Electrocardiography Changes During Adjuvant Breast Cancer Therapy: Incidence and Risk Factors

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Abstract. *Background/Aim: Breast cancer survivors have a higher cardiovascular morbidity/mortality rate, when compared with healthy age-matched general population. Electrocardiography (ECG) changes have been found to be associated with chemo- and radiation therapy. In the present study we investigated changes in ECG patterns following modern adjuvant therapy for breast cancer. Patients and Methods: A standard 12-lead electrocardiogram was recorded at rest three times (prior and after adjuvant therapy) and retrospectively analyzed in 414 breast cancer patients, who participated in the open prospective phase III randomized trial (BREX) of exercise training 2005-2007. Results: New electrocardiographic changes in the T-wave or ST-segment (depression or elevation) after the adjuvant therapy were recorded in 49 patients (13%). In multivariate analyses, hypertension treated with anti-hypertensive medication was the only significant factor associated with irreversible ECG changes (OR=4.71; 95% CI=1.36-16.38; p=0.015). Conclusion: New irreversible pathological electrocardiographic changes, which acquired during the adjuvant therapy, had a clear relationship with hypertension This patients subgroup needs to be studied further.*

Breast cancer survivors have a higher cardiovascular (CV) morbidity/mortality rate, when compared with the age-matched population (1-3). This has been partially related to adjuvant treatments because most adjuvant treatments are associated with unique and varying degrees of CV adverse effects. In previous studies, the irradiation to the left breast has been found to be associated with an increased rate of coronary arteriosclerosis and myocardial ischemic alterations with the cumulative risk of 6.4% for left-sided irradiation, when compared with 3.6% for right-sided irradiation during a follow-up of 20 years (4-9). Anthracyclines have been observed to cause acute and chronic heart failure in 2.1% of treated cases (10), but the incidence of sub-clinical left ventricular dysfunction is even higher – up to 10-15% in some investigations (11-13). Trastuzumab causes significant left ventricular ejection fraction (LV-EF) reduction and grade III-IV Congestive Heart Failure (CHF) in 7% of the patients (14). Combination therapy with radiotherapy and chemotherapy seems to further increase the risk of congestive heart failure (4). In addition, multiple additional risk factors such as advanced age, prior cardiac disease and smoking also render cardiac toxicity (4, 9). However, symptomatic heart failure often occurs years after cancer treatment, making it difficult to evaluate the preventive strategies.

ECG changes have been noted to be associated with chemotherapy (CT) and radiation therapy (RT) in historical studies (12, 15-19). During the last decades, however, CT and RT for breast cancer have changed fundamentally. Consequently, in the present study, we set out to investigate acute changes in the ECG patterns following modern adjuvant therapy in breast cancer.

Patients and Methods

ECG was analyzed in 414 breast cancer patients, who participated in the open prospective phase III randomized trial (BREX) of exercise training between 2005-2007 at the Departments of Oncology in Helsinki University Hospitals. Women aged from 35 to 68 years with newly-diagnosed invasive breast cancer who received adjuvant CT and/or RT within 4 months (or started endocrine therapy no more than 4 months earlier) were included in the study. Exclusion

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criteria included no medical adjuvant therapy, a history of NYHA class III or greater cardiac disease, myocardial infarction within 12 months, uncontrolled hypertension, verified osteoporosis, other serious comorbidities, and patients not capable of training (20). Overall, 361 out of 414 women were included in this ECG analysis; 40 were excluded because of lack of pre-treatment ECG and 13 patients were excluded because of ECG changes other than ST (bradycardia, frequent extrasystoles, prolonged QT interval, P-wave changes, *etc*.).

Adjuvant treatment was administered according to local clinical guidelines. RT was given after breast-conserving surgery to the whole breast using tangential 6-MV photon fields to 50 Gy in 2-Gy fractions. When appropriate, the tumor bed was boosted with electrons to 60 Gy. After mastectomy, RT to 50 Gy in 2-Gy fractions was given either with the 4-12-MeV electron field alone (mastectomy scar) or including regional axillar and clavicular lymph node areas to the adjacent 6-MV photon field. The RT after breast-conserving surgery was performed using three-dimensional CT-based planning, whereas post-mastectomy RT was given using traditional two-dimensional planning without CT-based dose calculation and target delineation. However, even in the 2-D planning of post-mastectomy RT, the estimation of the chest wall thickness used for the selection of electron beam energy was based on imaging (either CT or ultrasound). The radiation dose was prescribed according to the ICRU 50 recommendations in all cases.

