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FULL PAPER

$^{15}O-H_2O$ PET/CT as a tool for the quantitative assessment of early post-radiotherapy changes of heart perfusion in breast carcinoma patients

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Objective: Studies examining radiation-induced heart toxicity in breast cancer patients are inconclusive. The aim of this study was to prospectively and quantitatively asses myocardial blood flow (MBF) with, for the first time, $^{15}O-H_2O$ PET/CT as a marker of heart damage in irradiated breast cancer patients.

Methods: 15 breast cancer patients receiving intact breast or chest wall irradiation were included in the analysis (six with right-sided and nine with left-sided breast cancer). They underwent $^{15}O-H_2O$ PET/CT before radiotherapy (RT) and 2 and 8 months after RT. MBF was quantitatively assessed at rest and under stress conditions in 17 heart segments distinguished according to the American Ultrasound Association classification. Regional MBF values were derived in each of the coronary artery territories.

Results: MBF decreased in 53% and increased in 33% of cases 2 months after RT in both left-sided and right-sided breast cancer patients. Stress testing was more sensitive than at-rest testing, demonstrating decreased perfusion in the segments supplied by the left anterior descending coronary artery (LAD) [5.41 ± 1.74 *vs* 4.52 ± 1.82 ml (g*min)$^{-1}$; $p = 0.018$], which persisted at 6 months [5.41 ± 1.74 *vs* 4.40 ± 1.38 ml (g*min)$^{-1}$; $p = 0.032$] and a decrease in global heart perfusion [5.14 ± 1.49 *vs* 4.46 ± 1.73 ml (g*min)$^{-1}$; $p = 0.036$]. A minimal radiation dose applied to the LAD correlated with MBF changes observed 2 months after RT ($r = -0.57$; $p = 0.032$). Radiological findings were not correlated with clinical symptoms of heart toxicity.

Conclusion: $^{15}O-H_2O$ PET/CT is safe and effective for the early detection and quantitative analysis of subclinical post-RT changes in heart perfusion in breast cancer patients. The LV segments supplied by the LAD are the main site of MBF changes. A minimum radiation dose deposited in the LAD may be a predictor of radiation-induced heart toxicity.

Advances in knowledge: This is the first time that $^{15}O-H_2O$ PET/CT has been used to assess MBF after RT and the first granular description of the distribution of blood flow changes after breast cancer RT.

INTRODUCTION

Early observations from the 1960s on irradiated Hodgkin's disease patients[1,2] and later on Hiroshima and Nagasaki A-bomb survivors[3–5] showed that the heart is radiosensitive and that both high- and low-dose radiation are cardiotoxic. The clinical consequences of radiation-induced heart damage are varied and include pericardial and valvular disease, myocardial infarction, conduction defects, congestive heart failure, and rheumatic and hypertensive heart disease.[5–7] However, studies examining heart toxicity in breast cancer patients receiving low- and intermediate-dose radiation to the breast or chest wall do not unequivocally confirm previous observations, with some indicating a significant increase in cardiovascular mortality[8–12] and others suggesting the opposite[4,13–19] or cardiotoxicity only in left-sided breast cancer patients.[9–20]

There is also debate as to whether radiation-induced toxicity results from damage to the microvasculature (injury to the myocardial endothelial cells) or macrovasculature (injury to coronary vessels). Both of these mechanisms could disturb organ perfusion[21] and ultimately tissue function.

Table 1. Patient characteristics

Characteristics	Total ($n = 15$)	Right side ($n = 6$)	Left side ($n = 9$)	p-value
Age: mean (SD)	50.5 (11.5)	52.83 (12.7)	49.2 (11.2)	0.56
Radiation dose (%)				
45 Gy	5 (33)	2 (33)	3 (33)	0.89
45 + 11.25 Gy	4 (27)	2 (33)	2 (22)	0.58
42.5 + 10 Gy	6 (50)	2 (33)	4 (45)	0.54
Pre-RT CHTH (%)				
Yes	8 (56)	3 (50)	5 (55)	0.72
No	7 (47)	3 (50)	4 (45)	
Post-RT HTH (%)				
Yes	11 (73)	5 (83)	6 (67)	0.58
No	4 (27)	1 (17)	3 (33)	
Co-morbidities	4 (27)	1 (17)	3 (33)	0.58

CHTH, chemotherapy; HTH, hormonal therapy; RT, radiotherapy; SD, standard deviation.

