ANTICANCER RESEARCH *38*: 2207-2215 (2018)
doi:10.21873/anticanres.12463

Radiotherapy-induced Early ECG Changes and Their Comparison with Echocardiography in Patients with Early-stage Breast Cancer

SUVI SIRKKU TUOHINEN[1,2,3], KONSTA KESKI-PUKKILA[2,3], TANJA SKYTTÄ[2,4], HEINI HUHTALA[5], VESA VIRTANEN[2,3], PIRKKO-LIISA KELLOKUMPU-LEHTINEN[2,4], PEKKA RAATIKAINEN[1] and KJELL NIKUS[2,3]

[1]Heart and Lung Center, Helsinki University Hospital and Helsinki University, Helsinki, Finland; [2]Faculty of Medicine and Life Sciences, and [5]Faculty of Social Sciences, University of Tampere, Tampere, Finland; [3]Heart Center, and [4]Department of Oncology, Tampere University Hospital, Tampere, Finland

Abstract. *Background: Early electrocardiogram (ECG) changes after breast cancer radiotherapy (RT) have been reported, but their characteristics and associated factors are largely unknown. This study aimed to explore early RT-induced ECG changes and to compare them with echocardiography changes. Materials and Methods: Sixty eligible patients with chemotherapy-naïve left-sided and 20 with right-sided breast cancer were evaluated with echocardiography, blood samples and ECG before and after RT. Results: RT-induced ECG changes in the anterior leads. T-Wave changes were most frequent. T-Wave decline was associated independently with patient age ($\beta=-0.245$, $p=0.005$), mean heart radiation dose ($\beta=1.252$, $p=0.001$) and global systolic strain rate change ($\beta=7.943$, $p=0.002$). T-Wave inversion was associated independently with mean heart radiation dose ($\beta=0.143$, $p<0.001$), global longitudinal strain change ($\beta=0.053$, $p=0.017$) and posterior calibrated integrated backscatter ($\beta=-0.022$, $p=0.049$). Conclusion: RT-induced ECG changes were prevalent and associated with functional and structural changes in echocardiography. ECG could be used for post-RT cardiac screening.*

Breast cancer is the most common cancer in women, with an estimated incidence of 94-96 per 100,000 in the Western world (1, 2). Early diagnosis, surgery and adjuvant therapy have resulted in excellent prognosis. The 5-year survival rate of patients with early-stage breast cancer in Finland is greater than 90% (2). However, adjuvant radiotherapy (RT) in the thoracic region increases late cardiovascular morbidity and mortality (3, 4). Cancer survivors have a 7.4% risk of ischaemic heart disease per 1 Gy mean dose to the heart within 20 years after irradiation (5). Other manifestations of RT-induced heart disease (RIHD) include left-sided valvular lesions, myocardial fibrosis, disturbances in the conduction system and constrictive pericarditis (5-9). These conditions develop several years after RT and seem to be progressive (4, 7, 8). Early subclinical changes precede late sequelae. Given the progressive nature of the lesions, these changes might indicate an elevated risk for evolution towards RIHD. However, knowledge on the early changes is limited.

RT induces electrocardiogram (ECG) changes in 13 to 37% of patients with breast cancer (10-12). Changes in the ST segment and a reduction in R wave have been described in the early phase after RT (10, 13), whereas changes in the T wave seem to be the most prevalent findings (12). In the follow-up, 27-42% of the initial changes persist, and fragmentation of the QRS complex has been described in 37% of breast cancer patients 1 year after treatment (10, 11, 13). The changes were more prevalent in patients using tamoxifen and after post-mastectomy left-sided RT. Hypertension was found to increase the risk of irreversible ECG changes in a study by Eime *et al*. (10). The initial ECG alterations appear during treatment or within a few weeks after RT treatment (13). They are similar to ECG changes induced by acute pericarditis (14). However, the exact mechanisms and the clinical significance of the changes are not well known.

The aim of our study was to characterize RT-induced ECG changes in patients with early-stage breast cancer in the early phase after RT. In addition, by comparing these changes with simultaneous changes in echocardiography and blood sample analysis, we aimed to identify the possible aetiology and

Correspondence to: Suvi Sirkku Tuohinen, Heart and Lung Center, Helsinki University Central Hospital and Helsinki University, PO Box 340, 00029 Helsinki, Finland. Tel: +358 504270565, e-mail: suvi.tuohinen@fimnet.fi

Key Words: Breast cancer, radiotherapy, ECG, speckle tracking, integrated backscatter.

mechanisms behind the ECG changes. ECG is an elementary cardiac diagnostic tool with wide availability. The method is simple and does not pose excess risks for the patient. Thereby, this method has a high potential as a useful tool in the screening of the cardiac impact of RT.

Materials and Methods

Patient selection. In total, 80 eligible female patients with early-stage breast cancer were included in this single-centre, prospective observational clinical study between July 2011 and November 2013. Sixty patients had left-sided breast cancer, and 20 patients had right-sided breast cancer. All patients received adjuvant conformal three-dimensional (3D) RT after breast cancer surgery. Given the early stage of the disease, there was no indication for chemotherapy. The exclusion criteria were age under 18 years or over 80 years; other malignancy, pregnancy or breast feeding; acute myocardial infarction within the previous 6 months; symptomatic heart failure (New York Heart Association Functional Classification 3-4); dialysis; permanent anticoagulation; and severe psychiatric disorders. To optimize the image quality of echocardiography, patients with atrial fibrillation, left bundle branch block, permanent pacemaker and severe lung disease were also excluded. The study complied with the Helsinki declaration, and the local Institutional Board of Ethics approved the protocol. All participants signed an informed consent before enrolment.

