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USE OF NATRIURETIC PEPTIDES FOR DETECTING CARDIAC DYSFUNCTION IN LONG-TERM DISEASE-FREE BREAST CANCER SURVIVORS

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ABSTRACT

Background

Plasma natriuretic peptides are increased in patients with cardiac dysfunction. We measured N-terminal (NT-ANP) and B-type (BNP) natriuretic peptides in disease-free breast cancer survivors, during long-term follow-up after epirubicin (360 mg/m² or 450 mg/m² cumulatively) and chest irradiation.

Patients and methods

Plasma samples for natriuretic peptide measurement were repeated after extended follow-up in 54 patients, who had participated in two studies evaluating cardiotoxicity.

Results

From a median follow-up of 2.7 to 6.5 years, median BNP was raised almost three-fold ($P < 0.001$). Symptomatic heart failure was now present in two patients. Compared to the epirubicin 360 mg/m² group, BNP was higher ($P = 0.006$) in the 450 mg/m² group, with a trend ($P = 0.054$) for higher NT-ANP.

Conclusions

These findings suggest that anticancer therapy initiates an autonomically progressive process that may ultimately lead to symptomatic cardiac dysfunction, years after treatment. BNP measurement may be of value to identify patients requiring intensive cardiac follow-up.

INTRODUCTION

The most encountered late adverse effect of the anti-neoplastic anthracyclines is heart failure as a consequence of cumulative dose-dependent, and irreversible, cardiomyopathic alterations. With the improved prognosis and survival of cancer patients over the last years, potential development of late cardiac dysfunction increasingly becomes an issue with respect to the use of anthracyclines in clinical practice. In addition to anthracycline chemotherapy, chest wall irradiation can contribute to the development of cardiac dysfunction. Earlier detection of cardiac injury, enabling earlier intervention, may limit the development of functional loss, thereby limiting symptoms.

B-type natriuretic peptide (BNP) is secreted by the ventricles, in response to increased wall stress or ventricular dilation. N-terminal atrial natriuretic peptide (NT-ANP) is a linear peptide from the pro-hormone of ANP mainly secreted by the atria following atrial wall stretch. Plasma BNP and NT-ANP levels are elevated in patients with heart failure and increase with the New York Heart Association (NYHA) class.¹⁻³ Measurement of BNP in the emergency setting of acute dyspnea, showed that increased plasma BNP can be used to discriminate between left ventricular dysfunction and non-cardiac causes for the dyspnea.¹ BNP and NT-ANP are also elevated in patients with asymptomatic left ventricular dysfunction.^{4,5} Furthermore, increased natriuretic peptide levels have been related to decreased left ventricular ejection fraction (LVEF) values in patients with left ventricular dysfunction or coronary artery disease.^{6,7} As a consequence, elevated natriuretic peptide values are considered to be indicative of left ventricular dysfunction.

Evidence with regard to the value of measuring natriuretic peptide levels during long-term follow-up of cancer survivors is limited and is mainly derived from childhood cancer survivors. NT-pro-ANP plasma levels increased during long-term follow-up after anthracycline-treatment for childhood malignancy, and correlated positively with echographic cardiac functional parameters, such as the left atrial stroke volume, left ventricular end systolic volume and peak ventricular ejection rate.⁸ In high-risk breast cancer patients, we previously observed that BNP and NT-ANP levels were higher one year after adjuvant anthracyclines and chest wall irradiation, compared to before treatment.⁹ In these patients, LVEF values declined during the first year after chemotherapy, without the occurrence of symptomatic heart failure. In addition, in non-Hodgkin's lymphoma patients without symptomatic cardiac dysfunction during anthracycline treatment, increased BNP and NT-ANP levels correlated inversely with echographically determined fractional shortening and E/A ratio.¹⁰ These data indicate that natriuretic peptide levels increase with the development of (sub-clinical) anthracycline-induced cardiac damage.

