Prevalence of Perfusion Defects Detected by Stress ^{99m}Technetium Sestamibi Myocardial Perfusion Single-photon Emission Computed Tomography in Asymptomatic Patients with Breast Cancer

BOHUSLAV MELICHAR[1,4,5], JIŘÍ DOLEŽAL[2], VLASTISLAV ŠRÁMEK[1], HANA KALÁBOVÁ[1], LENKA KUJOVSKÁ KRČMOVÁ[3,6], RADOMÍR HYŠPLER[3], HANA ŠTUDENTOVÁ[1], MILAN VOŠMIK[4], MIROSLAV PECKA[5], ADAM SVOBODNÍK[7], LADISLAV PECEN[7], MARTIN DOLEŽEL[1] and DAGMAR SOLICHOVÁ[2]

[1]*Department of Oncology, Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic;*
[2]*Department of Nuclear Medicine,* [3]*Third Department of Medicine,*
[4]*Department of Oncology and Radiotherapy, and* [5]*Fourth Department of Medicine,*
Charles University Medical School and Teaching Hospital, Hradec Králové, Czech Republic;
[6]*Department of Analytical Chemistry, Charles University School of Pharmacy, Hradec Králové, Czech Republic;*
[7]*International Clinical Research Center–Department of Clinical Development and Technology Transfer,*
St. Anne's University Hospital, Brno, Czech Republic

Abstract. *Aim: The aim of the present study was to investigate myocardial perfusion in relation to disease history and laboratory parameters of atherosclerosis risk in asymptomatic patients with breast carcinoma. Patients and Methods: One-hundred and eighty-one patients with breast carcinoma were studied. Myocardial perfusion was assessed using single-photon emission computed tomography (SPECT) with ^{99m}technetium sestamibi. Results: Perfusion defects were detected in 12 patients (7%). Higher body-mass index, increased concentrations of D-dimers, C-reactive protein, fibrinogen, glucose, triglycerides, and urinary albumin, a history of hypertension and of radiotherapy to the left chest wall were all associated with increased risk of perfusion defects. In a multivariate stepwise selection logistic regression model, body mass index, albuminuria and radiotherapy to the left hemithorax were significantly associated with the presence of perfusion defects. Conclusion: In addition to other factors, treatment history may be associated with the presence of perfusion defects in patients with breast cancer.*

Correspondence to: Martin Doležel, MD, Ph.D., Department of Oncology, Palacký University Medical School, I.P. Pavlova 6, 775 20 Olomouc, Czech Republic. Tel: +420 588444288, Fax: +420 588442522, e-mail: dolezelm@email.cz

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Substantial progress accomplished in cancer therapy has been translated into improved survival of patients with different types of primary tumors. As the result of improvement of survival or even cure of patients with advanced cancer, some long-term sequelae have emerged, including metastases in unusual sites (1), second primary cancer (2), or atherosclerosis and associated disorders (3-5). In fact, in many patients, comorbidity rather than cancer is the ultimate cause of death (6). Advanced age, smoking, obesity and oxidative stress are all linked with increased risk of both atherosclerosis and malignant tumors (7). Consequently, cardiovascular disorders currently represent an important issue in cancer survivors. Moreover, the toxicity of anticancer therapy may result in progression of atherosclerosis (8, 9). Clinical data from retrospective series indicate increased incidence of cardiovascular disorders in survivors of childhood cancers or germ-cell tumors to be associated with a history of chemotherapy (3-5). The information on the prevalence of complications of atherosclerosis is limited for most of the common cancer types (7, 10-12). For patients with breast carcinoma, different reports have indicated both increased and decreased incidence of complications of atherosclerosis (13, 14).

Much effort has been devoted in the past several decades to identify biomarkers of risk of atherosclerosis, and many laboratory parameters, *e.g.* cholesterol, homocysteine or C-reactive protein (CRP) (15), have been shown to predict cardiovascular events associated with atherosclerosis.

Strategies have also been developed for early diagnosis of asymptomatic cardiovascular disease. The identification of patients at increased risk or early diagnosis of asymptomatic disease opens the way for interventions that could prevent cardiovascular events. Stress/rest myocardial perfusion scan using single-photon emission computed tomography (SPECT), and measurement of carotid intima media thickness have been the most widely used diagnostic tests in asymptomatic individuals. Stress/rest myocardial perfusion has been demonstrated to predict cardiovascular events in asymptomatic patients with different risk of coronary artery disease (16, 17).

