Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients

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Background: With increasing doses the highly tumoricidal anthracycline drugs cause heart damage. Based on empirical drug limitations about 10–15% of patients will develop congestive heart failure (CHF) with a mortality of ~50% within 2 years on digitalo–diuretic therapy alone. To avoid CHF there is a consensus recommendation that cardiac function should be monitored in close connection with anthracycline administration. As no prospective studies in a larger series have been performed, these recommendations are based on retrospective data on small numbers of patients.

Patients and methods: In a prospective, blinded observational study 120 patients with advanced breast cancer were followed before, during, and a median 3 years after treatment with epirubicin. They had 604 serial radionuclide measurements of left ventricular ejection fraction (LVEF) that were stored without calculations except in patients who developed a well-defined CHF.

Results: Anthracycline cardiotoxicity was closely correlated with the cumulative dose, with a great variability in individual susceptibility and a dramatic increase with advancing age. With a delayed onset of 3 months or more, epirubicin induced a threatening, slowly progressive deterioration of cardiac function continuing years after treatment. An actuarial estimation of 59% of the patients experienced a 25% relative reduction in LVEF 3 years after 850–1000 mg/m² of epirubicin and 20% had deteriorated into a CHF. The patients did not spontaneously regain cardiac function whereas continued therapy with a circadian angiotensin-converting enzyme inhibitor for more than 3 months caused a remarkably potent and long-lasting recovery.

Conclusions: Due to the displaced cardiotoxic manifestation, functional monitoring in close connection with anthracycline administration appears to be a poorly effective method while later monitoring is essential. Current monitoring recommendations should therefore be revised.

Key words: angiotensin-converting enzyme inhibition, anthracyclines, cardiotoxicity, free radical toxicity, radionuclide ejection fraction, recurrent breast cancer

Introduction

The anthracycline semiquinone doxorubicin and the stereo-isomer epirubicin are among the most effective and widely used anti-cancer drugs with particularly widespread use in the therapy of breast cancer, sarcomas and leukemia. Their use, however, is limited by the risk of a delayed, life-threatening, dilatory congestive heart failure (CHF), an unexpected side-effect first reported by Lefrak et al. in 1973 [1]. Recovery from anthracycline-induced CHF on digitalo–diuretic therapy alone seldom occurs [1–5]. Mortality of patients deteriorating into New York Heart Association (NYHA) class III–IV exceeds 50% within 2 years [1, 2, 5, 6], resembling the general prognosis of CHF and idiopathic cardiomyopathy [7–10]. A rapidly growing number of people, including an alarming fraction of the 150000 or more adults in the USA who have survived childhood cancer, will have substantial morbidity and mortality because of anthracycline-related cardiac disease, calling for effective protection and therapy [3, 11]. This grave prognosis has led to recommendations of extensive and expensive functional monitoring programs during anthracycline treatment to identify high-risk patients [4, 12, 13]. In the guidelines from the Cardiology Committee of the Children’s Cancer Study Group [12], the American College of Cardiology, the American Heart Association and the American Society of Nuclear Cardiology [13], radionuclide angiographic measurement of ventricular function is recommended during anthracycline therapy timed 10–14 days after the last dose.
They state that it is safe to continue therapy if the left ventricular ejection fraction (LVEF) remains above the lower limit of normal, and that if the LVEF becomes subnormal and anthracycline therapy is discontinued LVEF usually stabilizes at that point. These statements, however, are mostly based on retrospective data limited by a relatively small number of patients [3, 14], factors that may confound the concept of monitoring efficacy and the accuracy of clinical predictions. Review of the data on which these recommendations were based has raised doubt about the reliability and sensitivity of monitoring of the ejection fraction for identification of early cardiotoxicity [14, 15]. There has therefore been a strong call for prospective, blinded data in a larger series [3, 14]. Based on our previous experience of anthracycline cardiotoxicity lacking predictability for development of CHF by radionuclide monitoring [5, 6], we performed a prospective, blinded, observational study on the time windows for developing anthracycline-induced cardiotoxicity. The majority of patients were allocated to treatment with a high cumulative dose (HCD) of 1000 mg/m² epirubicin and a smaller control group to a low cumulative dose (LCD) of 500 mg/m². The final end points were the clinical development of CHF and the degrees of subclinical cardiotoxicity evaluated by close functional monitoring of radionuclide-estimated LVEF before and during more than 3 years of follow-up.