Based on their anti-tumour efficacy, the use of anthracyclines in the adjuvant setting of breast cancer has increased in recent years. To date, evidence regarding the detection of late cardiotoxicity, with ongoing decline of function, following

adjuvant anthracyclines by measuring plasma natriuretic peptide values is limited. We evaluated whether in relapse-free breast cancer survivors, in whom natriuretic peptides were previously measured following moderate-dose adjuvant anthracycline chemotherapy and chest wall irradiation, cardiac injury was present after a median follow-up duration of more than 6 years, based on repeated measurement of plasma BNP and NT-ANP.

PATIENTS AND METHODS

Patients and treatments

Natriuretic peptides were determined routinely in breast cancer survivors visiting the oncology outpatient clinic of the University Medical Centre Groningen, The Netherlands, between October 2002 and November 2003. Patients had participated previously in two trials evaluating cardiotoxicity after adjuvant breast cancer treatment.^{9,11} Both the cardiac evaluation trials, conducted between 1997 and 2000, were side studies of a large randomised trial comparing anti-tumour efficacy of two adjuvant chemotherapy regimens.¹² In the cross-sectional study, the existence of cardiac dysfunction at a median follow-up of 3.1 (range 2.0-6.6) years since the start of chemotherapy was evaluated.¹¹ The prospective trial studied the development of cardiac dysfunction during the first year following the onset of breast cancer treatment.⁹ In both studies, cardiac evaluations included a history and physical examination, radionuclide ventriculography for LVEF determination, and natriuretic peptide measurement. The study protocols were approved by the medical ethics committee and written informed consent was obtained from all participants.

Chemotherapy regimens consisted of either 5 cycles of standard-dose 5-fluorouracil (500 mg/m²), epirubicin (90 mg/m²) and cyclophosphamide (500 mg/m²) once every 3 weeks (FEC), or 4 cycles FEC, followed by high-dose carboplatin (1600 mg/m²), thiotepa (480 mg/m²) and cyclophosphamide (6000 mg/m²) (CTC). Patients in the high-dose group underwent peripheral blood stem cell reinfusion 7 days after the start of CTC. Locoregional irradiation, with a total dose of 40-50 Gy on the chest wall, was applied after bone marrow recovery. To the area of the primary tumour an extra dose of 16-20 Gy was administered. Tamoxifen was started after recovery from the final course of chemotherapy at a dose of 40 mg per day orally.

Cardiac evaluation

In the present study, a history and physical examination with special attention to signs and symptoms related to heart failure was performed to detect symptomatic heart failure. If present, heart failure severity was classified according to the NYHA scale. LVEF had been determined only as a part of the first cardiac

assessment in the previous studies, using radionuclide ventriculography, and values below 50% were considered abnormal.

Natriuretic peptides

For the determination of plasma BNP and NT-ANP, peripheral blood samples were collected and transferred in 10 mL disposable tubes containing 2-natrium-ethylenediamine tetra-acetic acid. After sampling, tubes were placed immediately on ice. Plasma was separated within 30 min of collection by centrifugation at 4°C, and stored at -80 °C until determination. BNP was measured with an immunoradiometric assay. Normal values range between 1.0-10.0 pmol/L (Shionoria, Osaka, Japan). NT-ANP plasma levels were assessed using a radioimmunoassay. Normal values range between 150-500 pmol/L (Biotop, Oulu, Finland).

Statistics

Values are given in mean \pm SD for normal distributed variables and median (range) for variables with a skewed distribution. Quantitative variables were compared between two groups using a Mann-Whitney-U two-sample test for skewed distributed variables. Paired analysis was performed in patients with a Wilcoxon paired samples test. Correlations between variables were calculated using Pearson's correlation coefficient test. Linear regression analysis was performed to determine the influence of age on the natriuretic peptide levels. All P values are two-sided and $P < 0.05$ is considered statistically significant.