In an earlier investigation, we reported that in patients with breast cancer, the intima media thickness, an indicator of the presence of atherosclerosis, is associated not only with clinical and laboratory risk factors, but also with the history of anticancer therapy (18). The aim of the present study was to assess the prevalence of perfusion defects, assessed by SPECT, in asymptomatic patients with breast carcinoma in relation to disease history and laboratory risk factors of atherosclerosis in part of the same cohort of patients.

Patients and Methods

One-hundred and eighty-one female patients with histologically-verified carcinoma and no history of cardiac disorder, aged (mean±standard deviation) 53±11 (range=28-76) years, were included in the present study. The investigations were approved on April 14, 2005 by the Institutional Ethical Committee (file number 200504 S14P), and the patients signed informed consent.

Body mass index (BMI) was calculated with the formula: weight (kg)/height $(m)^2$. The menopausal status, history of breast cancer, including the time from diagnosis, earlier radiotherapy, chemotherapy, or the presence of distant metastases, history of smoking, cardiac disorder, hypertension, diabetes, disorders of lipid metabolism and thyroid disorders were recorded. Blood samples were drawn from a peripheral vein after overnight fast and processed for the determination of hemoglobin, leukocyte and platelet counts, fibrinogen, antithrombin, D-dimers, glycosylated hemoglobin, serum CRP, lipoprotein (a), serum cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, homocysteine, glucose, creatinine, magnesium, uric acid, albumin, alpha-tocopherol and retinol as described (19). Early urine samples were collected and the measurement of urinary neopterin, creatinine, *N*-acetyl-β-D-glucosaminidase (NAG) and albumin was performed as described earlier (19, 20). One-day stress (bicycle exercise) and rest electrocardiogram gated SPECT myocardial ^{99m}technetium sestamibi perfusion scintigraphy was performed as described in an earlier report (19).

Differences between groups of patients were analyzed by the Mann–Whitney *U*-test. Categorical data were analyzed with univariate logistic regression. Multivariate analysis was performed using stepwise selection logistic regression. The decision on statistical significance was based on $p=0.05$ level. The analyses were performed using SAS software (Version 9.2; SAS Institute, Cary, NC, USA).

Results

The median time from diagnosis for the present cohort was 18 months (range=0-96 months). Perfusion defects were detected in only 12 patients (7%), including reversible ischemia in 11 cases and scar in one patient. Patients with perfusion defects had significantly higher BMI, fibrinogen, glucose and urinary albumin concentrations (Table I). The continuous clinical and laboratory parameters were then dichotomized based on the upper limit of normal [D-dimers, fibrinogen, glucose, uric acid, total cholesterol, LDL cholesterol, lipoprotein (a) and CRP] or lower limit of normal (serum albumin), or, in the case of parameters where fewer than 10% of values were above (or below) the normal range or the normal range was difficult to define, above the third quartile (age, BMI, leukocyte and platelet counts, antithrombin, creatinine, triglycerides, homocysteine, glycosylated hemoglobin, retinol and alpha-tocopherol, urinary NAG, albumin and neopterin) and below the first quartile (hemoglobin, magnesium and HDL cholesterol).

After this dichotomization, in addition to increased BMI, fibrinogen, glucose and urinary albumin, increased D-dimers, CRP and triglycerides were also associated with increased risk of perfusion defects (Table II). The decreased risk associated with higher HDL cholesterol concentrations was of borderline significance. The distribution of perfusion defects in subgroups of patients defined by categorical variables is shown in Table III. Fifty-eight patients had previous radiotherapy of the left hemithorax, and perfusion defects were detected more frequently in these patients. Perfusion defects were also more common in patients with history of hypertension (Table III).

Because the significance of some parameters in the univariate analysis was borderline around $p=0.05$, the threshold *p*-value in a multivariate stepwise selection logistic regression model (where the choice of predictive variables was carried out by an automatic procedure from all variables) was set at $p=0.07$. In this model, BMI ≥29.76 mg/m^2, albuminuria ≥0.88 g/mol creatinine and radiotherapy to the left hemithorax were significantly associated with the presence of perfusion defects ($p=0.005$, $p=0.034$, and $p=0.031$, respectively), while the significance of alpha-tocopherol ≥21.18 μmol/l was of borderline statistical significance ($p=0.068$; Table IV).