With this putative mechanism in mind, quantification of heart perfusion rates might be a suitable and informative approach to investigate the pathogenesis of radiation-induced cardiovascular disease. Several functional heart imaging methods including single-photon emission CT (SPECT) and cardiac magnetic resonance have been used to directly analyze heart perfusion in radiation-exposed patients, and several prospective studies describe myocardial perfusion deficits in irradiated breast cancer patients.[21–29] However, these modalities are not considered the best tools for heart perfusion testing by specialist cardiologists, with ^{15}O-H$_2$O PET/CT the established gold standard for quantitative myocardial blood flow (MBF) imaging *in vivo*. ^{15}O-H$_2$O PET/CT is characterized by both high specificity and significantly higher diagnostic accuracy than SPECT.[30] Additionally, ^{15}O possesses the characteristics of an ideal tracer for quantifying MBF due to its short half-life (about 2 min), low absorbed dose (around 1 mSv) per examination, free diffusion, and metabolic inertia.[31] Perhaps surprisingly, ^{15}O-H$_2$O PET/CT has never been used to estimate radiation-induced heart perfusion disturbances. We, therefore, conducted the pilot study of MBF in irradiated breast cancer patients using for the first time ^{15}O-H$_2$O PET/CT.

Aims

The primary aim of this study was to prospectively assess MBF in irradiated breast cancer patients with ^{15}O-H$_2$O PET/CT before radiotherapy (RT) and 2 and 8 months after completion of RT. The secondary aim was to analyze the location of MBF disturbances within the heart and correlations with individual radiation dose distribution.

METHODS AND MATERIALS

A pilot group of 15 females [mean age 50.5 years; range 32–68 years; (Table 1)] were included in the analysis. Six had right-sided breast cancer and nine left-sided breast cancer. All patients received three-dimensional tangential photon RT with 6/15 MV X-rays to the breast ($n = 10$) or chest wall ($n = 5$) to standard total doses of 42.5 or 45.0 Gy at 2.5 or 2.25 Gy per fraction, respectively.

Figure 1. AHA. A 17-segment model of the left ventricular myocardial surface. The individual coronary artery territories are distinguished. Abbreviations: AHA, American Heart Association; Cx, left circumflex artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.

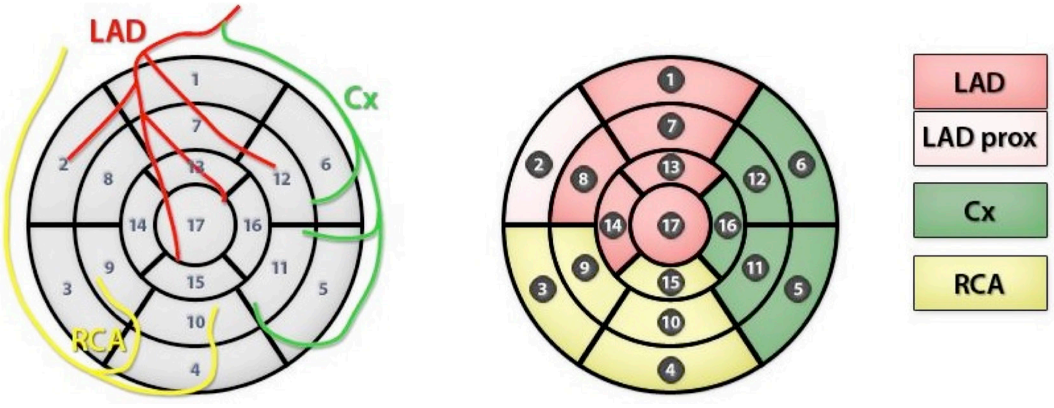
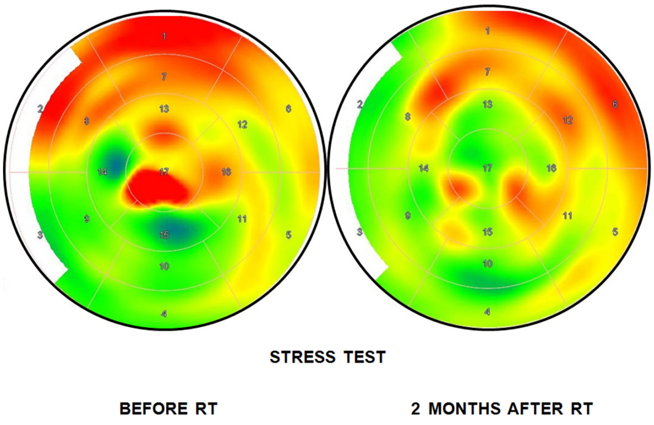


Figure 2. Myocardial blood flow images at PET stress test before and 2 months after radiotherapy. RT, radiotherapy.