RESULTS

Clinical characteristics

A total of 91 patients had participated in the aforementioned cardiac studies. Of these 91 patients, 76 were still alive at the time of the current evaluation. Progression of breast cancer was the cause of death in 14. One patient died due to the consequences of a second primary malignancy. Another nine patients had received additional chemotherapy for recurrent breast cancer and were excluded. Three patients were lost to follow-up and in 10 patients blood samples could not be obtained due to other reasons. From the remaining 54 disease-free patients, blood samples were collected for the current extended follow-up study.

Of these 54 patients, 26 women had received standard-dose chemotherapy and 28 high-dose CTC. Locoregional irradiation followed chemotherapy in all, except one patient who developed a pericarditis after CTC.¹³ 27 patients underwent left-sided chest wall irradiation. The remaining 27 had received right-sided chest wall irradiation.

Natriuretic peptide measurement

At the time of the first cardiac evaluation, performed in the above mentioned cardiac sub-studies of the nation-wide randomised trial, plasma natriuretic peptide concentrations had been measured in women with a median age of 49 (range 26-56 years) at a median follow-up after the start of chemotherapy of 2.7 (range 0.5-5.1) years. In the current evaluation, plasma BNP and NT-ANP levels were determined after a median of 6.5 (range 4.1-11.0) years since the start of chemotherapy, at a median age of 54 (range 32-61) years. The median time between the first and second natriuretic peptide measurement was 4.1 (range 2.9-6.3) years.

Cardiac evaluation

At the time of the current study, a median of 6.5 years after chemotherapy start, clinical heart failure (NYHA class II) was present in two patients. One of these patients already had symptoms of heart failure at the time of the previous studies. In one patient, diastolic dysfunction was the cause for heart failure, systolic functional impairment was present in the other. After a median of 2.7 years following chemotherapy, subnormal LVEF values were observed in eight of the 54 patients. Seven of the eight patients had received high-dose CTC and left sided chest wall irradiation had been applied in four.^{9,11}

Natriuretic peptides and cardiac dysfunction

Figure 1 represents BNP and NT-ANP levels at both time points. Median BNP levels were higher after a median follow-up of 6.5 years, compared to after a median of 2.7 years ($P < 0.001$) (Table 1 and Figure 1A). No differences were observed regarding NT-ANP levels between the first cardiac evaluation and the second time point (Figure 1B). Figure 2 represents the change in terms of percentage for BNP (A) and NT-ANP (B) plasma levels between the two time points, for individual patients. Linear regression analysis showed that the increase in BNP plasma levels were not significantly influenced by the time between the first and second evaluation.

Table 1. Natriuretic peptide plasma levels

	Median 2.7 years after chemotherapy start	Median 6.5 years after chemotherapy start
BNP (pmol/L)	2.2 (0.5-51.1)	5.8 (0.8-25.5)*
BNP > 10.0 pmol/L	4	14
NT-ANP (pmol/L)	313 (164-909)	296 (121-651)
NT-ANP > 500 pmol/L	5	4

