow. TBF heterogeneity was then defined as the voxel-wise coefficient of radioactivity variation (standard deviation [SD] within the ROI divided by mean radioactivity). Tumour vascular resistance was calculated as MAP divided by corresponding TBF.

Statistical methods

Results are presented as mean $\pm$ SD and, where appropriate, median and range. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (version 8.0). Dependent Student's *t*-test was used to compare rest and exercise values. For secondary analyses, mixed-effects models for repeated measures were applied to examine tumour, time, and tumour $\times$ time interaction effects. Correlations were evaluated using two-tailed Pearson's correlation coefficient. A *p*-value <0.05 was considered statistically significant.

Results

In total, 21 participants were contacted and found eligible in the screening phase. Of them, two women and six men (38%) volunteered for this study. Pedalling power of the exercise ranged from 20 to 90 watts (average 57 ± 25) between subjects. According to the subject's own experience and their sense of fatigue, RPE ranged from 11 to 16 (average 13 ± 1) on the Borg scale (20 corresponds to maximal exhaustive effort). HR increased from rest (77 ± 14 bpm) to exercise (112 ± 20 bpm). The latter was $68 \pm 14\%$ of the age-predicted maximal HR. Also MAP (from 89 ± 9 mmHg to 104 ± 25 mmHg) and RPP (from $9,792 \pm 1,934$ bpm $\cdot$ mmHg to $16,642 \pm 4,122$ bpm $\cdot$ mmHg) increased by exercise. All of these physiological exertion measures increased from rest to exercise ($p < 0.05$). The index tumour volume showed a highly skewed distribution (median 7.7 cm ^{3} , range 2.2–1332.7; mean 224.3 ± 469.4 cm ^{3} , $n = 8$), reflecting substantial interindividual variability. The mean secondary tumour volume was 4.9 ± 3.1 cm ^{3} (median 3.2 cm ^{3} , range 3.0–8.6; $n = 3$). Individual index tumour volumes are shown in Table 1.

Representative TBF PET radiowater images at rest and during exercise, along with corresponding diagnostic CT and [^{18}F]FDG PET/CT scans of two patients, are shown in Figures 2A and 2B. The resting baseline TBF in lymphoma index tumours was high (median 49.6 mL/dL/min, range 30.3–105.0; mean 57.6 ± 26.4 mL/dL/min), and remained similar during exercise (median 44.6 mL/dL/min, range 23.8–74.0; mean 48.1 ± 16.1 mL/dL/min) (Figure 3). Mean TBF heterogeneity at rest was $36 \pm 16\%$ and during exercise $34 \pm 13\%$. TBV was significantly ($p = 0.038$) reduced and tumour vascular resistance tended ($p = 0.055$) to increase (Figure 3). Exercise-induced change in TBF (Figure 4) correlated positively with age and negatively with the tumour volume, but not with any other exercise exertion measures such as power output or HR (data not shown). Tumour volume did not correlate with TBF at rest ($r = 0.46$, $p = 0.15$) or during exercise ($r = 0.07$, $p = 0.84$).

Inclusion of secondary tumours in the analyses revealed that the interaction of tumour $\times$ time was not significant in terms of TBF ($p = 0.43$), thus TBF responses did not depend on the index/location/size of the tumours. As expected, TBF was significantly lower ($p = 0.02$) in the three secondary tumours compared to eight index tumours, both at rest and during exercise (secondary TBF at rest 24.2 ± 6.9 mL/dL/min and in exercise 25.5 ± 11.3 mL/dL/min). Furthermore, vascular resistance tended ($p = 0.08$) to be higher in the secondary tumours than that in the index tumours, but no main or interaction effects were seen between the index versus secondary tumour BV and MTT variables (all *p*-values > 0.14 , data not shown). Lymph node or inactive muscle (deltoid muscle in the image area) blood flow did not change from rest to exercise (Figure 5). Lymph node or muscle BV, blood MTT or vascular resistance did not change either from rest to exercise (data not shown).

Discussion and conclusion

To the best of our knowledge, this is the first prospective clinical study to evaluate TBF during acute exercise in human cancer patients. Using [^{15}O]H $_2$ O PET/CT, we demonstrated the feasibility of non-invasive, quantitative imaging of TBF in patients with lymphoma under physiological exercise stress. Although pre-clinical studies have suggested that aerobic exercise may enhance tumour perfusion [14–16, 26], our findings do not support these preclinical findings regarding TBF during acute exercise in human lymphoma. Instead, TBF responses in these patients were heterogeneous, with several patients demonstrating reduced TBF during exercise. These results underline the complexity of human tumour vascular regulation and the challenges in translating exercise-oncology findings from animal models to the clinical setting.