After the approval of the ethics committee of the Helsinki University Hospital, a written informed consent was signed by all participants before study entry. The trial is registered in the Clinical Trials Register under the unique trial number NCT00639210 (http://www.clinicaltrials.gov/).

A standard 12-lead electrocardiogram was recorded at rest three times; firstly, prior to adjuvant therapy; secondly, on randomization into the BREX study, *i.e*. after the completion of adjuvant CT or RT; and thirdly, during 1-year follow-up visit. All ECGs were studied retrospectively by a specialist in internal medicine and all ECG changes were examined/confirmed by a cardiologist. ST segment depression was defined as at least 0.1-mV horizontal or down-sloping ST segment depression, when compared with baseline ST levels. New or presumed new ST segment was defined as elevation at the J point in two or more contiguous leads with the cut-off points of ≥0.2 mV in leads V1, V2, or V3 and ≥0.1 mV in other leads.

Statistical analyses. Data are presented as means±standard deviations (SD), counts with percentages, or medians with interquartile ranges (IQR). The most notable outcomes are given with 95% confidence intervals (95% CI). Comparisons between groups were performed by chi-square test, *t*-test, permutation test, or Mann-Whitney test when appropriate. Multivariate logistic regression analysis was employed to determine variable associations with the ECG changes.

Results

The basic characteristics of patients with or without ECG changes are presented in Table I. All patients had sinus rhythm. New electrocardiographic changes in the T-wave or ST segment (depression or elevation) after adjuvant therapy were seen in 49 patients (13%). The ECG changes of one patient are presented in Figure 1. All patients were symptom-free regarding heart disease. The only significant differences between patients with and without ECG changes were higher incidence of hypertension among patients with ECG changes (31% *vs*. 17%; p=0.028) and left-sided breast cancer (63% *vs*. 46%, p=0.029) (Table I).

Table I. *Baseline characteristics of the patients with and without ST-changes after the adjuvant treatments.*

	Patients with ST-changes n=49	Patients without ST changes n=312	*p*-Value
Age, mean (SD)	53 (9)	52 (7)	
Postmenopausal, n (%)	24 (49.0)	171 (54.8)	0.45
Height, cm, mean (SD)	164 (6)	165 (6)	0.64
Weight, kg, mean (SD)	71.3 (13.9)	71.0 (12.2)	0.89
BMI, mean (SD)	26.5 (4.8)	26.2 (4.6)	0.72
Smoking, n (%)	6 (12.2)	40 (12.8)	0.91
Alcohol consumption, median (IQR)	3 (1, 7)	3 (1, 6)	0.58
Leisure time physical activity, n (%)			0.37
Low	12 (25)	57 (20)	
Moderate	28 (58)	158 (55)	
High	8 (17)	74 (26)	
Chronic diseases, n (%)	29 (59)	166 (53)	0.44
CVD NYHA <3, n (%)	2 (4)	7 (2)	0.44
Cardiometabolic syndrome NCEP, n (%)	20 (41)	94 (30)	0.14
Waistline, cm, mean (SD)	88 (13)	88 (13)	0.85
Statin medication, n (%)	3 (6)	21 (7)	0.87
Diabetes treatment, n (%)	2 (4)	8 (3)	0.55
Anti-hypertensive treatment, n (%)	15 (31)	54 (17)	0.028
Blood pressure, mean (SD)			
Systolic	133 (22)	135 (19)	0.44
Diastolic	86 (13)	85 (11)	0.54
Total cholesterol, mean (SD)	5.17 (1.12)	5.12 (0.99)	0.75
HDL cholesterol, mean (SD)	1.84 (0.63)	1.92 (0.48)	0.33
LDL cholesterol, mean (SD)	2.75 (1.03)	2.67 (0.87)	0.58
Triglycerides, mean (SD)	1.37 (0.85)	1.19 (0.67)	0.11
Glycose, mean (SD)	5.56 (0.58)	5.48 (0.90)	0.51
Tumor diameter, cm, mean (SD)	28 (18)	24 (15)	0.089
Metastatic nodes, med (IQR)	1 (0, 3)	1 (0, 3)	0.93
Nodes investigated, med (IQR)	15 (12, 19)	16 (9, 20)	0.64
Estrogen Receptor	44 (90)	249 (80)	0.12
Progesteron Receptor	33 (67)	196 (63)	0.54
HER2	6 (13)	57 (19)	0.32
Left breast operated	31 (63)	145 (46)	0.029
Mastectomy	28 (57)	164 (53)	0.55
Axillary dissection	40 (82)	237 (76)	0.38
Radiotherapy	40 (82)	239 (77)	0.44
Radiotherapy + mastectomy	19 (39)	92 (29)	0.19
Herseptin	6 (12)	58 (19)	0.28
Chemotherapy	46 (94)	299 (96)	0.47
6 × CEF	11 (24)	64 (21)	
3 × D + 3 × CEF	23 (50)	168 (56)	
3 × DX + 3 × CEF	12 (26)	61 (20)	
Other	0 (0)	6 (2)	
Endocrine therapy	44 (90)	246 (79)	0.083
Aromatase inhibitors	13 (30)	84 (34)	
Tamoxifen	31 (70)	162 (66)	