Patients with intact breasts (n = 10) received an additional boost of 11.25 or 10 Gy at 2.25 or 2.5 Gy per fraction to the tumor bed, respectively (Table 1). When treated, the internal mammary nodes were included in the tangent fields.

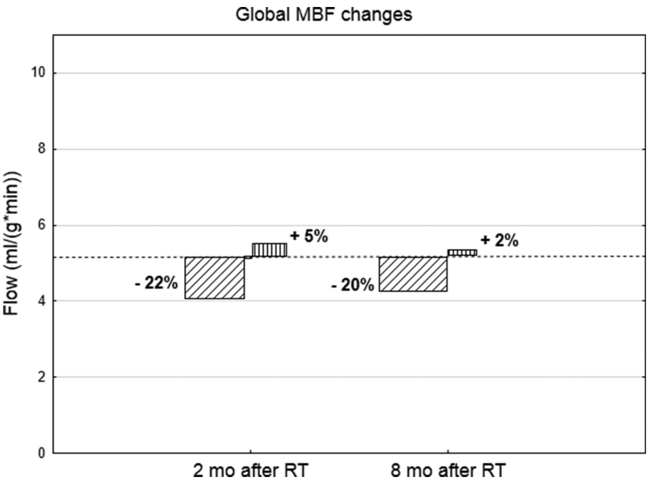
8 out of 15 (53%) females received pre-RT cyclophosphamide, doxorubicin and paclitaxel-based chemotherapy and 11 out of 15 (73%) received post-RT hormonal therapy (Table 1). None of the patients received Her2-inhibitors. 4 out of 15 (27%) females had co-morbidities: diabetes (n = 1) or hypertension (n = 3). None of the patients had a history of cardiovascular diseases including atherosclerosis, angina pectoris or myocardial infarction that might have influenced the study outcome. None of them has ever used cardioprotective drugs.

Ethical statement

The study was performed according to the principles of the Helsinki Declaration and was approved by the Ethics Committee of Nicolaus Copernicus University Collegium Medicum (KB 558/2012). All patients gave written informed consent before $^{15}O-H_2O$ PET/CT imaging.

Heart perfusion studies were carried out prior to RT and 2 and 8 months after completion of RT. Each patient underwent resting and stressed $^{15}O-H_2O$ PET imaging, the latter conducted after adenosine-induced vasodilation (Biograph mCT 128 scanner, Siemens, Germany) according to the previously described standard protocol.[32] MBF was quantified and expressed in milliliters per minute per gram (ml min^{-1} g^{-1}) of perfusable tissue and analyzed on a per-segment basis according to the 17-segment left ventricle (LV) myocardium model of the American Heart Association. This model presents the LV as a surface divided into basal, midcavity, and apical segments localized with reference to the long axis of the LV. Using this model, the anterior, posterior, lateral, and septal walls of the LV can be distinguished. Regional MBF values were derived in each of the coronary artery territories: the left anterior descending coronary artery (LAD), the left circumflex artery (Cx), and the right coronary artery (Figure 1). A typical image of PET results before and after radiation therapy is presented in Figure 2.

Figure 3. MBF changes (increases and decreases) 2 and 8 months after radiotherapy. Dotted line illustrates the mean MBF before RT. MBF, myocardial blood flow.



In each patient, CT for RT planning was performed without contrast prior to first PET study. In order to calculate radiation doses in the heart and coronary vessels, we delineated these structures on the 2 mm thick CT slices according to the published heart atlas proposed by Feng et al.[33]

Statistical analysis

All statistical analyses were performed using STATISTICA (v. 10.0, StatSoft Polska, Poland). The Shapiro–Wilk test was used to evaluate normality of individual parameters, and, due to normality, results were presented as the arithmetic mean (X) and standard deviation. The difference between individual values of a given parameter was estimated using the Student's t-test. Correlations between parameters were tested with Pearson's coefficients. The incidence of perfusion defects with respect to each patient-related factor was assessed using both univariate and multivariate logistic regression. A p-value less than 0.05 was considered statistically significant.