Cardiac examinations. All patients were examined 6±8 days prior to RT, and a control study was performed 1±1 days after the end of RT. Each visit included a 12-lead ECG recording with a 50 mm/s speed, echocardiographic examination and blood samples for high sensitivity troponin T (hsTnt) and pro-B-type natriuretic peptide (proBNP).

ECG. Of the 80 patients, the post-RT recording of one patient was missing. The ECG analyses of the baseline and post-RT ECGs were performed manually by two of the authors (KK-P and KN) using an ECG ruler and a magnifying glass. The amplitudes of each wave (P, Q, R, S and T) and the PQ and ST levels were measured with a threshold of 0.5 mm using the TP interval as baseline. The J point was used for the measurement of the ST level. The QRS amplitude represents the sum of the maximal positive and negative QRS deflections. Regarding T-wave changes, we also performed categorical classification comparing baseline and post-RT findings. T-Wave inversion was defined as T-wave polarity change or as a change from isoelectric to a negative T wave. T-Wave decline was defined as a negative change from baseline to post-RT independently of the polarity of the T wave. The cumulative T-wave decline was calculated as a sum of the T-wave changes in all of the 12 leads. In addition, we used manual measurements for the PQ and QT intervals and levels. The corrected QT interval was calculated by Bazzett's formula (15). Cornell criteria were used for left ventricular (LV) hypertrophy (16).

Echocardiographic examinations. All echocardiographic examinations were performed with a commercially available cardiac ultrasound machine (Philips iE33 ultrasound system; Bothell, WA, USA) and a 1-5 MHz matrix-array X5-1 transducer by the same cardiologist (SST). All images were acquired at rest with a simultaneous superimposed ECG. Subcostal imaging was performed in a supine position, and other imaging was performed with the patient in the left lateral decubitus position. Doppler recordings were acquired at end-expiration. The details for other specific measurements are described in detail in our previous work (17-19).

Radiotherapy. All patients underwent 3D computed tomographic (CT) scanning with Philips Big Bore CT (Phillips Medical Systems, Madison, WI, USA) or Toshiba Aquilon LB (Toshiba Medical System, Tokyo, Japan). A breast board was used for all patients with their arms above the head in supine position. A deep inspiration breath-hold technique was used in two patients, whereas the remaining patients were scanned and treated in free breathing. RT was given according to the local guidelines. Tangential photon fields were used after breast-conserving surgery and electron fields in one patient to treat the breast wall after mastectomy. Standard treatment doses were 50 Gy in 2 Gy fractions or hypofractionated doses of 42.56 Gy in 2.66 Gy fractions. An additional boost of 10-16 Gy in 2 Gy fractions was administered to the tumour bed if clinically indicated. The treatment planning and contouring was performed from 3-mm sliced 3D CT images. The cardiac structures were contoured by one radiation oncologist (TS) in all patients. For dose calculations, please see Table I.

Statistical analysis. We present the data as the means with standard deviations for normally distributed variables, medians with ranges for variables with skewed distribution, and numbers with percentage for categorical variables. Differences between groups were tested with the independent samples *t*-test, independent samples Mann-Whitney *U*-test or with chi-square or Fisher's exact test when appropriate. We tested the differences between baseline and post-RT values with Student's paired samples t-test or related samples Wilcoxon signed rank test for normally and non-normally distributed variables, respectively. Associations of the variables were tested using Pearson correlation (r) for normally distributed variables and with Spearman correlation (r_s) for others. Linear and logistic regression were used to test the univariate relationship between two variables, and linear forward regression analysis was used for multivariable analysis. The strain rate values were magnified by 10 for the univariate analysis for practical reasons. All tests were two-sided, and *p*-values of less than 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (Version 23; IBM Corp, Armonk, NY, USA).

Results

General characteristics. The mean age of the study group was 63±6 years. The body mass index (BMI) exceeded the threshold for being overweight (BMI >25 kg/m^2) in 63% and the threshold for obesity (BMI >30 kg/m^2) in 25% of the patients. Twenty (25%) patients were current or ex-smokers. Thirty-three patients (41%) had no concurrent diseases other than breast cancer. Table II presents detailed baseline characteristics.

Electrocardiogram. General changes: All the ECGs preceding RT were normal with a sinus rhythm. None of the patients fulfilled the criteria of LV hypertrophy. RT-induced

Table I. *Radiation doses to the heart.*

	Entire group n=80		Patients with T-wave inversion n=44		
	Median	Range	Median	Range	*p*-Value
Mean total heart (Gy)	2.2	0.3-6.8	3.4	0.4-6.8	<0.001
Mean left ventricle (Gy)	3.2	0.0-12.3	4.6	0.1-12.3	<0.001
LV45 (%)	0.0	0.0-12.0	0.0	0.0-12.0	0.001
LV10 (%)	5.0	0.0-38.0	9.0	0.0-38.0	<0.001
Mean right ventricle (Gy)	1.8	0.2-9.2	2.6	0.3-9.2	<0.001
RV45 (%)	0.0	0.0-5.0	0.0	0.0-5.0	0.053
RV10 (%)	0.0	0.0-24.0	3.0	0.0-24.0	<0.001

LV45/RV45 and LV10/RV10, volume percentage of the left ventricle/right ventricle exposed to 45 Gy and 10 Gy radiation, respectively. *p*-Value indicates the difference between patients with and without T-wave inversion.