Values are presented as median (range). * $P < 0.001$

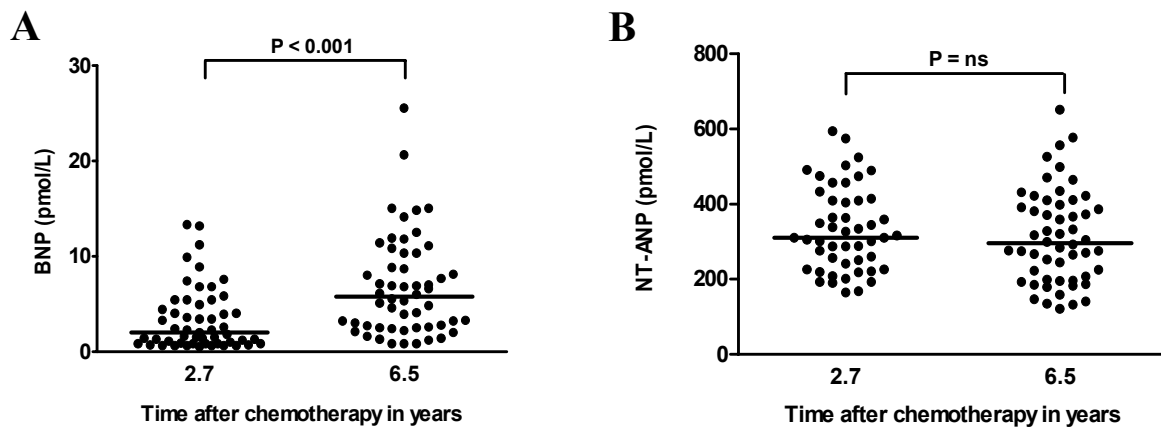


Figure 1. Dot plot of plasma BNP (A) and NT-ANP (B) levels at a follow-up duration of median 2.7 vs. 6.5 years after the start of chemotherapy. Lines represent median values. P-value is based on Wilcoxon paired samples test.

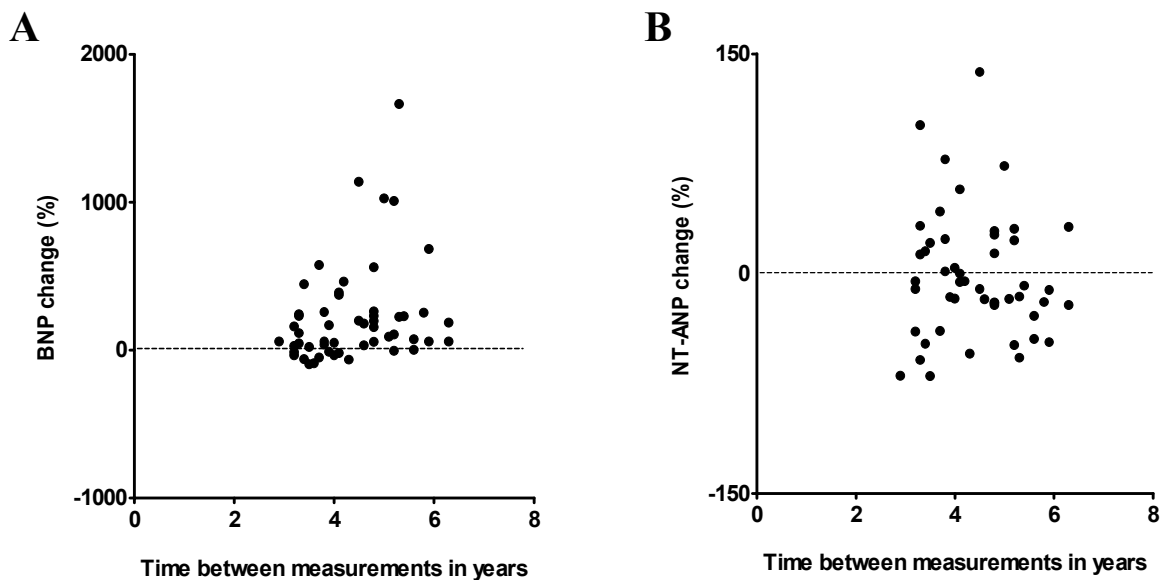


Figure 2. Dot plot of the change in plasma BNP (A) and NT-ANP (B) levels between the first and the second measurement, expressed as the percentage of the first measurement (Y-axis). The X-axis represents the time between the two measurements.

At a median follow-up of 6.5 years after chemotherapy start, BNP levels were above the upper limit of normal (> 10 pmol/L) in 14 patients. In two of these 14 women plasma BNP was already above the upper limit of normal at the time of the first evaluation. NT-ANP levels above the normal range (> 500 pmol/L) were observed in four patients in the current study. One of these four patients had an elevated plasma NT-ANP concentration at the time of the first evaluation.