Table II. *Multivariate analyses of factors associated with reversible and irreversible ECG changes*

	ST changes (all)		Irreversible ST-changes	
Variable	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Hypertension	2.40 (1.12 to 5.11)	0.024	4.71 (1.36 to 16.38)	0.015
No radiotherapy (RT)	1 (reference)			
RT right resection	0.87 (0.32 to 2.37)	0.79	1.04 (0.16 to 6.79)	0.097
RT right mastectomy	0.98 (0.33 to 2.88)	0.97	1.79 (0.27 to 11.86)	0.54
RT left recection	1.26 (0.48 to 3.27)	0.64	0.66 (0.08 to 5.24)	0.70
RT left mastectomy	2.65 (1.00 to 7.01)	0.050	3.18 (0.48 to 21.21)	0.23
Endocrine therapy				
No treatment	1 (reference)		1 (reference)	
Tamoxifen	2.88 (1.04 to 8.01)	0.042	4.32 (0.48 to 38.7)	0.19
Aromatase inhibitor	2.26 (0.70 to 7.31)	0.17	2.20 (0.22 to 22.4)	0.50
Triglyceride	1.38 (0.92 to 2.06)	0.24	1.81 (0.92 to 3.59)	0.087
Postmenopausal	0.67 (0.31 to 1.45)	0.31	1.76 (0.42 to 7.43)	0.44

In multivariate analyses, hypertension treated with anti-hypertensive medication (OR=2.40; 95% CI=1.12-5.11; p=0.024), tamoxifen treatment (OR=2.88; 95% CI=1.04-8.01; p=0.040) and post-mastectomy left-sided radiotherapy (OR=2.65; 95% CI=1.00-7.00; p=0.050), were significantly associated with ECG changes (Table II).

Irreversible ECG changes. After a 12-month follow-up, the ECG changes resolved spontaneously in 36 patients (73%) out of 49, and remained unchanged in 13 (27%) patients. In multivariate analyses, hypertension treated with anti-hypertensive medication was the only significant factor associated with irreversible ECG changes (OR=4.71; 95% CI=1.36-16.38; p=0.015) (Table II) (Figure 2).

Discussion

Our study confirmed previous findings of electrocardiographic abnormalities that occur during breast cancer therapy. In coherence with previous investigations (18, 21), most of these changes were reversible. However, hypertension increased the risk of irreversible ECG changes by 4.7-fold, when compared to non-hypertensive cases.