Table II. *Baseline characteristics of the study population.*

	Entire group n=80		Patients with T-wave inversion n=44		
	Mean	SD	Mean	SD	*p*-Value
Age (years)	63.4	6.3	63.4	6.9	0.930
Systolic blood pressure (mmHg)*	144	(130, 160)	140	(130, 154)	0.180
Diastolic blood pressure (mmHg)*	78	(70, 86)	79	(70, 85)	0.617
Body mass index (kg/m^2)*	26.4	(24.3, 30.0)	27.4	(24.5, 31.0)	0.152
	n	%	n	%	*p*-Value
Smoking					
Previous	9	11.3	5	11.4	>1.000
Current	11	13.8	4	9.1	0.201
Prior diagnosis					
Hypertension	35	43.8	20	45.5	0.627
Diabetes mellitus	7	8.8	5	11.4	0.219
Hypercholesterolemia	18	22.5	11	25.0	0.599
Hypothyroidism	10	12.5	7	15.9	0.499
No concurrent diagnosis	33	41.3	16	36.4	0.359
Medical treatment					
Beta blocker	12	15.0	6	13.6	>1.000
Calcium channel blocker	8	10.0	5	11.4	>1.000
ACE/ARB	25	31.3	14	31.8	0.755
Diuretic	15	18.8	9	20.5	0.476
Aspirin	10	12.5	5	11.4	0.740
Statin	16	20.0	11	25.0	0.239
Oral diabetes medication	7	8.8	5	11.4	0.219
Aromatase inhibitor	30	37.5	14	31.8	0.312
Tamoxifen	6	7.5	5	11.4	0.219

ACE, Angiotensin-converting enzyme blocker; ARB, angiotensin receptor blocker. *Median with (Q1, Q3). *p*-Value indicates the difference between patients with and without T-wave inversion.

changes were observed in most of the patients (Figure 1). T-Wave changes were observed in 63 (80%), S-wave changes in 51 (70%), ST-level changes in 26 (33%), and PQ-level changes in 20 (25%) of the patients. P or R waves were not significantly altered in individual leads. The average changes of the different ECG components are displayed in Table III.

T-Wave changes: Changes in the T waves were the most prevalent findings and were most often found in the precordial leads and in standard leads I, aVL and III (Figure 2). Overall T-wave decline appeared in 63 patients (80%). A cumulative decline of 4, 6, 8 and 10 mm was noted in 38 (48%), 21 (26%), 16 (20%) and eight patients (10%), respectively. The average cumulative T-wave decline was 4.0±5.2 mm. Patient age (β=–0.245, p=0.005), mean heart radiation dose (β=1.252, p=0.001) and speckle tracking echocardiography (STE) global systolic strain rate (s') change (β=7.943, p=0.002) were independently associated with cumulative T-wave decline.

T-Wave inversion occurred in 44 patients (55%), including 39 (69%) of the patients with left-sided and five (25%) with right-sided breast cancer (p=0.003). T-Wave inversions in two, three and four leads were noted in nine (11%), six (8%) and three (4%) patients, respectively. In patients with T-wave inversion, myocardial reflectivity increased significantly. In addition, septal cyclic variation of integrated backscatter declined, and changes in diastology were also noted (Table IV). In multivariable analysis, mean heart RT dose (β=2.135, p=0.004), GLS change (β=0.784, p=0.010), and posterior tissue reflectivity changes (β=0.346, p=0.030) were independently associated with T-wave inversion. T-Wave inversion in three to four leads was independently associated with the mean heart dose (β=0.995, p=0.059) and patient age (β=–0.227, p=0.055). Table V presents age-related factors.

S-Wave changes: The S wave changed in 51 patients (70%). An increase in the S wave in precordial leads V2 to V4 was observed in 27 (53%) patients, and a decrease was noted in 24 (47%) patients. The cumulative S-wave change exhibited a weak association with mean lung RT dose (r=0.344, p=0.002), left atrial volume change (r=–0.257, p=0.023), and pulsed tissue Doppler septal, lateral and anterior a' changes (r=0.318, p=0.004), (r=0.262, p=0.019) and (r=0.264, p=0.023). In univariate analysis, the mean lung dose explained 12% of the cumulative S-wave change, and the pulsed tissue Doppler a' changes in the septal, lateral and anterior walls explained 10%, 7% and 7%, respectively. In multivariable analysis, the mean lung radiation dose (β=1.475, p=0.002) and the pulsed tissue Doppler septal a' (β=1.260, p=0.011) had an independent relationship with changes in the S waves.