RESULTS

Radiation-induced MBF changes were observed in both left- and right-sided breast cancer patients. 2 months after RT MBF decreased in 8/15 (53%) of females: 5/9 (55%) females with left-sided breast cancer and 3/6 (50%) with right-sided breast cancer. Interestingly, 5/15 (33%) females had an increase in MBF: 3/5 (60%) females with left-sided breast cancer and 2/5 (40%) with right-sided breast cancer. 8 months after RT, MBF decreased in 10/15 (66%) of females: 7/9 (77%) females with left-sided breast cancer and 3/6 (50%) with right-sided breast cancer. An increased MBF was noted in 5/15 (33%) females: 2/9 (33%) females with left-sided breast cancer and 3/6 (50%) with right-sided breast cancer (Figure 3). Although the measurable MBF changes were statistically significant, they did not achieve a threshold [2.3 ml (g*min)$^{-1}$ for stress perfusion] considered predictive for hemodynamically significant coronary artery disease.[32]

Table 2. At-rest testing

Area	MBF [ml/(g*min)] before RT	MBF [ml/(g*min)] 2 months after RT	MBF [ml/(g*min)] 8 months after RT	*p*-value
Global	1.15 ± 0.33	1.14 ± 0.35	1.15 ± 0.25	1 *vs* 2 *p* = 0.841 1 *vs* 3 *p* = 0.960
LAD	1.20 ± 0.35	1.16 ± 0.36	1.11 ± 0.27	1 *vs* 2 *p* = 0.472 1 *vs* 3 *p* = 0.197
Cx	1.30 ± 0.42	1.23 ± 0.33	1.27 ± 0.28	1 *vs* 2 *p* = 0.230 1 *vs* 3 *p* = 0.735
RCA	0.99 ± 0.30	1.08 ± 0.45	1.36 ± 0.94	1 *vs* 2 *p* = 0.411 1 *vs* 3 *p* = 0.204
Seg 1	1.03 ± 0.28	0.94 ± 0.30	0.93 ± 0.18	1 *vs* 2 *p* = 0.058 1 *vs* 3 *p* = 0.053
Seg 2	0.81 ± 0.16	0.79 ± 0.21	0.79 ± 0.12	1 *vs* 2 *p* = 0.574 1 *vs* 3 *p* = 0.728
Seg 3	0.85 ± 0.23	0.84 ± 0.29	0.89 ± 0.27	1 *vs* 2 *p* = 0.851 1 *vs* 3 *p* = 0.526
Seg 4	1.01 ± 0.30	1.06 ± 0.42	1.80 ± 2.60	1 *vs* 2 *p* = 0.578 1 *vs* 3 *p* = 0.319
Seg 5	1.15 ± 0.39	1.10 ± 0.36	1.15 ± 0.23	1 *vs* 2 *p* = 0.204 1 *vs* 3 *p* = 0.995
Seg 6	1.25 ± 0.29	1.17 ± 0.33	1.19 ± 0.31	1 *vs* 2 *p* = 0.072 1 *vs* 3 *p* = 0.334
Seg 7	1.23 ± 0.30	1.10 ± 0.27	1.09 ± 0.24	**1 *vs* 2 *p* = 0.009** **1 *vs* 3 *p* = 0.026**
Seg 8	0.88 ± 0.20	0.87 ± 0.24	0.86 ± 0.17	1 *vs* 2 *p* = 0.759 1 *vs* 3 *p* = 0.752
Seg 9	0.88 ± 0.24	0.89 ± 0.28	0.98 ± 0.28	1 *vs* 2 *p* = 0.882 1 *vs* 3 *p* = 0.291
Seg 10	1.07 ± 0.37	1.16 ± 0.54	1.91 ± 2.36	1 *vs* 2 *p* = 0.451 1 *vs* 3 *p* = 0.225
Seg 11	1.27 ± 0.44	1.25 ± 0.40	1.36 ± 0.27	1 *vs* 2 *p* = 0.862 1 *vs* 3 *p* = 0.385
Seg 12	1.40 ± 0.47	1.27 ± 0.31	1.28 ± 0.31	1 *vs* 2 *p* = 0.173 1 *vs* 3 *p* = 0.252
Seg 13	1.28 ± 0.39	1.22 ± 0.34	1.13 ± 0.34	1 *vs* 2 *p* = 0.170 1 *vs* 3 *p* = 0.054
Seg 14	0.99 ± 0.30	1.01 ± 0.35	1.03 ± 0.29	1 *vs* 2 *p* = 0.762 1 *vs* 3 *p* = 0.679
Seg 15	1.13 ± 0.40	1.42 ± 0.80	2.07 ± 2.33	1 *vs* 2 *p* = 0.199 1 *vs* 3 *p* = 0.175
Seg 16	1.44 ± 0.51	1.32 ± 0.31	1.41 ± 0.45	1 *vs* 2 *p* = 0.226 1 *vs* 3 *p* = 0.722
Seg 17	1.53 ± 0.63	1.44 ± 0.51	1.38 ± 0.50	1 *vs* 2 *p* = 0.505 1 *vs* 3 *p* = 0.181

Cx, left circumflex artery; LAD, left anterior descending artery; MBF, myocardial blood flow; RCA, right coronary artery; RT, radiotherapy.