At rest, TBF in lymphoma tumours was relatively high, ranging from 30.3 to 105.0 mL/dL/min, with a mean value several-fold higher than that typically reported, for instance, in resting skeletal muscle (~ 2 –4 mL/dL/min) [27]. Compared to solid tumours studied with [^{15}O]H $_2$ O PET, such as prostate (16–26 mL/dL/min) [28], breast (30 mL/dL/min before therapy) [29], or head and neck cancers (30–65 mL/dL/min) [30], TBF in our lymphoma

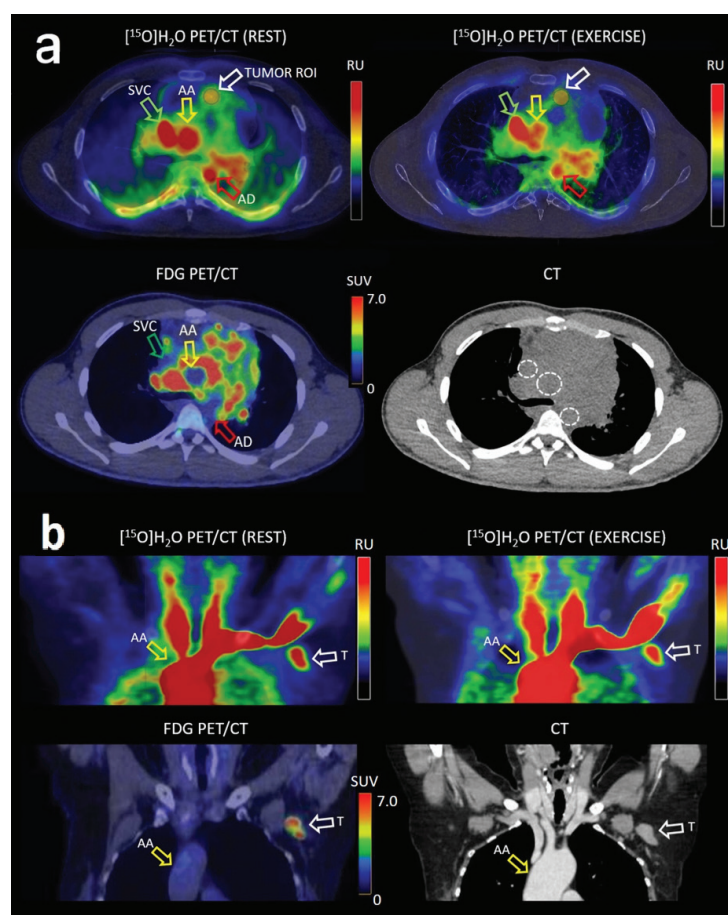


Figure 2. Two patient cases illustrating tumour identification and analyses. (A) Axial $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT summed radioactivity images (0–90 s) at rest and during acute exercise in a 20-year-old man with Hodgkin's lymphoma. Images were reconstructed using the scanner-specific GE reconstruction algorithm, as described in the Methods. This patient (No. 4) presented with dyspnoea due to a bulky mediastinal tumour (index tumour) showing highly heterogeneous perfusion and metabolism. The retrosternal part of the tumour with the highest regional TBF and the corresponding ROI (green circle) are indicated with an open white arrow. The superior vena cava (SVC), ascending aorta (AA), and descending aorta (AD) are marked with green, yellow, and red open arrows, respectively. Colour scale bars indicate relative uptake (RU). The diagnostic $[^{18}\text{F}]\text{FDG}$ PET/CT and low-dose CT scans highlight the large size of the tumour. On CT, the great vessels are outlined with dashed white circles. SUV, standardised uptake value; ROI, region of interest; T, tumour. (B) Coronal $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT summed radioactivity images (0–90 s) at rest and during acute exercise in a 69-year-old woman with follicular lymphoma. Images were reconstructed using the scanner-specific GE reconstruction algorithm, as described in the Methods. She had previously achieved complete remission following chemotherapy and rituximab for diffuse large B-cell lymphoma and now presented with recurrence in the left axilla confirmed by diagnostic $[^{18}\text{F}]\text{FDG}$ PET/CT and contrast-enhanced CT. The tumour (T) is clearly visible on all coronal scans (white arrow), together with the ascending aorta (AA). Colour scale bars indicate relative uptake (RU) and standardised uptake value (SUV).

cohort appears notably high. Historical clearance-based studies have also described relatively high blood flow in lymphoma, with average values around 35 mL/dL/min [31], but our quantitative and validated values are thus even higher.