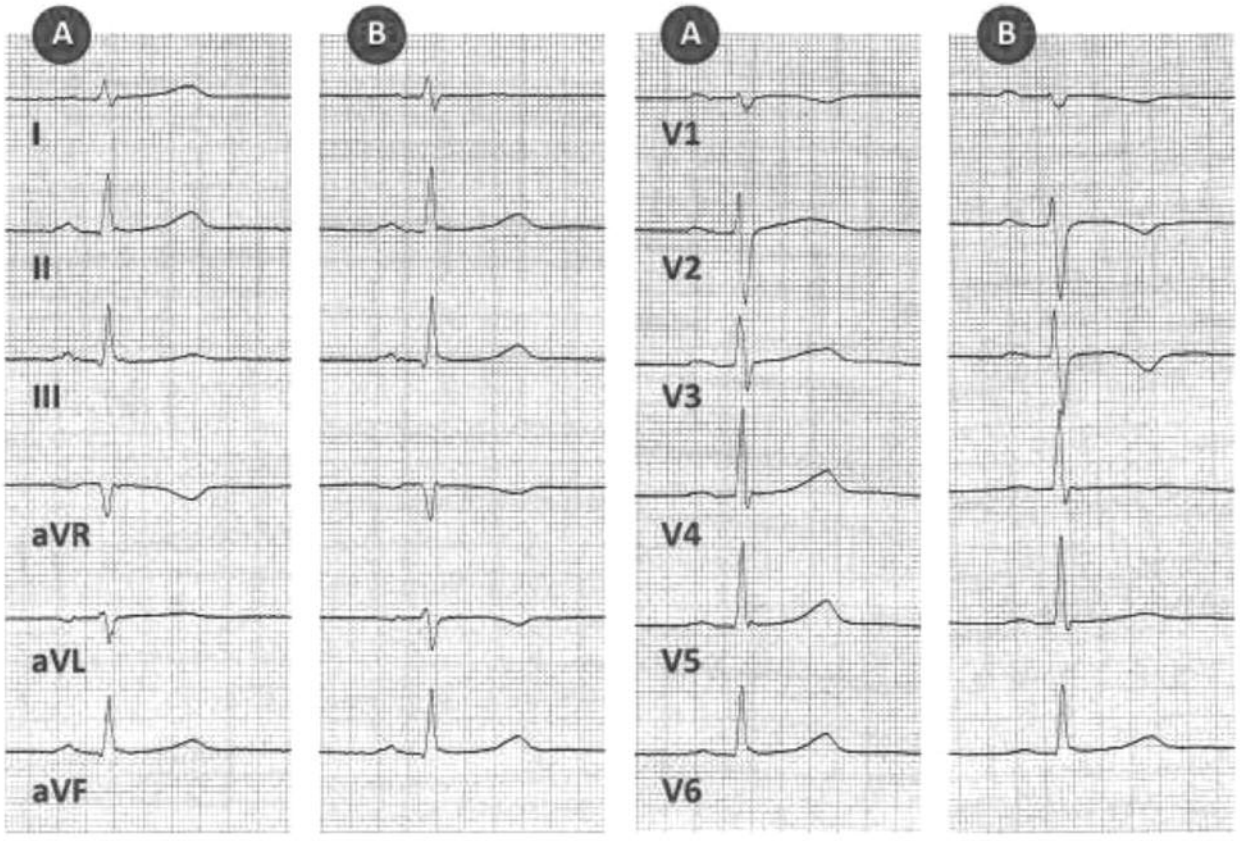

Figure 1. *Typical electrocardiogram (ECG) changes before (A) and after (B) radiation therapy. T-Wave inversion developed in leads aVL and V2-V3. T-Wave decline is evident in leads I and V4-V6. The ECG recordings were obtained with a 50 mm/s speed.*

Table III. *Echocardiographic measurements and their changes after radiotherapy (RT).*

	Entire group n=80				Patients with T-wave inversion n=44			
	Baseline		After RT		Change after RT			
Measurement	Mean	SD	Mean	SD	*p*-Value	Mean	SD	*p*-Value
P-Wave								
Amplitude (mm)	0.8	0.4	0.8	0.4	0.580	0.0	0.4	0.566
Duration (ms)	94	12	94	10	0.736	−1	10	0.602
QRS complex								
QRS amplitude (mm)	11.2	2.5	11.3	2.5	0.541	−0.1	1.0	0.697
R amplitude (mm)	6.9	1.9	6.9	1.9	0.954	−0.1	0.6	0.422
S amplitude (mm)	3.9	1.3	4.1	1.3	0.002	0.3	0.8	0.024
QRS duration (ms)	88	12	88	13	0.957	−1	7	0.204
T-Wave amplitude (mm)	1.5	0.7	1.1	0.6	<0.001	−0.4	0.5	<0.001
PQ interval (ms)	164	23	163	22	0.535	−1	12	0.445
cQT interval (ms)	428	43	417	18	0.023	−13	36	0.025
Heart rate (beats/min)	64.2	9.8	64.9	9.6	0.521	0.2	10.0	0.881

cQT, Heart rate-corrected QT interval using Bazzett's formula. The average value from all 12 leads was used for the calculations, except for the QT and PR intervals, which are derived from lead II and V1 for practical reasons. In amplitude measurements 1 mm = 0.1 mV. *p*-Values indicate the difference between values at baseline and those after RT.

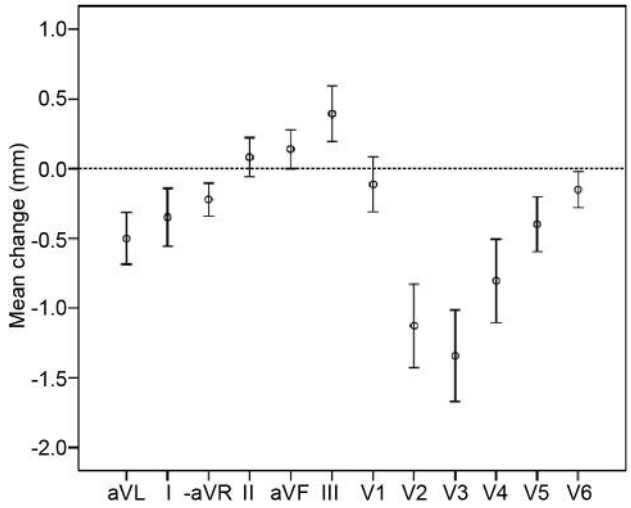

Figure 2. *The distribution of T-wave changes after radiotherapy in the entire group. The changes represent mean values with 95% confidence intervals, and the leads are arranged according to their anatomical order (Cabrera lead system).*

PQ-level changes: The change of the PQ level remained <1 mm in all patients. A 0.5-mm change in the PQ level was observed in 20 patients (25%) in at least one lead. Twelve patients (60%) had a PQ-level change in one lead, six patients (30%) in two and two patients (10%) in three leads. The location of the PQ-level changes was evenly distributed over all ECG leads in patients with left-sided breast cancer. In contrast, patients with right-sided breast cancer exhibited a more localized distribution of their PQ-level changes, including three patients in the lead aVR and in one patient each in leads I and V1-3. The changes in PQ levels had no associations with other factors.