Discussion

Present data indicate a relatively low prevalence of myocardial perfusion defects in asymptomatic patients with breast cancer during the first decade after diagnosis. It has been demonstrated that SPECT myocardial perfusion predicts cardiac events in patients with cancer (21). The presence of perfusion defects in patients with breast cancer after anticancer therapy has been well-documented (22-25). Considering the

Table I. *Comparison of clinical and laboratory parameters in patients with and without perfusion defects. Data are mean±standard deviation.*

Parameter	No perfusion defects	Perfusion defects	*p*-Value
Age (years)	53±10 (n=169)	58±7 (n=12)	0.078
BMI (kg/m^2)	26.5±4.9 (n=169)	32.6±6.2 (n=12)	<0.001
Leukocytes (10^9/l)	5.8±1.7 (n=167)	5.8±1.7 (n=12)	0.982
Hemoglobin (g/l)	138±10 (n=167)	139±11 (n=12)	0.599
Platelets (10^9/l)	237±53 (n=167)	238±59 (n=12)	0.771
D-Dimers (mg/l)	0.68±1.69 (n=164)	0.67±0.59 (n=12)	0.226
Antithrombin (%)	106±13 (n=163)	102±12 (n=12)	0.166
Fibrinogen (g/l)	3.63±0.81 (n=166)	4.06±0.47 (n=12)	0.018
Glucose (mmol/l)	5.1±1.1 (n=168)	6.0±2.2 (n=12)	0.016
Magnesium (mmol/l)	0.86±0.06 (n=169)	0.84±0.10 (n=12)	0.782
Creatinine (μmol/l)	66±11 (n=169)	73±18 (n=12)	0.212
Uric acid (μmol/l)	278±75 (n=169)	308±104 (n=12)	0.371
Total cholesterol (mmol/l)	5.54±1.01 (n=168)	5.32±0.92 (n=12)	0.584
HDL cholesterol (mmol/l)	1.72±0.45 (n=167)	1.52±0.36 (n=12)	0.092
LDL cholesterol (mmol/l)	3.40±0.93 (n=166)	3.32±0.81 (n=12)	0.841
Triglycerides (mmol/l)	1.24±0.71 (n=165)	1.47±0.69 (n=12)	0.159
Lp(a) (g/l)	0.31±0.42 (n=157)	0.32±0.34 (n=12)	0.515
Albumin (g/l)	45.6±2.8 (n=166)	45.1±3.2 (n=12)	0.520
CRP (mg/l)	4.0±6.8 (n=165)	4.6±3.6 (n=12)	0.188
Homocysteine (μmol/l)	11.2±3.7 (n=168)	11.7±5.9 (n=12)	0.646
Glycosylated hemoglobin (%)	3.5±0.9 (n=164)	3.7±0.9 (n=12)	0.099
Retinol (μmol/l)	1.77±0.53 (n=168)	1.94±0.77 (n=12)	0.576
Alpha-tocopherol (μmol/l)	24.52±5.28 (n=168)	25.71±4.99 (n=12)	0.348
Urinary neopterin (μmol/mol creatinine)	150±72 (n=168)	124±41 (n=12)	0.263
Urinary NAG (μkat/mol creatinine)	14.3±10.4 (n=157)	17.8±10.5 (n=12)	0.199
Urinary albumin (g/mol creatinine)	1.04±3.03 (n=162)	0.96±0.57 (n=12)	0.021

BMI: Body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein (a); CRP: C-reactive protein; NAG: *N*-acetyl-β-D-glucosaminidase.

fact that a substantial proportion of patients in the present cohort were pre-treated with systemic chemotherapy and irradiation of the left chest wall, the incidence of myocardial perfusion defects may seem to be rather low. In previous studies, perfusion defects were reported in up to 24% of patients treated with chemotherapy and left-sided irradiation (23), and in other series, the rate of perfusion defects was even higher (24, 25). Perfusion defects have also been reported in patients with other primary tumors treated with the combination of chemotherapy and thoracic radiation therapy (26). The lower incidence of perfusion defects in the present cohort is probably due to the short duration of follow-up after therapy. Left-sided irradiation has been shown to result in an increased rate of cardiovascular events (27, 28). However, these events manifest late, and maximum increased risk is observed after 20 years (28). From this perspective, the duration of follow-up in the present cohort may be too short.