Significant MBF decreases after RT were only observed in one segment localized in the anterior mid-cavity wall supplied by the LAD. Significant differences are highlighted in bold.

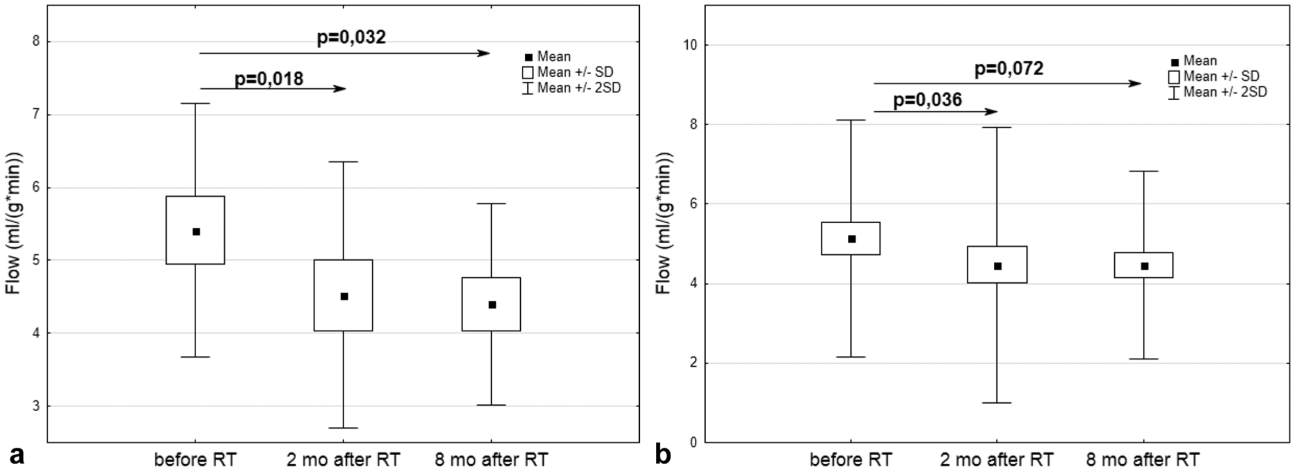
At-rest testing

In the at-rest testing case, only the seventh myocardial segment (anterior midcavity wall supplied by the LAD) showed decreased perfusion after both 2 (1.23 ± 0.30 *vs* 1.10 ± 0.27; *p* = 0.009) and 8 months (1.23 ± 0.30 *vs* 1.09 ± 0.24; *p* = 0.026) after RT completion (Table 2).

Stress testing

2 months after RT, stress testing demonstrated decreased perfusion in the segments supplied by the LAD (5.41 ± 1.74 *vs* 4.52 ± 1.82; *p* = 0.018) (Figure 4a), two segments (11th and 16th) supplied by the Cx (5.12 ± 1.39 *vs* 4.49 ± 1.76; *p* = 0.048 and 5.58 ± 1.60 *vs* 4.66 ± 2.01; *p* = 0.015, respectively), and a global decrease in heart

Figure 4. (a) MBF changes in the myocardial segments supplied by the LAD during stress testing: before RT and 2 and 8 months after its completion. (b) Global MBF changes during stress testing: before RT and 2 and 8 months after its completion. LAD, left anterior descending artery; MBF, myocardial blood flow; RT, radiotherapy; SD, standard deviation.



perfusion (5.14 ± 1.49 *vs* 4.46 ± 1.73; p = 0.036) (Figure 4b). In the anterior apical and midcavity wall areas supplied by the LAD, the perfusion decrease persisted for the next 6 months (Table 3 and Figure 4a). Although a significant global MBF decrease was observed 2 months after RT, this did not persist to 8 months although there was a trend to this effect (Figure 4b).

The effects of RT on perfusion seen in the area supplied by the LAD may be a function of the radiation dose, which was highest for the LAD compared to the other coronary arteries as assessed by the RT planning system (Table 4).

The effects of RT on perfusion seen in the area supplied by the LAD may be a function of the radiation dose, which was highest for the LAD compared to the other coronary arteries as assessed by the RT planning system (Table 4).

Only the minimum radiation dose absorbed by the LAD was correlated with MBF changes observed 2 months after RT (Table 5). Only LAD doses above 2 Gy caused a decrease in heart perfusion compared to baseline (Figure 5).