ST-level changes: One patient displayed a 1-mm change in her ST level, whereas all other ST changes were less than 1 mm. A 0.5-mm change in the ST-level change was observed in 26 patients (33%). The majority (17 patients, 65%) had a ST-level change in only one lead. Seven patients (26.9%) had an ST-level change in two leads and one patient each in three and four leads (3.8%). The changes were predominantly located in leads V1-4 (92%). Univariate analysis revealed an association of the LV systolic and diastolic strain rates and ST depression after RT. A 0.1/s change in LV systolic strain rate imposed a 1.256-fold increased risk for ST depression (95% CI=1.001-1.576, p=0.049). A 0.1/s change of diastolic strain rate value induced a 0.798-fold increased risk for ST depression (95% CI=0.661-0.964, p=0.019).

Echocardiographic measurements. Echocardiographic measurements are displayed in Table IV. RT induced both structural and functional changes. In general, the LV mass

Table IV. *Echocardiographic measurements of the study population.*

	Entire group n=80			T-Wave inversion n=44		
	Change			Change		
Measurement	Mean	SD	*p*-Value	Mean	SD	*p*-Value
Structure						
LVEDV (ml)	2	17	0.288	−2	12	0.363
LVESV (ml)	−2	12	0.120	0	7	0.745
LV mass (g)	4	11	0.010	4	11	0.056
IVS (mm)	0.4	1.0	0.004	0.4	0.9	0.007
PW (mm)	0.5	1.3	<0.001	0.6	1.3	0.006
rcIBS (dB)	1.7	7.4	0.048	3.3	8.9	0.030
scIBS (dB)	2.3	5.8	0.001	3.1	6.2	0.004
pcIBS (dB)	0.3	5.4	0.667	1.7	5.8	0.079
Diastology and filling pressure						
IVC (mm)	−0.7	3.8	0.115	−1.1	4.0	0.095
IVC variability (%)	0.0	0.2	0.901	3.3	18.5	0.251
RV Ee' ratio	0.1	1.3	0.457	0.2	1.5	0.876
Tr gradient (mmHg)	0	5	0.167	0	5	0.919
IVRT (ms)	4	24	0.109	8	27	0.045
Mitral E (cm/s)	−4	10	0.005	−5	10	0.012
Mitral dt (ms)	14	43	0.018	7	43	0.170
Mitral a (cm/s)	−2	13	0.151	−3	13	0.110
LV Ee' ratio	−0.2	1.9	0.250	−0.2	1.8	0.381
Systolic function						
LVEF (%)	−1	6	0.279	−1	6	0.331
Anterior s' (cm/s)	−0.52	1.54	<0.001	−0.49	1.79	0.009
GLS (%)	−0.7	2.7	0.028	−0.4	2.8	0.342
SR (1/s)	0.0	0.2	0.384	−0.1	0.2	0.302
GCS (%)	−1.5	5.4	0.027	−1.0	5.6	0.342
sCVIBS (dB)	−1.4	3.5	0.002	−1.6	3.7	0.012
pCVIBS (dB)	−0.9	3.5	0.035	−0.7	3.6	0.252
TAPSE (mm)	−1.8	3.4	<0.001	−2.3	3.5	<0.001

LVEDV, LVESV and LV mass, left ventricular end diastolic and systolic volumes and end-diastolic mass; IVS and PW, LV septum and posterior wall thicknesses; rcIBS, scIBS and pcIBS, integrated backscatter value of the right ventricular free wall, interventricular septum and the LV posterior; IVC, inferior vena cava; RV Ee'-ratio, the ratio between right ventricular inflow E-wave velocity and the pulsed tissue Doppler e' velocity; Tr gradient, the maximal gradient derived from the tricuspid regurgitation; IVRT, LV isovolumetric relaxation time; Mitral E, dt and a, mitral inflow early (E) and late (a) diastolic velocities and declaration time of the E-wave; LV Ee' ratio, the ratio between mitral inflow E-wave velocity and averaged pulsed tissue Doppler e'-wave velocities; LVEF, left ventricular ejection fraction; Anterior s', LV systolic pulsed tissue Doppler velocity derived; GLS and GCS, global longitudinal and circumferential strains in speckle tracking analysis; SR, LV global systolic strain rate; sCVIBS and pCVIBS, LV septal and posterior wall cyclic variation of the integrated backscatter; TAPSE, tricuspidal annular plane systolic excursion. A negative value indicates declining value or function after RT, whereas a positive value indicates increasing value or function. *p*-Values indicate the difference between baseline and after RT values.