In studies performed during the 1970s, ECG changes were observed in 35% of patients, compared to 13% of patients for whom ECG changes were recorded in our study. The lower prevalence of ECG changes in the present study could be the result of improved radiation techniques, different chemotherapy agents and patient selection (*i.e.* patients aged 68 years or older and patients with severe comorbidities were excluded). The risk for reversible ECG changes in our study was higher in cases with left-side post-mastectomy irradiation, similar to earlier studies in which these changes were valued as functionally insignificant (22). Left-side post-mastectomy irradiation increased the risk of irreversible ECG changes by three-fold, but this was not statistically significant and needs to be evaluated further. Nevertheless, in the present study, hypertension contributed significantly to increased risk of irreversible ECG changes during cancer therapies. This is especially significant because high blood pressure is the most frequent CV comorbidity reported in cancer registries (23). ECG changes during anthracycline-containing CT have been described for a long time, but whether they predict for myocardial dysfunction, is unclear.

Radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease; as reported by Darby *et al*., this increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with pre-existing cardiac risk factors have greater absolute increase in risk from radiotherapy compared to other women (9). In previous studies, myocardial perfusion defects were found after radiotherapy for breast cancer and occurred significantly more often after radiotherapy for the left breast cancer. A study by Nilsson *et al*. revealed an association between radiotherapy and stenosis in hot-spot areas for radiation, thus implying a direct link between radiation and location of coronary stenosis (24). Studies investigating left-side irradiated patients with breast cancer examined by cardiac single-photon emission computed tomography and stress echocardiograms have shown perfusion defects in the anterior part of the left ventricle, conforming to the hot-spot areas reported in the

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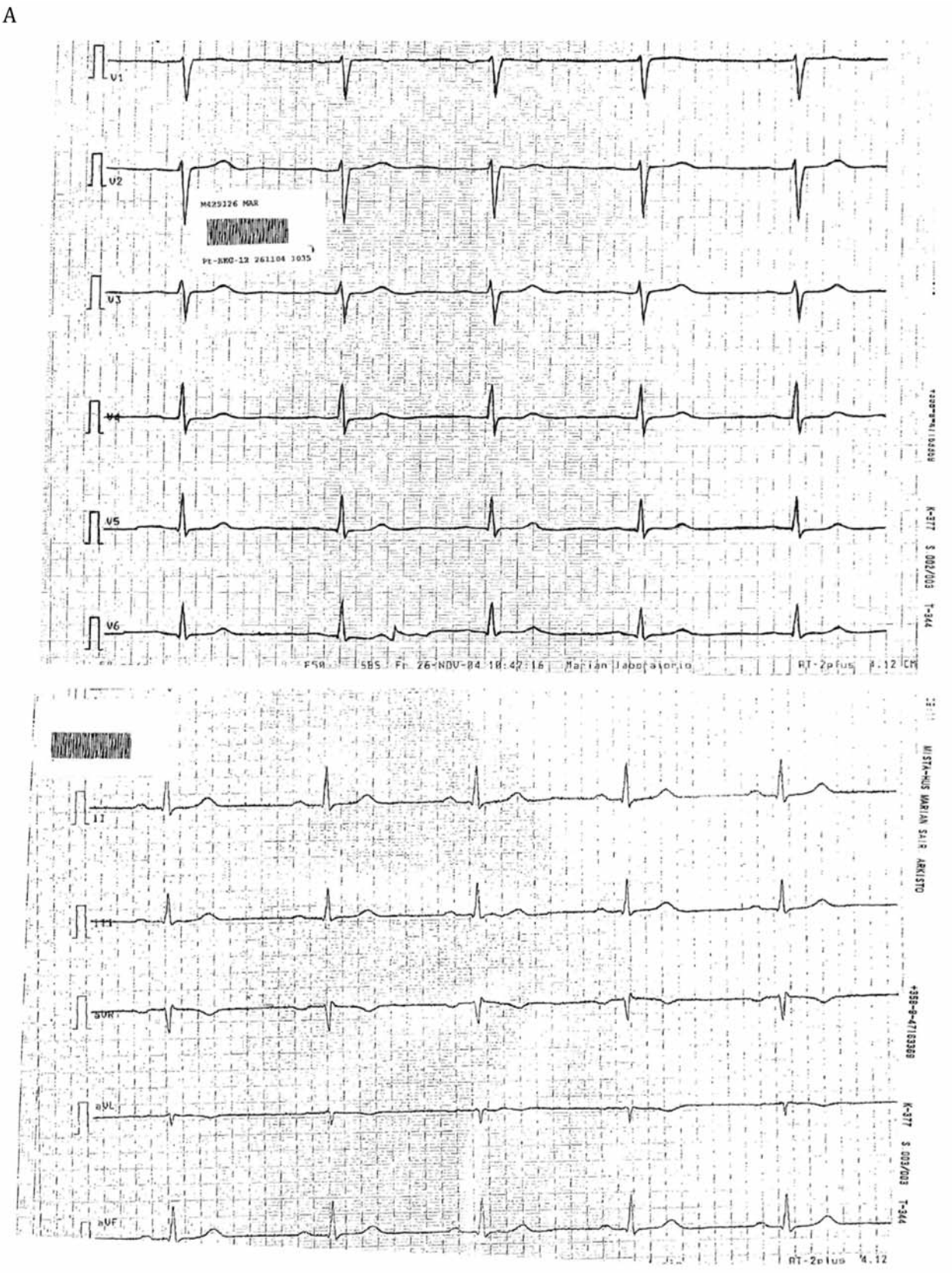