The most important question for the present investigation was whether TBF increases from rest to exercise, as suggested by preclinical studies [14, 15]. This is an important question to answer as it has been suggested and studied [32], based on only preclinical evidence, that chemotherapy should be administered during exercise, with the rationale that increased TBF during exercise would direct more chemotherapy to the tumour, leading to improved treatment responses. However, our results do not support this assumption in the context of acute exercise in lymphoma. While a few patients demonstrated increased TBF during exercise, most patients showed decreased TBF, whereas the mean group response did not differ from resting baseline

values. Furthermore, the significant decrease in TBF during exercise, alongside a tendency for increased vascular resistance, may rather reflect exercise-induced functional vasoconstriction in the tumour during exercise, suggesting that (sympathetic) regulatory mechanisms may be well-functioning in patients.

Notably, the change in TBF during exercise correlated positively with age and negatively with tumour volume (Figure 4). Thus, older age and smaller tumour volume were associated with larger increases in TBF, whereas younger patients and those with larger tumours tended to show little change or even reductions, indicating that vascular reactivity is not uniform across patients and tumours. These associations may partly be interrelated, as the two youngest patients in this cohort were HL patients with the largest tumours. Owing to the small sample size, these findings should therefore be interpreted as exploratory. Such variability is consistent with prior findings

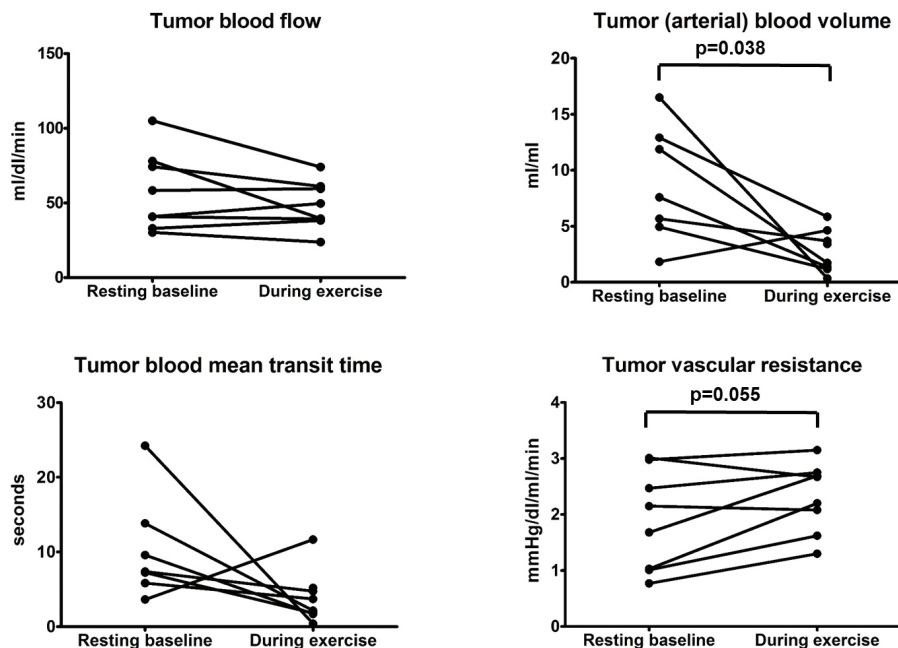


Figure 3. Tumour blood flow (TBF), tumour (arterial) blood volume (BV), tumour blood mean transit time (MTT), and tumour vascular resistance at resting baseline and during exercise. The resting baseline TBF in lymphoma index tumours was high (median 49.6 mL/dL/min, range 30.3–105.0; mean 57.6 ± 26.4 mL/dL/min), and during exercise TBF was 44.6 mL/dL/min (range 23.8–74.0; mean 48.1 ± 16.1 mL/dL/min).