Other potential factors influencing MBF defects

The incidence of perfusion defects with respect to each patient-specific and treatment-specific factor was assessed using both univariate and multivariate logistic regression. *Ad hoc* methods to detect colinearity were applied. For this analysis, perfusion defects were scored as either present or absent, irrespective of severity. Of the analyzed variables, age was considered a continuous variable and all others were considered categorical (Table 6). There were no associations between MBF defects and other clinicopathological factors including: age, left-sided cancer, the presence of heart risk factors (hypertension, diabetes), or additional treatment modalities (chemotherapy, hormonal therapy).

DISCUSSION

Here, we show that ^{15}O-H$_2$O PET/CT is valuable for detecting early heart perfusion changes in irradiated patients. This is the first study to assess the utility of PET for monitoring MBF after RT. Previous analyses of heart perfusion in oncology patients used SPECT performed under resting and stressed conditions, similar to the ^{15}O-H$_2$O PET protocol used here. In most previous studies, the evaluation of MBF changes was qualitative with the presence or absence of MBF disturbances in individual heart areas estimated by a nuclear medicine specialist, although in some cases a semi-quantitative MBF scoring scale was applied.[22,28] For the first time, our study applies a quantitative assessment of MBF changes presented as the difference in their absolute values measured in ml per min per g in each individual heart region before and after RT. Our method eliminates the risk of error resulting from the subjective evaluation of heart perfusion. Furthermore, these quantitative data enable other researchers to directly compare their results with our own.

Of note, we detected both MBF decreases and increases in 53 and 33% of females, respectively, which were independent of the side of the chest wall irradiated. Radiation-induced MBF changes occurred as early as 2 months after RT; previous studies examining post-radiation myocardial perfusion disturbances by SPECT have reported MBF deficits in up to 60% of left-sided breast cancer patients as early as 6 months after RT.[21,24–26,28] Using SPECT in a case-control study, Sioka et al showed that myocardial perfusion abnormalities also occur in right-sided breast cancer patients compared to controls without significant differences according to the irradiated side,[22] which is consistent with our results. However, the group size was small and the authors did note a statistical trend toward greater perfusion disturbances in left-sided breast cancer patients.[22] There were no associations between MBF defects and other clinicopathological factors including age, the presence of heart risk factors (hypertension, diabetes), and additional treatment modalities (chemotherapy, hormonal therapy); however, a larger cohort of patients would be useful to further examine these associations.

MBF disturbances are usually presented as collective or global results for the entire heart.[22,28] Here, we also assessed perfusion in individual heart segments, the results of which suggested a