Figure 1. *Continued*

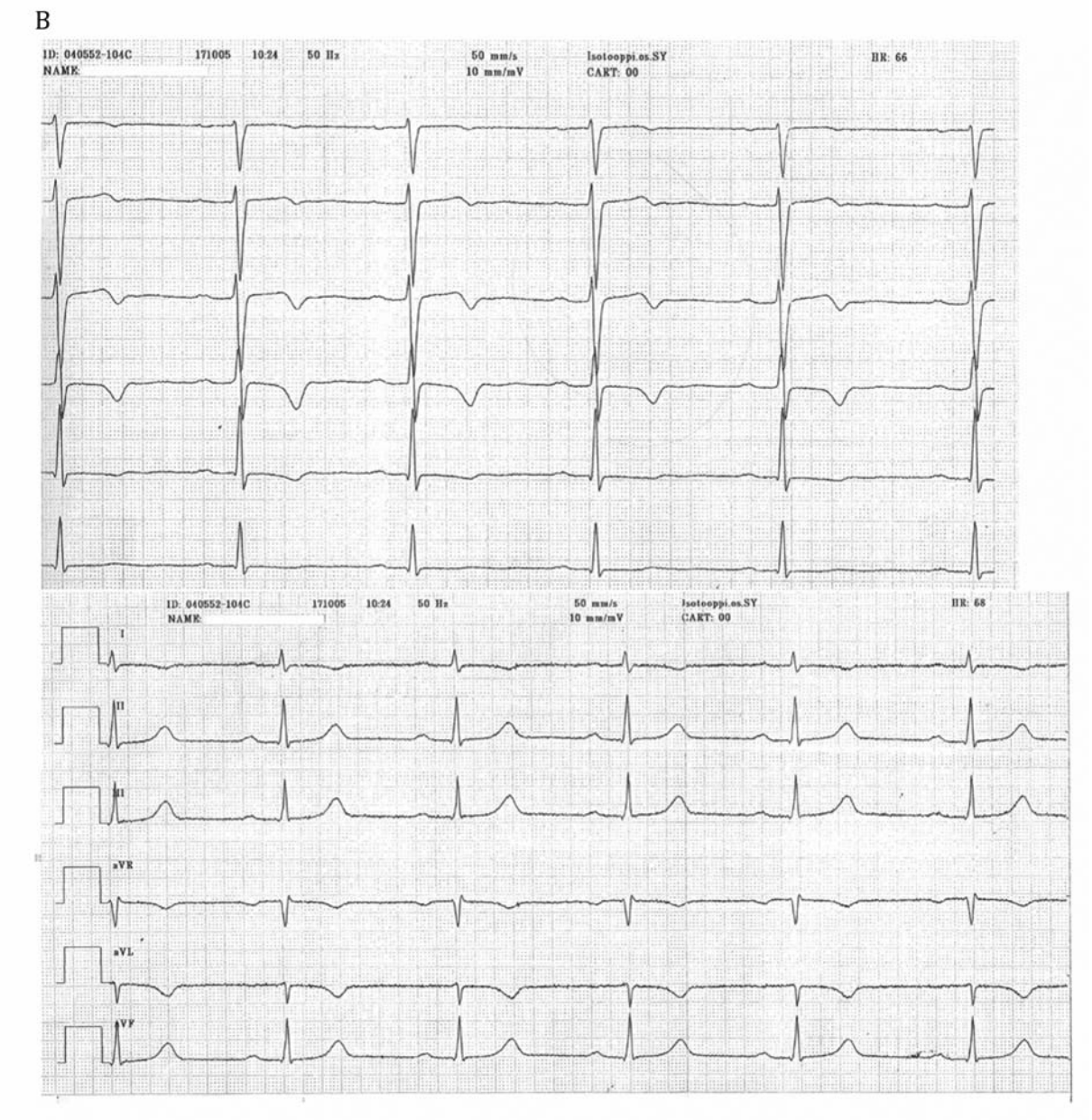

Figure 1. *ECG changes: A) Before and B) after the adjuvant therapy in previously healthy 63-year-old women.*

study by Nilsson *et al*. (25, 26). Vascular damage is considered to be the underlying mechanism of cardiac toxicity in irradiated cancer patients. If coronary endothelial damage is involved in thoracic radiotherapy and if a microvascular damage can occur from anthracycline administration, then the electrocardiogram can be a suitable tool to unmask early abnormalities.

The mechanism behind the irreversible ST segment and T-wave changes in ECG is not yet known. Furthermore, whether these ECG changes are of clinical relevance or implicate further progression of cardiac disease by amplifying cardiotoxicity on a pre-damaged heart warrant further investigation. The importance of our findings rests on the fact that ECG changes do infact represent phenomena of some vascular or myocardial damage, and can be considered as a "caveat" sign in patients who face a high mortality rate as a result of CV disease.