showing that tumour vasculature differs markedly between patients and even within tumours, contributing to spatially heterogeneous perfusion and drug delivery [33]. Abnormal vessel architecture, elevated interstitial pressure, and stromal resistance are known to limit perfusion and may explain the reductions in TBF observed in some participants despite increased flow in systemic circulation. In contrast, no relationship was found between TBF changes and conventional markers of exertion, such as cycling power or HR. These dynamic responses contrast with the well-documented baseline vascular heterogeneity in lymphoma [34] and are consistent with the broader variability reported in exercise-oncology studies [35]. In this cohort, tumour MTT and perfusion heterogeneity remained unchanged during exercise, suggesting that exercise-induced blood flow alterations were likely due to limited vasodilatory capacity rather than intratumoural blood redistribution. Secondary tumours exhibited lower TBF than index tumours at both rest and exercise, with no interaction between tumour site and condition. No significant vascular changes were detected in reference tissues such as lymph nodes or skeletal muscle, indicating stable background perfusion. Other vascular parameters in secondary tumours, including BV and MTT, also showed no condition-dependent effects, although vascular resistance tended to be higher.

Some degree of methodological variability should also be considered when interpreting individual TBF responses. Although $[^{15}\text{O}]\text{H}_2\text{O}$ PET is a validated quantitative perfusion method, repeated dynamic measurements during exercise are susceptible to variability related to motion, ROI delineation, and image-derived input functions. Previous test–retest studies suggest repeatability coefficients in the range of approximately 30–40% [36–39]. Thus, modest individual changes should be

interpreted cautiously. However, the concurrent decrease in TBV, tendency towards increased vascular resistance, and associations between TBF changes, age, and tumour volume suggest that the observed heterogeneity is unlikely to be explained by measurement variability alone.

The present findings differ from several preclinical studies in murine models, where acute exercise – particularly in orthotopic tumours – enhanced perfusion, reduced hypoxia, and improved drug delivery [14, 15]. In contrast, ectopic tumours such as subcutaneous implants often demonstrate blunted or contrasting responses, likely due to poor vascular integration and normal or even heightened susceptibility to sympathetic vasoconstriction [16]. Although human lymphomas are not ectopic in this sense, the limited perfusion response observed here may reflect similar physiological constraints, including aberrant vessel architecture, elevated interstitial pressure, and impaired vasoregulatory capacity [40, 41]. In cases where vasoregulatory mechanisms are preserved, acute exercise is likely to elicit functional vasoconstriction within the tumour, reducing TBF despite increased systemic circulation, which may partly explain our findings.

The absence of a systematic TBF increase raises questions regarding the timing and durability of exercise-induced vascular effects. Peak changes may occur after, rather than during, exercise, and repeated aerobic sessions may be required to induce vascular remodelling or normalisation, thereby improving oxygenation and treatment efficacy [18, 40]. The observed associations between TBF changes, age, and tumour volume suggest that both host and tumour characteristics influence vascular responsiveness, warranting further study into determinants such as autonomic nervous system regulation and microenvironmental heterogeneity [19, 42].