Patients and methods

Patients with their first sign of recurrent metastatic breast cancer were referred for first-line anthracycline-based therapy. Inclusion criteria were: prior chemotherapy limited to one regimen without anthracyclines; age 18–65 years; WHO performance status <3 and a life expectancy greater than 3 months, adequate hematological, hepatic and renal function; and no history of severe heart failure or myocardial infarction. All patients referred to our department between June 1991 and November 1993 satisfying the above criteria were asked to participate. At initiation of the monitoring program all patients had monotherapy with epirubicin, aiming at an HCD not exceeding 1000 mg/m². After inclusion of the first 40 patients, 54 patients entered a randomized investigation of either HCD monotherapy with epirubicin every third week, or epirubicin every 6 weeks alternating with four courses of cyclophosphamide (3 g/m² per course) corresponding to an LCD of epirubicin 500 mg/m². In this period, 26 patients refused randomization and had monotherapy leaving 92 HCD patients (Table 1). Epirubicin was administered as a 5-min infusion of 130 mg/m². Radionuclide cardiography of the LVEF was performed after intravenous injection of 1000 MBq human serum albumin 99mTc. Beside pre-treatment evaluation, the history and clinical evaluation were repeated before each dose of epirubicin and ECG, chest X-ray, measurement of LVEF before and after 500, 780, 900 and 1000 mg/m² and 1, 3, 6 and a median 33 months later, or when it was considered necessary from the clinical status. Patients in the LCD regimen had their second measurement of LVEF 1.5 months after the last epirubicin injection.

During the investigation period, hard copies of LVEF data were stored without calculations of LVEF. Six months after the last included patient had terminated epirubicin therapy, all serial hard-copied LVEF data from each patient were analyzed by one of three skilled technicians. The mean of three measurements not deviating by more than 5 units from each other was used from each examination. If a patient developed clinical signs of CHF, however, the treating doctor could demand determination of LVEF in order to confirm an echocardiographic diagnosis of left ventricular dysfunction. In the case of progressive deterioration of CHF on digital–dihydrate therapy, angiotensin-converting enzyme (ACE) inhibition with a long-acting circadian ACE inhibitor was initiated. The local Ethics Committee approved the study, and informed, written consent was required.

End points

The primary end point was clinical CHF comprising a triplet of diagnostic criteria: exercise intolerance according to the NYHA, pulmonary congestion on chest radiograph or edema, and left ventricular dysfunction on echocardiography. Secondary end points were the degrees of subclinical cardiotoxicity given by a relative percent decline from pre-treatment LVEF values.

Statistical analysis

Median values of LVEF at various cumulative dose levels and times after chemotherapy were compared by a Wilcoxon matched-pairs signed ranks test with a display of average performance at various points of the therapeutic process. Studies of the present kind on cancer patients are, however, hampered by missing measurements either because some patients skip one or more of the planned examinations or because of premature death from cancer. Survival statistics with Kaplan–Meier estimates provide a tool for a graphical display and calculations of differences in risk-adjusted cumulative figures for cardiotoxicity. A cardiotoxic decline was registered if LVEF exceeded a predefined relative percent reduction from pre-treatment exceeding the inherent variation in the radionuclide cardiographic technique. This intraobserver variability was evaluated by a blind re-analysis of 357 of the 604 measurements of LVEF, including all serial hard copies from the patients who eventually developed clinical CHF by use of the Bland–Altman method [16]. The mean difference was zero, and values were neatly fitted under a normal distribution curve. The standard deviations were 4 absolute LVEF units and 7.5 relative percent changes. The coefficients of repeatability were 8 absolute LVEF units [95% confidence interval (CI) 7.2 units to 8.6 units] and 15 relative percent changes [95% CI 14.2% to 16.5%, n = 295]. Subsequently only changes exceeding 15 relative percent were considered for further analysis. Curves of dose and/or time-to-cardiotoxic decline were generated with the use of Kaplan–Meier estimates censoring LVEF data at the last measurement. Probabilities of cardiotoxic decline were expressed as percentages. Comparison of cumulative decline distributions between subgroups was made with the log-rank test. The incidence of CHF and the probability of recovery with and without ACE inhibition were evaluated with the use of Kaplan–Meier estimates. SPSS statistical software for Windows (version 9) was used.