At the second time point, plasma BNP was elevated in the patient with heart failure based on systolic left ventricular dysfunction (11.4 pmol/L). The patient with diastolic dysfunction-based heart failure had a normal plasma BNP concentration. NT-ANP plasma levels were within the normal range for both patients with heart failure.

Natriuretic peptide plasma concentrations at the time of the current study, were not associated with LVEF values determined as a part of the first cardiac evaluation, at a median follow-up of 2.7 years. Natriuretic peptide plasma levels, at a median of 6.5 years since the start of treatment, in the eight patients with subnormal LVEF values at the first time point were not different compared to the patients with a LVEF > 50%.

Natriuretic peptides and anticancer treatment

At a median follow up of 6.5 years, median plasma BNP levels were higher in breast cancer survivors who had received standard-dose chemotherapy (total epirubicin dose 450 mg/m²), compared to the high-dose CTC-treated patients (total epirubicin dose 360 mg/m²), 2.9 (range 0.8-25.5) vs. 7.4 (range 0.8-20.6) pmol/L, respectively (P = 0.006) (Figure 3A). A trend was observed for higher median plasma NT-ANP levels in patients after standard-dose chemotherapy (349 (range 132-577) pmol/L), compared to after high-dose CTC, (259 (range 121-651) pmol/L) (P = 0.054) (Figure 3B). These differences were not present at the time of the first cardiac evaluation, at a median follow-up of 2.7 years. Left sided chest wall irradiation was not associated with higher plasma natriuretic peptide concentrations at both time points.

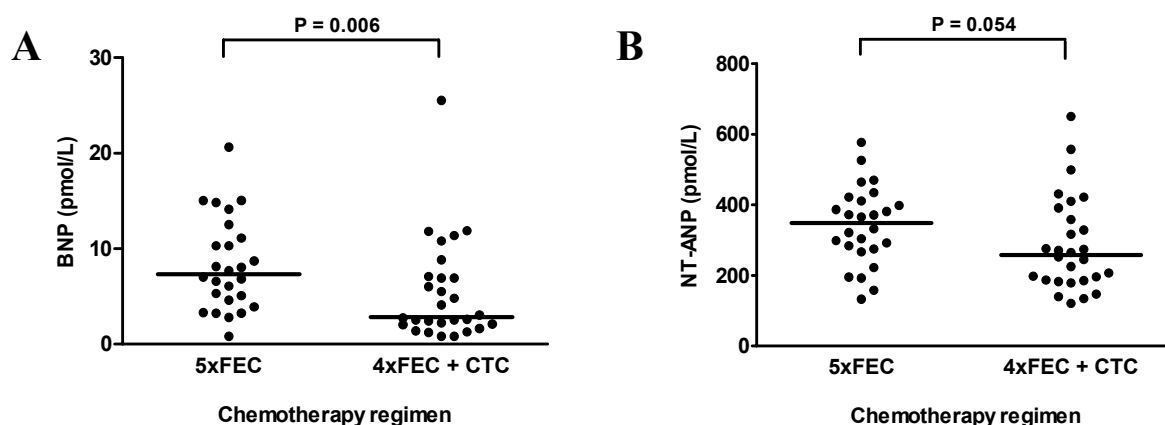


Figure 3. Dot plot of plasma BNP (A) and NT-ANP (B) levels in patients treated with a total dose of 450 mg/m², compared to patients who had received a total dose of 360 mg/m² epirubicin, at a median of 6.5 years after chemotherapy start. Lines represent median values. P-value is based on Mann-Whitney-U two sample test.