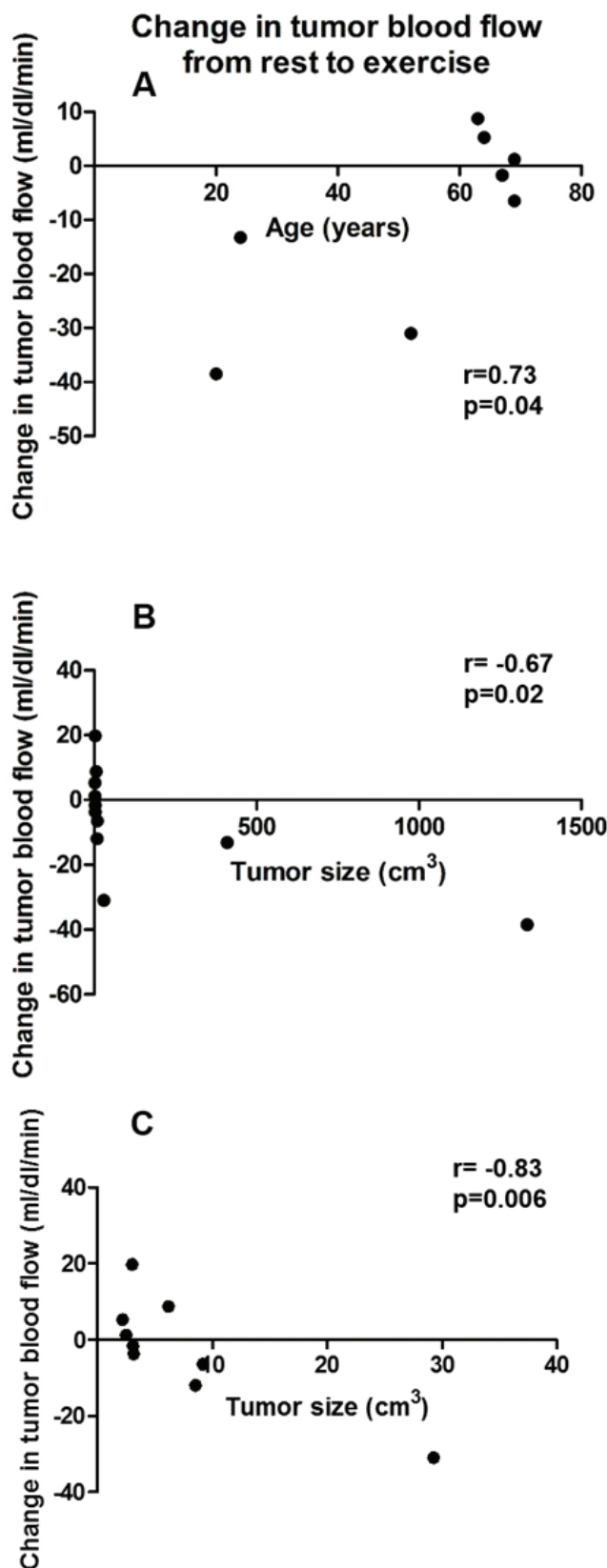


Figure 4. Correlations between the change in tumour blood flow (TBF) from rest to exercise and patient or tumour characteristics. (A) Exercise-induced change in TBF correlated positively with age ($r=0.73$, $p=0.04$), and (B) negatively with tumour volume ($r=-0.67$, $p=0.02$). (C) When the two largest tumours were excluded, the negative correlation between tumour volume (cm^3) and change in TBF remained significant and stronger ($r=-0.83$, $p=0.006$).

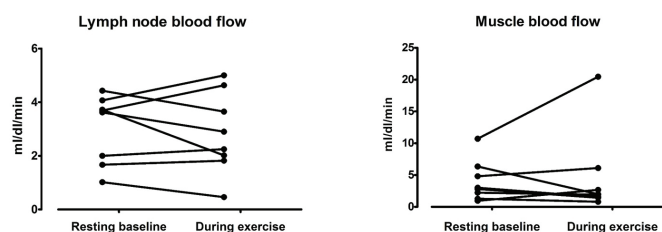


Figure 5. Blood flow in lymph nodes and skeletal muscle (m. deltoideus) at resting baseline and during exercise. There was no significant change in lymph node or (inactive) skeletal muscle blood flow from rest to exercise.

Despite the modest sample size ($n=8$) and biological heterogeneity from the inclusion of both HL and NHL, this study demonstrates the technical feasibility of $[^{15}\text{O}]\text{H}_2\text{O}$ PET during exercise in a clinical setting. The generalisability of these findings to other cancer types remains uncertain. Lymphoma differs from many solid tumours in vascular architecture and micro-environment, and exercise-induced perfusion responses may therefore vary between tumour types and anatomical locations. These findings highlight the need for tumour-specific studies investigating haemodynamic responses to exercise.

In summary, this study is, to the best of our knowledge, the first to quantify TBF during acute exercise using validated $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT. The findings provide novel insights into lymphoma vascular behaviour under physiological stress and support further investigation of exercise as a modulator of tumour haemodynamics. However, the present results caution against assuming that tumour perfusion uniformly increases during acute exercise in human cancers.

Strengths and limitations

This study has several important strengths. The study quantified TBF at rest and during acute exercise using validated dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CT imaging. The protocol thus enabled real-time assessment of tumour perfusion under physiological exercise stress in a clinically feasible setting. In addition, the high sensitivity and spatial resolution of the method enabled detection of physiologically relevant perfusion patterns in both primary and secondary tumours.

The study also has limitations. The sample size was small and included both HL and NHL, limiting subgroup analyses and generalisability. Exercise intensity was individually adjusted rather than standardised to a fixed workload, which may have contributed to interindividual variability in haemodynamic responses. Respiratory motion, patient movement during exercise, and manual co-registration of ROIs between rest and exercise scans may also have affected perfusion estimates, particularly in smaller lesions. In addition, the current supine cycling protocol is most suitable for thoracic tumours and may not be directly applicable to other anatomical regions. Furthermore, $[^{15}\text{O}]\text{H}_2\text{O}$ PET quantifies total vascular volume rather than exclusively perfused vessels, which may influence absolute TBF estimates. In addition, repeated dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ PET measurements during exercise are subject to methodological

variability related to motion, ROI delineation, and image-derived input functions, and modest individual changes should therefore be interpreted cautiously in the light of previously reported repeatability coefficients.