Because of the small number of patients with perfusion defects in the present study, only limited information may be derived regarding the risk factors for cardiovascular disease in this population. In addition to the risk factors of atherosclerosis that are common in the general population, in patients with history of breast cancer the parameters associated with therapy may also determine the presence of perfusion defects. As expected, the BMI was significantly associated with the presence of perfusion defects in multivariate analysis. The presence of perfusion defects also seems to be associated with previous irradiation of the left chest wall. Albuminuria was also an independent predictor of the presence of perfusion defects in the present study. Both BMI and albuminuria have been reported to increase in cancer survivors as a result of prior treatment, including chemotherapy (8, 29).

Most of the data on increased incidence of cardiovascular events associated with atherosclerosis in patients with cancer were reported for pediatric or young adult patients surviving long after the cure to allow for the manifestation of these chronic complications (3-5, 8). The data on atherosclerosis in survivors of more common adult solid tumors, including breast cancer, are limited and sometimes even conflicting. While the risk of stroke was reported to be increased (14), the risk of myocardial infarction or coronary artery disease was significantly lower in patients with early breast cancer treated with radiation therapy (13).

In a review on the topic of coronary artery disease in patients with cancer published in 1978, Kopelson and Herwig noted that coronary artery disease is rare in patients with

Table II. *Perfusion defects and odds ratios (ORs) of categorized clinical and laboratory parameters.*

Parameter	Cut-off level	Perfusion defects (n)		OR	95% CI	*p*-Value
		No	Yes			
Age (years)	≥ *vs.* <61	169	12	2.30	0.69-7.66	0.173
BMI (kg/m^2)	≥ *vs.* <29.76	169	12	7.14	2.04-25.01	0.002
Leukocytes (10^9/l)	≥ *vs.* <6.89	167	12	0.99	0.26-3.84	0.991
Hemoglobin (g/l)	≥ *vs.* <133	167	12	0.82	0.21-2.20	0.780
Platelets (10^9/l)	≥ *vs.* <270	167	12	1.49	0.43-5.19	0.533
D-Dimers (mg/l)	≥ *vs.* <0.51	164	12	3.49	1.05-11.53	0.041
Antithrombin (%)	≥ *vs.* <116	163	12	0.96	0.25-3.72	0.953
Fibrinogen (g/l)	≥ *vs.* <4.01	166	12	3.76	1.14-12.47	0.030
Glucose (mmol/l)	≥ *vs.* <5.7	168	12	5.46	1.63-18.25	0.006
Magnesium (mmol/l)	≥ *vs.* <0.82	169	12	0.93	0.24-3.60	0.917
Creatinine (μmol/l)	≥ *vs.* <72	169	12	0.95	0.25-3.66	0.937
Uric acid (μmol/l)	≥ *vs.* <361	169	12	1.49	0.30-7.29	0.623
Total cholesterol (mmol/l)	≥ *vs.* <5.21	168	12	0.86	0.26-2.83	0.806
HDL cholesterol (mmol/l)	≥ *vs.* <1.44	167	12	0.30	0.09-1.00	0.050
LDL cholesterol (mmol/l)	≥ *vs.* <3.37	166	12	0.70	0.21-2.29	0.552
Triglycerides (mmol/l)	≥ *vs.* <1.51	165	12	3.34	1.02-10.97	0.047
Lp(a) (g/l)	≥ *vs.* <0.31	157	12	1.21	0.35-4.20	0.768
Albumin (g/l)	≥ *vs.* <43.6	166	12	0.61	0.18-2.15	0.446
CRP (mg/l)	≥ *vs.* <6	165	12	4.16	1.26-13.74	0.020
Homocysteine (μmol/l)	≥ *vs.* <13.38	168	12	1.00	0.26-3.87	1.000
Glycosylated hemoglobin (%)	≥ *vs.* <3.7	164	12	2.21	0.67-7.36	0.195
Retinol (μmol/l)	≥ *vs.* <1.40	168	12	0.94	0.24-3.63	0.926
Alpha-tocopherol (μmol/l)	≥ *vs.* <21.18	168	12	3.78	0.47-30.17	0.209
Urinary neopterin (μmol/mol creatinine)	≥ *vs.* <169	168	12	0.55	0.12-2.59	0.447
Urinary NAG (μkat/mol creatinine)	≥ *vs.* <18.3	157	12	2.32	0.69-7.73	0.172
Urinary albumin (g/mol creatinine)	≥ *vs.* <0.88	162	12	4.73	1.4215.78	0.011

BMI: Body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein (a); CRP: C-reactive protein; NAG: *N*-acetyl-β-D-glucosaminidase. CI confidence interval.