Table V. *Relationship of patient age with other baseline characteristics and medication.*

	Age of patients with T-wave inversion			Age of patients without T-wave inversion			
Characteristic	n	Mean	SD	n	Mean	SD	*p*-Value
Hypertension	35	65.9	6.1	45	61.5	5.9	0.002
Diabetes	7	66.1	8.4	73	63.1	6.1	0.233
Hypothyroidism	10	62.8	6.7	70	63.5	6.3	0.751
Current smoker	11	61.3	4.2	69	63.7	6.6	0.233
Left-sided breast cancer	60	63.6	6.8	20	62.9	4.7	0.657
Beta blocker	12	65.4	6.4	68	63.0	6.3	0.234
Calcium channel blocker	8	68.1	4.9	72	62.9	6.3	0.025
ACE/ARB	25	65.8	6.6	55	62.3	6.0	0.024
Diuretic	15	66.2	6.6	65	62.8	6.1	0.057
Statin	16	66.2	5.1	64	62.7	6.5	0.048
		β	*p*-Value				
Height	80	–0.136	0.273				
Weight	80	0.021	0.710				
BMI	80	0.163	0.338				

ACE, Angiotensin-converting enzyme blocker; ARB, angiotensin receptor blocker; BMI, body mass index.

Table VI. *T-Wave inversion explaining changes in central echocardiography parameters.*

Change from baseline	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
TAPSE >2 mm	41	35	65	17
LVEF >10%	82	11	74	17
GLS >20%	87	15	73	30

PPV, Positive predictive value; NPV, negative predictive value; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain.

and wall reflectivity increased after RT along with changes in diastology and sensitive measurements of the LV systole. The ability of the T-wave inversions to predict >2 mm decline in tricuspid annular plane systolic excursion (TAPSE), a greater than 10% absolute decline in LV ejection fraction (LVEF) or a greater than 20% relative decline in global longitudinal strain (GLS) are presented in Table VI.

Blood tests. The hsTnt level increased from 5.8±3.8 ng/l to 6.4±3.2 ng/l after RT (p=0.004). ProBNP increased from 110±126 ng/l to 135±169 ng/l (p=0.002). Patients with T-wave inversion exhibited significant increase in hsTnt by 0.5±3.0 ng/l (p=0.048) and proBNP by 38±81 ng/l (p=0.002).

Discussion

The results of the present study demonstrate that breast cancer RT induces ECG changes in the majority of the patients. T-Wave changes were the most prevalent findings. These changes were observed in the RT-prone regions and were associated with the mean heart radiation dose and functional and structural cardiac changes. In addition, a novel finding of changes in the ST and PQ levels were discovered in 33% and 25% of the patients after RT, respectively. These changes are similar to those previously described in pericarditis (20).

T-Wave changes in our patients. T-Wave changes and RT treatment were found to have a close relationship. The mean heart dose was independently associated with both T-wave decline and T-wave inversion. In the entire group, the highest T-wave decline and most frequent T-wave inversions were observed in leads V2 to V4, corresponding to the anteriorly located RT fields and logically with a stronger impact in patients with left-sided breast cancer. Furthermore, T-wave changes were associated with simultaneous structural and

functional changes in echocardiography. The cumulative T-wave decline was independently associated with a global systolic strain rate reduction in STE, whereas T-wave inversions were independently associated with a simultaneous reduction in GLS and increasing posterior LV myocardial tissue reflectivity. The systolic strain rate is a more sensitive detector of systolic dysfunction than strain (21). It can be hypothesized that the T-wave decline in association with global systolic strain rate represents a milder form of RT impact than T-wave inversions, which are associated with a more robust GLS and changes in structural parameters. In addition, patients with frank T-wave inversions had a statistically, although not clinically, significant increase in hsTnT, which is another indicator of myocardial damage.

Changes in the PQ and ST levels. RT-induced pericardial changes in the early phase are inflammatory; however, clinically significant early post-RT pericardial reactions are nowadays rare (3, 22). ECG changes indicating pericarditis are typically widespread changes in the PQ and ST levels, but PQ-level changes in single leads also have high sensitivity to detect pericarditis (22, 23). Thereby, the novel finding of PQ-level changes in our patients could indicate pericardial irritation. However, none of our patients presented with pericardial changes in echocardiography. Furthermore, PQ-level changes exhibited no significant association with any other parameter, including RT doses. The ST-level changes were located similarly to the T-wave changes and had partially similar associations with the changes in echocardiography. Whether these changes represent the same myocardial process as the T-wave changes or are indicators of pericardial irritation induced by RT remains unknown.

Changes in S-wave and cQT intervals. S-Wave changes in leads V2 to V4 occurred in a seemingly unpredictable manner, with an association with lung radiation dose and atrial function. We were unable to logically explain these findings. Similarly, the clinically insignificant shortening of the cQT interval seemed to have no clear logical explanation.

Other cardiac changes in our study. Several structural and functional changes in echocardiography were noted after RT. The LV myocardium became thicker, and the myocardial reflectivity increased. Furthermore, several changes in diastology and sensitive systolic parameters were detected. In addition, slight increases in hsTnt and proBNP were observed after RT. All of these simultaneous changes after RT clearly imply a real cardiac impact. The ability of the ECG to predict changes in TAPSE, LVEF or GLS was relatively good, whereas the absence of the changes in ECG was not impressive in predicting unaltered echocardiography, nor were the ECG changes specific in predicting certain type of changes in echocardiography.

Possible mechanisms causing the ECG changes in our patients. Based on our study results, we can only hypothesize on the possible mechanisms involved. RT produces RIHD, the clinically significant sequela, several years after the RT treatment, and the main mechanisms include fibrotic tissue changes. Early RT-induced tissue changes have a different character. The initial changes are inflammatory. These changes appear within a few hours after radiation exposure and last for several days (24, 25). Thereafter, a latent phase of at least 1 month follows with on-going endothelial damage, leading to capillary changes and a reduced capillary to myocardium ratio (24). Our control study was performed 1±1 days after RT, which is well within the range of the inflammatory phase. The independent association with several structural and functional echocardiography parameters and changes in myocardial biomarkers are consistent with the observed cardiac impact. T-Wave decline was associated with sensitive functional changes in echocardiography and different baseline characteristics. T-Wave inversion exhibited an additional association with increasing myocardial reflectivity and an hsTnt increase.