Conclusion

This study demonstrates the feasibility of using [^{15}O]H $_2$ O PET/CT to quantify TBF in lymphoma patients in real time not only at rest but also during acute exercise. The protocol provides a robust platform for future investigations into the effects of physical activity on tumour haemodynamics and its therapeutic relevance. Importantly, our findings caution against assuming that acute exercise consistently augments TBF in human cancers. The observed associations with age and tumour volume further highlight the role of host and tumour characteristics in modulating vascular responses. Future studies should explore whether repeated bouts of exercise or chronic training can induce vascular remodelling, improve blood flow and oxygenation, and enhance treatment efficacy in cancers other than lymphoma.

Acknowledgements

The authors would like to thank the staff of the Turku Cyclotron and Radiochemistry Laboratory for technical support and advice, and the staff of the Turku PET Centre and the Department of Oncology and Radiotherapy for their assistance with patient imaging. We also thank biostatistician Eliisa Löyttyniemi for statistical consultation. The authors used ChatGPT (OpenAI, version GPT-5.0) to assist with language editing. All scientific content was written, verified, and approved by the authors. This work was financially supported by the Academy of Finland and the Hospital District of Southwest Finland. The funders had no role in study design; collection, analysis, or interpretation of data; writing of the manuscript; or the decision to submit the article for publication.

Disclosure Statement

The authors report that there are no competing interests to declare.

Data availability statement

The datasets generated and/or analysed during this study are available from the corresponding author on reasonable request.

Ethics declarations & trial registry information

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Hospital District of Southwest Finland (approval no.: 72/2018). Written informed consent was obtained from all participants. ClinicalTrials.gov NCT03987724. Registered 17 June 2019.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SL, TK and IH. TT and AK took part in data collection. LN contributed to CT image review by identifying tumour locations. The first draft of the manuscript was written by SL and further developed by MP. All authors commented on previous versions of the manuscript and approved the final version.

References

- [1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74:229–63. <https://doi.org/10.3322/caac.21834>
- [2] Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet.* 2012;380:848–57. [https://doi.org/10.1016/S0140-6736\(12\)60605-9](https://doi.org/10.1016/S0140-6736(12)60605-9)
- [3] Strain T, Flaxman S, Guthold R, Semenova E, Cowan M, Riley LM, et al. National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: a pooled analysis of 507 population-based surveys with 5.7 million participants. *Lancet Glob Health.* 2024;12:e1232–43. [https://doi.org/10.1016/S2214-109X\(24\)00150-5](https://doi.org/10.1016/S2214-109X(24)00150-5)
- [4] McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc.* 2019;51:1252–61. <https://doi.org/10.1249/MSS.0000000000001937>
- [5] Fiuza-Luces C, Valenzuela PL, Gálvez BG, Ramírez M, López-Soto A, Simpson RJ, et al. The effect of physical exercise on anticancer immunity. *Nat Rev Immunol.* 2024;24:282–93. <https://doi.org/10.1038/s41577-023-00943-0>
- [6] Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med.* 2016;176:816–25. <https://doi.org/10.1001/jamainternmed.2016.1548>
- [7] Bai P, Ning X, Gao R, Shao X, Zhou S, Li J, et al. Association between circadian physical activity patterns and cancer incidence through regulation of inflammation: a UK Biobank study. *Prev Med.* 2024;179:107831. <https://doi.org/10.1016/j.ypmed.2023.107831>
- [8] Cormie P, Atkinson M, Bucci L, Cust A, Eakin E, Hayes S, et al. Clinical Oncology Society of Australia position statement on exercise in cancer care. *Med J Aust.* 2018;209:184–7. <https://doi.org/10.5694/MJA18.00199>
- [9] Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the Health Professionals Follow-up Study. *J Clin Oncol.* 2011;29:726–32. <https://doi.org/10.1200/JCO.2010.31.5226>
- [10] Cormie P, Zopf EM, Zhang X, Schmitz KH. The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. *Epidemiol Rev.* 2017;39:71–92. <https://doi.org/10.1093/epirev/mxx007>
- [11] Grønset C, Bech MN, Jarden M, Høgdal N, Hutchings M, Suetta C, et al. The effectiveness of exercise-based interventions on muscle mass, muscle strength, functional performance, aerobic capacity, and health-related quality of life in adults with malignant lymphoma undergoing chemotherapy: a systematic review of randomized controlled trials. *Acta Oncol.* 2025;64:129–42. <https://doi.org/10.2340/1651-226X.2025.42056>
- [12] Pedersen L, Christensen JF, Hojman P. Effects of exercise on tumor physiology and metabolism. *Cancer J.* 2015;21:111–6. <https://doi.org/10.1097/PPO.0000000000000096>
- [13] Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. *Nat Rev Cancer.* 2017;17:620–32. <https://doi.org/10.1038/nrc.2017.78>