Table III. *Proportions of patients with perfusion defects and odds ratios (ORs) in subgroups defined by categorical variables.*

Parameter	Value	Perfusion defect (n)		OR	95% CI	*p*-Value
		No	Yes			
Previous radiotherapy of the left hemithorax	No	118	5	1.0		0.054
	Yes	51	7	3.24	0.98-10.69	
History of smoking	No	116	8	1.0		0.791
	Yes	49	4	1.18	0.34-4.11	
History of hypertension	No	129	5	1.0		0.014
	Yes	40	7	4.52	1.36-15.01	
History of thyroid disorder	No	155	10	1.0		0.334
	Yes	14	2	2.21	0.44-11.12	
History of diabetes mellitus	No	163	11	1.0		0.421
	Yes	6	1	2.47	0.27-22.37	
History of hyperlipidemia	No	144	10	1.0		0.860
	Yes	25	2	1.15	0.24-5.57	
History of chemotherapy	No	77	4	1.0		0.415
	Yes	92	8	1.67	0.49-5.77	
Metastatic disease	No	159	10	1.0		0.169
	Yes	10	2	3.18	0.61-16.51	
Postmenopausal	No	51	1	1.0		0.138
	Yes	117	11	4.79	0.60-38.13	

CI: Confidence interval.

Table IV. *Results of multivariable stepwise selection logistic regression. Only data from patients with complete data for all variables from Tables II and III (n=12 for patients with perfusion defects and n=133 for patients without perfusion defects) were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).*

Parameter	OR	95% CI	*p*-Value
BMI (≥ *vs*. < 29.76 kg/m^2)	7.43	1.86-29.73	0.005
Previous radiotherapy of the left hemithorax (yes *vs*. no)	4.67	1.15-18.91	0.031
Urinary albumin (≥ *vs*. <0.88 g/mol creatinine)	4.41	1.12-17.40	0.034
Alpha-tocopherol (≥ *vs*. <21.18 μmol/l)	8.79	0.85-91.11	0.068

BMI: Body mass index.

cancer (10). Obviously, this review covered an era when no metastatic cancer could be cured (10). Moreover, in earlier studies, some complications of atherosclerosis, *e.g.* coronary artery disease, might have appeared to be less common in patients with cancer due to the bias in selecting the control group. However, an effect of chest radiotherapy, notably when combined with chemotherapy, was noted even in early reports. Ogawa *et al*. in an autopsy series of 1,642 patients with cancer found an incidence of myocardial infarction of 6.5% (7). Compared to other patients with cancer, significantly higher incidence of myocardial infarction was found in patients with lung carcinoma, head and neck carcinoma and urothelial cancer. Risk factors associated with coronary artery disease in this population were smoking, hypertension and hyperlipidemia. Increased incidence of acute myocardial infarction in patients with lung carcinoma compared to other tumors was also reported by Fujiwara *et al*. (11). Pehrsson *et al*. took an opposite approach and examined cancer incidence in patients treated for acute myocardial infarction, angina pectoris and intermittent claudication (12). The incidence of cancer was slightly but significantly increased in this population, mostly due to increased incidence of tobacco-related cancer.

In addition to hypertension or hypercholesterolemia, anticancer therapy or advanced cancer itself may affect some more recently discovered laboratory parameters associated with the progression of atherosclerosis, including systemic inflammatory response. Atherosclerosis is currently considered to be an inflammatory disorder (30). Systemic inflammatory response resulting from chronic infections, reflected in increased serum concentrations of CRP, has been postulated to play an important role in the progression of atherosclerosis. CRP is increased in patients with advanced cancer as well as in patients with atherosclerosis. It has been demonstrated in numerous studies that parameters of systemic inflammatory response, *e.g.* serum CRP, are predictive of the risk of cardiovascular events (15, 31-33). Neopterin, a biomarker of systemic immune response produced by activated macrophages is increased in patients with acute myocardial infarction (34), and increased neopterin concentrations are associated with cardiovascular and all-cause mortality (35, 36). Moreover, high neopterin concentrations are linked to mortality in the elderly (36). In the present study, increased CRP was associated with the risk of perfusion defects in univariate, but not multivariate analyses. In contrast, no association between urinary neopterin concentrations and perfusion defects was observed.

In conclusion, perfusion defects suggestive of myocardial ischemia are rare in asymptomatic patients with breast cancer during the first decade after diagnosis. The presence of perfusion defects may be associated with higher BMI, albuminuria and history of radiotherapy to the left hemithorax.

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