The causative factors for the RT-induced T-wave changes are not known. In the human heart, the process of repolarization of the LV-free wall accounts for practically all ventricular repolarization, which is expressed in the standard 12-lead ECG by the T wave. Theoretically, inverted T waves should appear in the ECG when the process of repolarization in the epicardial myocardium is accomplished later than that in the endocardial myocardium (26). Therefore, it is not surprising that T-wave changes are typical of inflammatory and idiopathic myopericarditis, which mainly affects the outer layers of the ventricles (14). Both epicardial impact and myocardial oedema could be possible explanations for the T-wave changes observed in our patients, also supported by the concurrent changes in echocardiography (27, 28). The changes in the ST and PQ levels might represent pericardial inflammation caused by RT, a well-known RT-induced phenomenon. However, other findings indicating pericardial effects were absent.

Factors modifying ECG changes in our patients. Surprisingly, the T-wave changes seemed to be aggravated by younger age and mitigated by hypertension. This finding is in contrast with previous reports (10). Closer analysis of the patients' baseline factors according to their age revealed a difference in the distribution of other diagnoses and their treatments. Older patients were significantly more often hypertensive and used statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker or calcium channel blockers more often. Whether the paradoxical findings can be explained by

undiagnosed and untreated diseases in our younger patients or the beneficial effects of the concurrent treatments remains to be clarified in later studies.

Clinical implications. Our results are important for several reasons. Firstly, awareness of adverse effects on healthy tissue induced by RT is increased. The adverse effects of modern therapy protocols will not be apparent immediately, and surrogate markers of cardiac impact might serve in the continuous work of making RT protocols safer. ECG would be well suited for this purpose.

Secondly, the rising awareness of RIHD has provoked a discussion of whether patients with RT in the thoracic region should be routinely followed-up (3, 9). A reliable marker of early cardiac impact could theoretically identify those with increased risk of late sequelae, and resources could consequently be focused more efficiently. ECG is a widely available cheap method that would be well suited for this purpose.

Thirdly, our results demonstrate a high frequency of ECG changes after RT treatment. This is important when a patient with previous RT seeks medical attention. A new change in the ECG, especially frank new T-wave inversions, could raise suspicion of other cardiac pathologies and launch a cascade of timely, costly and potentially risky examinations. An awareness of an alternative aetiology of new ECG changes would be beneficial in this clinical scenario.

Limitations of our study. Our study has clear limitations. This study employed an observational follow-up study design, and the number of patients enrolled was limited. Furthermore, no myocardial biopsy samples were acquired because it was considered as unethical in this otherwise heart-healthy population. In addition, ST- and PQ-level changes were modest and generally restricted to a single lead, and the clinical significance of such minor changes can be questioned. Furthermore, the effect of medication requires further validation with larger studies. Finally, these results reflect only very short-term outcomes. A longer follow-up of this patient population is ongoing to reveal later development and clinical impact of these early changes.

Conclusion

RT-induced ECG changes are prevalent in patients with breast cancer. With the simultaneous association with structural and functional changes in echocardiography, ECG changes could be used as surrogate markers of RT-induced cardiac impact in the screening and follow-up of this patient population. On the other hand, the high prevalence of ECG changes should be kept in mind in the differential diagnosis of these patients in the clinical setting.

Acknowledgements

The Authors thank research nurses Virpi Palomäki and Hanna Näppilä for their valuable assistance during this study. This study was supported by the Paavo and Eila Salonen Legacy, Ida Montin Fund, The Finnish Medical Foundation, The Finnish Cultural Foundation, Pirkanmaa Regional Fund, The Finnish Foundation for Cardiovascular Research, Finnish Society of Oncology, Pirkanmaa Cancer Society, Finnish-Norwegian Medical Foundation, The Pirkanmaa Hospital District, The Aarne and Aili Turunen Foundation, Seppo Nieminen Fund (grant 150613), and the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (95021).

References

1 Ferlay J, Shin H, Bray F, Forman D, Mathers C and Parkin D: GLOBOCAN 2008 v1.2. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 (Internet). 2010.
2 http://www.cancer.fi/syoparekisteri/tilastot/.
3 Lancellotti P, Nkomo VT, Badano LP, Bergler J, Bogaert J, Davin L, Cosyns B, Coucke P, Dulghery R, Edvardsen T, Gaemperli O, Galderisi M, Griffin B, Heidenreich PA, Nieman K, Plana JC, Port SC, Scherrer-Grosbie M, Schwartz RG, Sebag IA, Voigt JU, Wann S and Yang PC: Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging *14(8)*: 721-740, 2013.
4 Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, Taylor CW and Van Leeuwen FE: Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst *99(5)*: 365-375, 2007.
5 Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C and Hall P: Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med *368(11)*: 987-998, 2013.
6 Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robinson CC and Leisenring WM: Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ *339*: b4606, 2009.
7 Bijl JM, Roos MM, van Leeuwen-Segarceanu EM, Vos JM, Bos WJ, Biesma DH and Post MC: Assessment of valvular disorders in survivors of Hodgkin's lymphoma treated by mediastinal radiotherapy +/- chemotherapy. Am J Cardiol *117(4)*: 691-696, 2016.
8 Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG and van Leeuwen FE: Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. Int J Radiat Oncol Biol Phys *64(4)*: 1081-1091, 2006.
9 Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip G, Lyon AR, Fernandez TL, Mohty D, Piepoli MF, Tamargo J, Torbicki A and Suter T: 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J *37(36)*: 2768-2801, 2016.