- [14] McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. *J Natl Cancer Inst.* 2014;106:dju036. <https://doi.org/10.1093/jnci/dju036>
- [15] McCullough DJ, Nguyen LMD, Siemann DW, Behnke BJ. Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol* (1985). 2013;115:1846–54. <https://doi.org/10.1152/japplphysiol.00949.2013>
- [16] Garcia E, Becker VGC, McCullough DJ, Stabley JN, Gittemeier EM, Opoku-Acheampong AB, et al. Blood flow responses to mild-intensity exercise in ectopic vs. orthotopic prostate tumors: dependence upon host tissue hemodynamics and vascular reactivity. *J Appl Physiol* (1985). 2016;121:15–24. <https://doi.org/10.1152/japplphysiol.00266.2016>
- [17] Heinonen I, Kalliokoski KK, Hannukainen JC, Duncker DJ, Nuutila P, Knuuti J. Organ-specific physiological responses to acute physical exercise and long-term training in humans. *Physiology* (Bethesda). 2014;29:421–36. <https://doi.org/10.1152/physiol.00067.2013>
- [18] Siemann DW, Horsman MR. Modulation of the tumor vasculature and oxygenation to improve therapy. *Pharmacol Ther.* 2015;153:107–24. <https://doi.org/10.1016/j.pharmthera.2015.06.006>
- [19] Heinonen I, Koga S, Kalliokoski KK, Musch TI, Poole DC. Heterogeneity of muscle blood flow and metabolism: influence of exercise, aging and disease states. *Exerc Sport Sci Rev.* 2015;43:117–24. <https://doi.org/10.1249/JES.0000000000000044>
- [20] Koivula T, Lempiäinen S, Rinne P, Hollmén M, Sundberg CJ, Rundqvist H, et al. Acute exercise mobilizes CD8+ cytotoxic T cells and NK cells in lymphoma patients. *Front Physiol.* 2023;13:1078512. <https://doi.org/10.3389/fphys.2022.1078512>
- [21] Koivula T, Lempiäinen S, Rinne P, Rannikko JH, Hollmén M, Sundberg CJ, et al. The effect of acute exercise on circulating immune cells in newly diagnosed breast cancer patients. *Sci Rep.* 2023;13:6685. <https://doi.org/10.1038/s41598-023-33432-4>
- [22] Koivula T, Uurasmaa TM, Han C, Maaniitty T, Latifi S, Lempiäinen S, et al. Myocardial blood flow in newly diagnosed breast cancer patients at rest and during exercise. *iScience.* 2024;27:111081. <https://doi.org/10.1016/j.isci.2024.111081>
- [23] Sipilä HT, Clark JC, Peltola O, Teräs M. An automatic [^{15}O]H $_2$ O production system for heart and brain studies. *J Label Compd Radiopharm.* 2001;44(Suppl 1):S1066–8. <https://doi.org/10.1002/jlcr.25804401381>
- [24] Bettinardi V, Presotto L, Rapisarda E, Picchio M, Gianolli L, Gilardi MC. Physical performance of the new hybrid PET/CT Discovery-690. *Med Phys.* 2011;38:5394–411. <https://doi.org/10.1118/1.3635220>
- [25] Rainio O, Han C, Teuho J, Nesterov SV, Oikonen V, Pirola S, et al. Carimas: an extensive medical imaging data processing tool for research. *J Digit Imaging.* 2023;36:1885–93. <https://doi.org/10.1007/s10278-023-00812-1>
- [26] Jones LW, Viglianti BL, Tashjian JA, Kothadia SM, Keir ST, Freedland SJ, et al. Effect of aerobic exercise on tumor physiology in an animal model of human breast cancer. *J Appl Physiol* (1985). 2010;108:343–8. <https://doi.org/10.1152/japplphysiol.00424.2009>
- [27] Heinonen I, Saltin B, Kemppainen J, Saraste A, Oikonen V, Nuutila P, et al. Skeletal muscle blood flow and oxygen uptake at rest and during exercise in humans: a PET study with nitric oxide and cyclooxygenase inhibition. *Am J Physiol Heart Circ Physiol.* 2011;300:H1510–7. <https://doi.org/10.1152/ajpheart.00996.2010>