The most significant limitation of the present study is the lack of prospective CV examinations other than ECG, and the lack of troponin levels in the studied patients. Also, our study

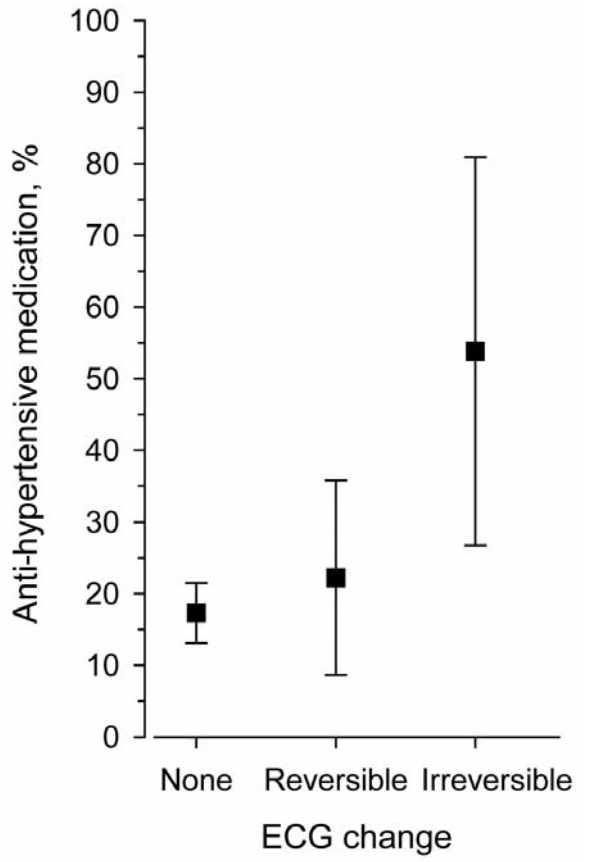

Figure 2. *Prevalence of hypertension in patients with reversible and irreversible ECG changes.*

is limited by the causality of different treatment modalities or their combinations on the ECG changes (*i.e.* one of the therapies or their combination could be responsible for the ECG changes).

In summary, cardiotoxicity continues to be the most significant long-term adverse effect of breast cancer therapy. Our findings, observing a relationship between hypertension and irreversible electrocardiographic changes after adjuvant treatments, may serve as a marker for patients at considerable risk. Identification of patients at-risk constitutes a strategy to reduce the morbidity and mortality posed by cardiotoxicity.

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