10 Elme A, Saarto T, Totterman KJ, Utrianen M, Kautiainen H, Jarvenpaa S, Tenhunen M and Blomqvist C: Electrocardiography changes during adjuvant breast cancer therapy: incidence and risk factors. Anticancer Res *33(11)*: 4933-4939, 2013.
11 Adar A, Canyilmaz E, Kiris A, Ilter A, Serdar L, Memis Y, Bahat Z and Onalan O: Radiotherapy induces development of fragmented QRS in patients with breast cancer. Breast Care *10(4)*: 277-280, 2015.
12 Lindahl J, Strender LE, Larsson LE and Unsgaard A: Electrocardiographic changes after radiation therapy for carcinoma of the breast. Incidence and functional significance. Acta Radiol Oncol *22(6)*: 433-440, 1983.
13 Gomez DR, Yusuf SW, Munsell MF, Welsh JW, Liao Z, Lin SH, Pan HY, Chang JY, Komaki R, Cox JD, McAleer MF and Grosshans DR: Prospective exploratory analysis of cardiac biomarkers and electrocardiogram abnormalities in patients receiving thoracic radiation therapy with high-dose heart exposure. J Thorac Oncol *9(10)*: 1554-1560, 2014.
14 Gerzen P, Granath A, Holmgren B and Zetterquist S: Acute myocarditis. A follow-up study. Br Heart J 34(6): 575-583, 1972.
15 Bazett HC: An analysis of the time-relatios of the electrocardiograms. Heart *7*: 353-70, 1920.
16 Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS and Philips MC: Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol *6(3)*: 572-580, 1985.
17 Tuohinen SS, Skytta T, Virtanen V, Virtanen M, Luukkaala T, Kellokumpu-Lehtinen PL and Raatikainen P: Detection of radiotherapy-induced myocardial changes by ultrasound tissue characterisation in patients with breast cancer. Int J Cardiovasc Imaging *32(4)*: 767-776, 2016.
18 Tuohinen SS, Skytta T, Poutanen T, Huhtala H, Virtanen V, Kellokumpu-Lehtinen PL and Raatikainen P: Radiotherapy-induced global and regional differences in early-stage left-sided *versus* right-sided breast cancer patients: speckle tracking echocardiography study. Int J Cardiovasc Imaging *33(4)*: 463-472, 2016.
19 Tuohinen SS, Skytta T, Huhtala H, Virtanen V, Virtanen M, Kellokumpu-Lehtinen PL and Raatikainen P: Detection of early radiotherapy-induced changes in intrinsic myocardial contractility by ultrasound tissue characterization in patients with early-stage breast cancer. Echocardiography *34(2)*: 191-198, 2017.
20 Lange RA and Hillis LD: Clinical practice. Acute pericarditis. N Engl J Med *351(21)*: 2195-2202, 2004.
21 Jamal F, Strotmann J, Weidemann F, Kukulski T, D'hooge J, Bijnens B, Van de Werf F, Schreeder DE and Sutherland GR: Noninvasive quantification of the contractile reserve of stunned myocardium by ultrasonic strain rate and strain. Circulation *104(9)*: 1059-1065, 2001.
22 Authors/Task Force Members, Adler Y, Charron P, Imazio M, Badano L, Baron-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Meisch B, Magosi B, Pavie A, Ristic AD, Sabate Tenas M, Seferovic P, Swedberg K, Tomkowski W, Achenbach S, Agewall S, Al-Ahar N, Angel Ferrer J, Arad D, Asteggiano R, Bueno H, Carorio AC, Carerj S, Ceconi C, Evangelista A, Flashkampf F, Gianni Koulas G, Gielen S, Habib G, Kohl P, Lamgriroun E, Lancellolli P, Lazaros G, Linhart A, Meurin P, Nieman K, Piepoli MF, Price S, Roos-Hesselink J, Roubille F, Ruschitzka F, Sagrista Sauleda J, Voigt JU, Zamorano LJ. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J *36(42)*: 2921-2964, 2015.
23 Porela P, Kyto V, Nikus K, Eskola M and Airaksinen KE: PR depression is useful in the differential diagnosis of myopericarditis and ST elevation myocardial infarction. Ann Noninvasive Electrocardiol *17(2)*: 141-145, 2012.
24 Fajardo LF and Stewart JR: Pathogenesis of radiation-induced myocardial fibrosis. Lab Invest *29(2)*: 244-257, 1973.
25 Westbury CB and Yarnold JR: Radiation fibrosis – current clinical and therapeutic perspectives. Clin Oncol (R Coll Radiol) *24(10)*: 657-672, 2012.
26 Pruitt RD, Klakeg CH and Chapin LE: Certain clinical states and pathologic changes associated with deeply inverted T waves in the precordial electrocardiogram. Circulation *11(4)*: 517-530, 1955.
27 Migliore F, Zorzi A, Marra MP, Basso C, Corbetti F, De Lazzari M, Tarantini G, Buja P, Lagocnata C, Thiene G, Corrado D and Iliceto S: Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. Heart Rhythm *8(10)*: 1629-1634, 2011.
28 Maeda S, Imai T, Kuboki K, Chida K, Watanabe C and Ohkawa S: Pathologic implications of restored positive T waves and persistent negative T waves after Q wave myocardial infarction. J Am Coll Cardiol *28(6)*: 1514-1518, 1996.

Received February 3, 2018
Revised March 1, 2018
Accepted March 6, 2018