DISCUSSION

In the current study, we evaluated plasma BNP and NT-ANP levels in disease-free patients after adjuvant anthracycline-containing chemotherapy and chest wall irradiation for high-risk breast cancer, at a median follow-up of more than 6 years. Plasma BNP levels were raised from 2.7 to 6.5 years of follow-up. Median natriuretic peptide plasma levels remained within the normal range. Among the two

patients with symptomatic heart failure, BNP levels were above the upper limit of normal in the one patient with systolic left ventricular dysfunction as the underlying cause for heart failure. In addition, patients who had been treated with standard-dose chemotherapy (epirubicin 450 mg/m²) had higher plasma BNP, than patients who had received high-dose CTC (epirubicin 360 mg/m²). To our knowledge, this is the first evidence of a rise in plasma BNP levels during follow-up of more than 6 years after anti-neoplastic treatment in an adult population of adjuvant anthracycline-treated breast cancer survivors.

With a median age of 54 years at the time of the second evaluation, our study population of breast cancer survivors is relatively young. Keeping in mind the improved prognosis of patients with breast cancer over the last decades, the issue of potential treatment-related late cardiotoxicity becomes increasingly important. An important question to be raised is whether the life expectancy of these patients is attenuated by adverse cardiac effects of prior anthracyclines and chest wall irradiation. Earlier detection of ongoing cardiac injury may enable oncologists to intervene, for instance by starting medical treatment using an angiotensin-converting enzyme inhibitor, before functional loss occurs. We found elevated BNP levels in 26% of the patients at a median of 6.5 years after chemotherapy, which is viewed as suggestive for ongoing cardiac injury that can ultimately lead to the development of heart failure. Natriuretic factors can become elevated before the development of cardiac functional loss.^{14,15} We previously reported that plasma NT-ANP and BNP levels increased during the first year after a similar adjuvant treatment regimen for high-risk breast cancer. This rise was already present one month following chemotherapy.⁹ Patients with an asymptomatic elevated plasma BNP level after anticancer treatment, may be at increased risk for developing cardiac dysfunction.

Anthracycline-induced cardiotoxicity is cumulative dose-dependent and can occur up to years after treatment.¹⁶ Recently, symptomatic heart failure and asymptomatic decreased fractional shortening or increased end-systolic wall pressure, determined echocardiographically, were described to occur in 39% of 229 survivors of childhood solid malignancies, after a mean follow-up duration of 18 years following anthracyclines and irradiation to the heart region.¹⁷ In breast cancer survivors, left ventricular dysfunction was reported in 20 of 85 relapse-free breast cancer survivors treated with 6 cycles of FEC (epirubicin 100 mg/m²), compared to one of 65 patients after 6 cycles FEC (epirubicin 50 mg/m²), more than 8 years after treatment.¹⁸ With regard to natriuretic peptide levels after anthracycline treatment, Poutanen et al. found higher serum NT-ANP levels, 5 years after treatment, in 39 childhood malignancy survivors, compared to healthy age-matched controls.⁸ In a study among high-risk breast cancer patients, comparing two anthracycline-containing chemotherapy regimens, serial measurements of serum NT-pro-ANP were performed during a follow-up period of up to 3 years after treatment. Patients who received 9 cycles FEC (epirubicin 744 mg/m²), had 19% higher NT-pro-ANP plasma levels than patients treated with 3 cycles FEC and

high-dose CTC (epirubicin 181 mg/m²).¹⁹ Furthermore, plasma NT-pro-ANP was higher in patients after left sided chest wall irradiation than after right sided irradiation.¹⁹ In the current study, patients treated with standard-dose chemotherapy (450 mg/m² epirubicin, total dose) had higher BNP values at a median of 6.5 years after start of chemotherapy, than patients who received 4 cycles FEC plus high-dose CTC (360 mg/m² epirubicin, total dose). This may be explained by the higher cumulative epirubicin dose in the standard-dose chemotherapy (450 mg/m²), compared to the high-dose CTC group (360 mg/m²). No clear association was detected between left sided chest wall irradiation and higher plasma natriuretic peptide concentrations.