Table 3. Stress testing results

Area	MBF [ml/(g*min)] Before RT	MBF [ml/(g*min)] 2 mo after RT	MBF [ml/(g*min)] 8 mo after RT	p-value
Global	5.14 ± 1.49	4.46 ± 1.73	4.47 ± 1.18	**1 *vs* 2 $p = 0.036$** 1 *vs* 3 $p = 0.207$
LAD	5.41 ± 1.74	4.52 ± 1.82	4.40 ± 1.38	**1 *vs* 2 $p = 0.018$** **1 *vs* 3 $p = 0.032$**
Cx	5.04 ± 1.36	4.48 ± 1.81	4.80 ± 1.22	1 *vs* 2 $p = 0.069$ 1 *vs* 3 $p = 0.937$
RCA	4.72 ± 1.45	4.44 ± 1.80	4.41 ± 1.21	1 *vs* 2 $p = 0.375$ 1 *vs* 3 $p = 0.527$
Seg 1	4.73 ± 1.68	4.10 ± 1.85	4.37 ± 1.26	1 *vs* 2 $p = 0.069$ 1 *vs* 3 $p = 0.897$
Seg 2	3.37 ± 1.07	3.24 ± 1.49	3.37 ± 1.14	1 *vs* 2 $p = 0.073$ 1 *vs* 3 $p = 0.993$
Seg 3	3.94 ± 1.50	3.81 ± 1.79	3.62 ± 1.37	1 *vs* 2 $p = 0.689$ 1 *vs* 3 $p = 0.756$
Seg 4	4.82 ± 1.46	4.20 ± 1.71	4.45 ± 1.20	1 *vs* 2 $p = 0.086$ 1 *vs* 3 $p = 0.414$
Seg 5	4.58 ± 1.27	4.63 ± 2.09	4.53 ± 1.02	1 *vs* 2 $p = 0.925$ 1 *vs* 3 $p = 0.884$
Seg 6	4.85 ± 1.20	4.52 ± 1.59	4.69 ± 1.15	1 *vs* 2 $p = 0.29$ 1 *vs* 3 $p = 0.566$
Seg 7	5.23 ± 1.46	4.32 ± 1.85	4.49 ± 1.26	**1 *vs* 2 $p = 0.009$** **1 *vs* 3 $p = 0.05$**
Seg 8	4.21 ± 1.41	3.66 ± 1.64	3.83 ± 1.21	**1 *vs* 2 $p = 0.038$** 1 *vs* 3 $p = 0.276$
Seg 9	3.98 ± 1.24	4.10 ± 1.92	3.91 ± 1.19	1 *vs* 2 $p = 0.718$ 1 *vs* 3 $p = 0.818$
Seg 10	4.89 ± 1.43	4.55 ± 1.76	4.68 ± 1.00	1 *vs* 2 $p = 0.335$ 1 *vs* 3 $p = 0.518$
Seg 11	5.12 ± 1.39	4.49 ± 1.76	4.95 ± 1.12	**1 *vs* 2 $p = 0.048$** 1 *vs* 3 $p = 0.657$
Seg 12	5.25 ± 1.47	4.57 ± 1.86	4.84 ± 1.22	1 *vs* 2 $p = 0.056$ 1 *vs* 3 $p = 0.218$
Seg 13	5.59 ± 1.93	4.42 ± 1.83	4.34 ± 1.47	**1 *vs* 2 $p = 0.008$** **1 *vs* 3 $p = 0.011$**
Seg 14	4.95 ± 1.84	4.41 ± 1.80	4.12 ± 1.33	1 *vs* 2 $p = 0.146$ 1 *vs* 3 $p = 0.089$
Seg 15	5.58 ± 1.78	5.22 ± 1.96	5.04 ± 1.26	1 *vs* 2 $p = 0.385$ 1 *vs* 3 $p = 0.212$
Seg 16	5.58 ± 1.60	4.66 ± 2.01	4.95 ± 1.37	**1 *vs* 2 $p = 0.015$** 1 *vs* 3 $p = 0.181$
Seg 17	6.24 ± 2.23	5.14 ± 2.17	4.81 ± 1.87	**1 *vs* 2 $p = 0.035$** **1 *vs* 3 $p = 0.029$**

Cx, left circumflex artery; LAD, left anterior descending artery; MBF, myocardial blood flow; RCA, right coronary artery; RT, radiotherapy. Mean doses applied to the coronary arteries.

Table 4. Mean doses applied to the coronary arteries

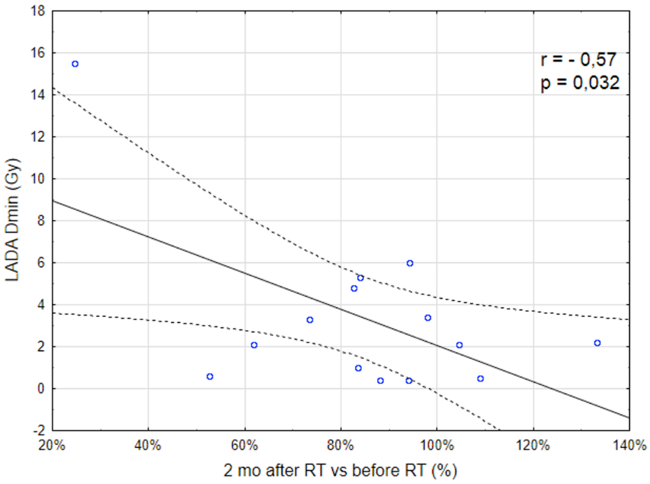
	Heart	LAD	Cx	RCA
D min (Gy)	0.77 ± 0.5	3.4 ± 3.9	1.5 ± 1.2	1.5 ± 0.3
D max (Gy)	31.72 ± 19.8	29.9 ± 21.9	1.8 ± 1.4	3.4 ± 2.0
D mean (Gy)	5.09 ± 3.98	25.5 ± 19.4	1.7 ± 1.3	2.2 ± 0.7

Cx, left circumflex artery. LAD, left anterior descending artery; RCA, right coronary artery.

non-uniform distribution of MBF changes and enabled us to establish which areas had the highest MBF disturbances. We also, for the first time, considered the heart vasculature and doses applied to individual arteries.