- [28] Jochumsen MR, Christensen NL, Iversen P, Gormsen LC, Sørensen J, Tolbod LP. Whole-body parametric mapping of tumour perfusion in metastatic prostate cancer using long axial field-of-view [^{15}O]H $_2$ O PET. *Eur J Nucl Med Mol Imaging.* 2024;51:4134–40. <https://doi.org/10.1007/s00259-024-06799-3>
- [29] Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Schubert EK, Tseng J, et al. Changes in blood flow and metabolism in locally advanced breast cancer treated with neoadjuvant chemotherapy. *J Nucl Med.* 2003;44:1806–14.
- [30] Lehtiö K, Oikonen V, Grönroos T, Eskola O, Kalliokoski K, Bergman J, et al. Imaging of blood flow and hypoxia in head and neck cancer: initial evaluation with [^{15}O]H $_2$ O and [^{18}F]fluoroerythronitroimidazole PET. *J Nucl Med.* 2001;42:1643–52.
- [31] Mäntylä MJ. Regional blood flow in human tumors. *Cancer Res.* 1979;39:2304–6.
- [32] Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. *Support Care Cancer.* 2020;28:625–32. <https://doi.org/10.1007/s00520-019-04871-5>
- [33] Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. *Nat Rev Clin Oncol.* 2010;7:653–64. <https://doi.org/10.1038/nrclinonc.2010.139>
- [34] Spira D, Adam P, Linder C, Spira SM, Pintoff J, Claussen CD, et al. Perfusion and flow extraction product as potential discriminators in untreated follicular and diffuse large B cell lymphomas using volume perfusion CT with attempt at histopathologic explanation. *Am J Roentgenol.* 2012;198:1239–46. <https://doi.org/10.2214/AJR.11.7858>
- [35] Esteves M, Monteiro MP, Duarte JA. The effects of physical exercise on tumor vasculature: systematic review and meta-analysis. *Int J Sports Med.* 2021;42:1237–49. <https://doi.org/10.1055/a-1533-1876>
- [36] De Langen AJ, Lubberink M, Boellaard R, Spreuwenberg MD, Smit EF, Hoekstra OS, et al. Reproducibility of tumor perfusion measurements using ^{15}O -labeled water and PET. *J Nucl Med.* 2008;49:1763–8. <https://doi.org/10.2967/jnumed.108.053454>
- [37] Lodge MA, Jacene HA, Pili R, Wahl RL. Reproducibility of tumor blood flow quantification with ^{15}O -water PET. *J Nucl Med.* 2008;49:1620–7. <https://doi.org/10.2967/jnumed.108.052076>
- [38] Van der Veldt AAM, Hendrikse NH, Harms HJ, Comans EFI, Postmus PE, Smit EF, et al. Quantitative parametric perfusion images using ^{15}O -labeled water and a clinical PET/CT scanner: test-retest variability in lung cancer. *J Nucl Med.* 2010;51:1684–90. <https://doi.org/10.2967/jnumed.110.079137>
- [39] Jochumsen MR, Sørensen J, Christensen NL, Haislund M, Borre M, Bouchelouche K, et al. Repeatability of tumour perfusion measurement with [^{15}O]H $_2$ O PET in prostate cancer. *EJNMMI Res.* 2026;16:13. <https://doi.org/10.1186/s13550-026-01375-2>
- [40] Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. *Nat Rev Drug Discov.* 2011;10:417–27. <https://doi.org/10.1038/nrd3455>
- [41] Nagy JA, Chang SH, Dvorak AM, Dvorak HF. Why are tumour blood vessels abnormal and why is it important to know? *Br J Cancer.* 2009;100:865–9. <https://doi.org/10.1038/sj.bjc.6604929>
- [42] Liao C, Liu X, Zhang C, Zhang Q. Tumor hypoxia: from basic knowledge to therapeutic implications. *Semin Cancer Biol.* 2023;88:172–86. <https://doi.org/10.1016/j.semcancer.2022.12.011>