The moderate cumulative amounts of anthracyclines administered in the current study (epirubicin 360-450 mg/m²) may account for the low incidence of cardiotoxicity encountered. On the other hand, in breast cancer patients who received a similar treatment, we previously described that an asymptomatic drop in LVEF occurred during the first year of follow-up after treatment.⁹ In addition, a large study among 1,576 doxorubicin/cyclophosphamide-treated breast cancer patients showed that an asymptomatic decrease in LVEF developed in 23.4%, shortly after a relatively low cumulative dose of 240 mg/m² doxorubicin.²⁰

BNP is considered to be more sensitive and specific for the detection of cardiac dysfunction than (NT-)ANP in chemotherapy-unrelated heart failure patients.^{2,21} ANP and BNP measurement in a small study among 13 daunorubicin-treated acute leukaemia patients, also suggested superiority of BNP for this purpose.²² This may be an explanation for the fact that we observed an increase in plasma BNP, but not NT-ANP levels, between 2.7 and 6.5 years median follow-up after anticancer treatment.

Plasma BNP measurement appears to be of value as an additional screening tool for the detection of cardiac toxicity in the follow-up after anticancer treatment. To date, detection and monitoring of cardiac dysfunction after anti-neoplastic therapy mostly involves multigated radionuclide angiography or cardiac ultrasound. However, these methods are less attractive for the routine cardiac evaluation of all patients after cardiotoxic anticancer treatment. The relatively simple and cheap BNP assay may therefore be of particular interest for screening patients who may be prone to treatment-related cardiac dysfunction. Especially for patients with increased BNP levels after anticancer treatment, cardiac follow-up with regular LVEF measurement and/or echographic functional assessment may be indicated. For this purpose, reliable cut-off values are of great importance. The suggested cut-off value used in the emergency setting to discriminate between a cardiac and pulmonary origin of acute dyspnea is 28.9 pmol/L (100 pg/mL).¹ However, for identifying patients at risk for cardiac dysfunction after anticancer treatment, the cut-off value should probably be much lower. In this study, we used a low cut-off value of 10.0 pmol/L.

For the interpretation of our findings, some considerations must be made. First, great intra- and interindividual biological variations have been reported for the

natriuretic peptides.²³ Natriuretic peptide values of individual patients must be interpreted carefully and whenever possible, the time-course of plasma natriuretic peptide levels should be evaluated.²³

Second, in the general population, natriuretic factors tend to increase with advancing age,²⁴ but in chronic heart failure patients, this relation appears to be less pronounced.²⁵ Here we present the data from relatively young breast cancer survivors, which is not comparable to a heart failure population or to healthy individuals. However, the time between both measurements (median 4 years) did not influence natriuretic peptide plasma levels.

Third, cardiac dysfunction was considered to be present with symptoms of heart failure. At the time of evaluation, no objective measures of cardiac function, such as LVEF or other functional parameters, were available. This may lead to an underestimation of the presence of asymptomatic cardiac dysfunction in our study population at the time of evaluation. A well designed, long-term prospective evaluation of plasma natriuretic peptide levels together with assessment of clinical symptoms of heart failure and functional parameters, such as LVEF measurement, is required to determine the clinical implications of the rise in plasma BNP, as observed in the current study.

In summary, in breast cancer survivors who had received anthracyclines and chest wall irradiation, we observed a significant rise in plasma BNP levels from median 2.7 to 6.5 years after the start treatment. These findings suggest that after the initial insult to the myocardium of anti-neoplastic therapy, an autonomically progressive process is initiated, which may lead to the development of symptomatic cardiac dysfunction up to years after anti-neoplastic therapy. Considering the fact that anthracyclines and chest wall irradiation are used widely in the adjuvant treatment of breast cancer, thousands of women will be at risk for developing cardiac dysfunction in late follow-up. Thus, determining the optimal time for intervention, aiming to prevent or limit the development of heart failure in these patients, is of great interest. Increased plasma BNP may become of value for identifying patients who require more intensive cardiac follow-up. Measuring plasma natriuretic peptide levels for this purpose is simple and appears promising and deserves further study.

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