The phenomenon of very early MBF disturbances at two months might suggest—contrary to a well-established opinion—that the heart is the organ early reacting to irradiation. The increased perfusion observed as early in 33% of patients might suggest the

Figure 5. Correlation between a minimal radiation dose absorbed by the LAD as assessed by the RT planning system and MBF changes observed 2 months after RT. LAD, left anterior descending artery; MBF, myocardial blood flow; RT, radiotherapy.



presence of an acute inflammatory response and, if confirmed, could be a therapeutic target to limit the late cardiovascular toxicity. The increased MBF did not usually persist to 6 months and actually decreased to baseline or even lower, it did persist in one female. One could speculate that MBF decrease commonly considered a direct risk factor for radiation induced heart diseases is a consequence of a former inflammatory process. The probable individual dynamics of the phenomenon might be the reason why MBF changes were stable or progressive in different patients. Marks et al showed that the incidence of perfusion decrease was mounting in time and 24 months after RT it attained the highest value.[26]

We observed correlation between MBF disturbances and the minimum radiation dose to the LAD, which, in breast cancer patients, usually receives the highest radiation doses. This minimum dose may reflect a threshold over which an inflammatory response is triggered. Our future studies will include measuring MBF earlier than 2 months after completion of RT.

Previous studies did not analyze the relationship between heart perfusion changes and the radiation dose applied to specific heart structures, with the mean heart dose usually used as a predictor of heart damage. Based on a population of 108 patients receiving radiation to the left side of the chest, Evans et al reported that the left ventricular volume was a significant predictor of heart perfusion disturbances.[34] Further, population studies have estimated that a mean heart dose of 10 Gy increases a risk of cardiovascular events by 3.2%, 30 years after RT.[35]

Table 5. Correlations between doses applied to the coronary arteries as assessed by the RT planning system and MBF changes 2 and 8 months after RT

	MBF changes 2 months after RT		MBF changes 8 months after RT	
	r	*p*-value	r	*p*-value
Heart Dmin	−0.22	0.455	−0.08	0.781
Heart Dmax	−0.01	0.983	−0.28	0.336
Heart Dmean	−0.35	0.226	0.07	0.808
LAD Dmin	**−0.57**	**0.032**	0.41	0.141
LAD Dmax	−0.02	0.937	−0.26	0.365
LAD Dmean	−0.03	0.912	−0.29	0.316
Cx Dmin	−0.45	0.105	0.30	0.306
Cx Dmax	−0.42	0.137	0.24	0.400
Cx Dmean	−0.44	0.116	0.28	0.332
RCA Dmin	−0.07	0.824	0.12	0.691
RCA Dmax	−0.28	0.335	0.42	0.133
RCA Dmean	0.06	0.833	0.09	0.765

Cx, left circumflex artery; LAD, left anterior descending artery; MBF, myocardial blood flow; RCA, right coronary artery; RT, radiotherapy.

In our study and previous reports, the observed heart perfusion disturbances were subclinical and there are currently no convincing data to suggest that they predict future, clinically relevant heart toxicities. Thus, implementing cardioprotection in this group of patients is currently not advised.

The pilot study we conducted has some limitations, mainly the small study group and a short time of observation, although this did allow us to assess early changes. Nevertheless, we

Table 6. Correlations between MBF defects and patient-specific/treatment-specific factors

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*-value[a]	OR (95% CI)	*p*-value[a]
Age	1.049 (0.955–1.153)	0.318	1.140 (0.930–1.397)	0.208
Left side (yes *vs* no)	0.667 (0.076–5.878)	0.715	2.119 (0.081–55.291)	0.652
Chemotherapy (yes *vs* no)	0.240 (0.027–2.116)	0.198	0.096 (0.003–3.481)	0.201
HTH (yes *vs* no)	2.800 (0.196–40.059)	0.448	0.387 (0.008–19.527)	0.635
Heart risk factors (yes *vs* no)	0.876 (0.084–8.240)	0.876	0.028 (0.000–5.699)	0.188

CI, confidence interval; HTH, hormonal therapy; MBF, myocardial blood flow; OR, odds ratio.
[a] Logistic regression Wald X^2 statistic probability.

demonstrated that $^{15}O\text{-}H_2O$ PET/CT is a valuable tool for evaluating radiation-induced heart perfusion changes. Our study shows a relationship between the irradiated heart area and its perfusion and suggests that the radiation dose applied to the LAD might be a potential predictor of MBF disturbances. Further, larger studies are required to confirm and develop our findings.

CONCLUSIONS

$^{15}O\text{-}H_2O$ PET/CT is safe and effective for the early detection and quantitative analysis of subclinical post-RT changes of heart perfusion in breast cancer patients. The LV segments supplied by the LAD are the main site of MBF changes. A minimum radiation dose deposited in the LAD may be a predictor of radiation-induced heart toxicity.

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