Results

Table 1 gives the clinical characteristics of the patients. Thirteen included patients were not assessable for cardiotoxicity, 11 because of early death, and two because they refused further examinations (one HCD and one LCD). No patients in the LCD group developed CHF compared with 10 patients in the HCD group with NYHA class III–IV, cardiomegaly, pleural effusion and/or lung stasis on chest X-ray, and weight gain. They were slightly older (P = 0.05) with lower
pre-treatment LVEF values ($P = 0.009$) than patients not developing CHF. The HCD group of patients had 506 measurements of LVEF and the LCD group 98 measurements, yielding a total of 604 measurements. The overall median survival after starting chemotherapy before the patients died of breast cancer was 22 months (range 0.3–84 months) without statistical differences in the HCD and LCD groups, and in patients with or without CHF.

Median months and 5-year survival (actuarial percent) were 21 months and 17% following therapy with epirubicin outside protocol, 21 months and 11% following therapy with epirubicin in protocol, and 29 months and 16% for patients following combined therapy, respectively.

In the whole group of assessable patients only 16% had survived their breast cancer 5 years after recurrence.

Figure 1A illustrates the laboratory cardiotoxicity for patients without CHF. Cardiac function during the 5–6 months of anthracycline therapy is illustrated along the first part of the $x$-axis while cardiac function during follow-up is along the second part. The number of patients with a measurement of LVEF at a given time is indicated above the $x$-axis. In the anthracycline period, patients treated with HCD had a gradual decline of a median 7 absolute LVEF units or 11 relative percent (from 61% to 54%, $P < 0.001$), with a further decrease to 51% in LVEF in the median 33 months during follow-up ($P = 0.0219$). Compared with pre-treatment LVEF values, the

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<th>Table 1. Characteristics of patients (values followed by parentheses are medians with ranges)</th>
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<td><strong>High cumulative dose (HCD)</strong> (26 patients registered; 66 treated outside protocol; 85 assessable)</td>
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<td>Clinical cardiotoxicity ($n$)</td>
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$^aP = 0.049$.

$^bP = 0.009$.

CHF, congestive heart failure; CMF, nine courses of cyclophosphamide (600 mg/m$^2$), methotrexate (40 mg/m$^2$) and 5-fluorouracil (600 mg/m$^2$); LVEF, left ventricular ejection fraction.
Figure 1. Median and range left ventricular ejection fraction (LVEF) values before, during and after epirubicin therapy. (A) Patients with high cumulative dose (HCD) and low cumulative dose (LCD) therapy not developing congestive heart failure (CHF); no, number of patients with measurement of LVEF. Median and range values are displayed. (B) Ten patients developing CHF after HCD epirubicin. Median and range values are displayed. Dashed lines indicate lower normal values. ACE, angiotensin-converting enzyme.
Figure 1B illustrates the impact of epirubicin on cardiac function in the 10 patients who deteriorated into a clinically severe, dilated CHF. No patient treated with cumulative doses below 850 mg/m² developed CHF in the observation period. The pre-treatment LVEF values of a median 53% were lower in this group than the 61% in the patients not developing CHF ($P = 0.009$). Median LVEF values during chemotherapy paralleled values in the group without CHF, but at a lower level. When presenting with symptomatic signs of CHF, the patients had an absolute LVEF value of a median 25% (18–35%).

Figure 2A shows the actuarial risk of developing CHF in the HCD group of patients censoring data at the last follow-up after terminating epirubicin therapy. Patients who died without signs of CHF were registered as being at risk. Median onset of CHF was delayed 3 months or more after terminating epirubicin therapy (1.5–60 months). After 1 year the risk was 11%, increasing after 2 and 5 years to 14% and 20% (95% CI 5% to 37%), respectively. The patients with a delay of 2 and 5 years before onset were also the youngest (50 and 44 years) to develop CHF. The diagnosis was confirmed by echocardiography. None of the 10 patients who developed CHF had pericardial effusion. They all had a severe reduction of wall motion in the anteroseptal and lateral regions, while the inferior wall was less affected.

As seen in Figure 1B, cardiac function continued to deteriorate on digitalo–diuretic therapy for the following median 3 months. Long-acting ACE inhibitor therapy was then started. Despite a low blood pressure of a median 100/70 mmHg, ACE inhibitor doses were progressively doubled twice a week from an initial 1.25–2.5 mg/day to 15 mg/day enalapril or 10 mg/day ramipril. The therapy was well tolerated. No patients had first-dose hypotension and blood pressure stabilized at about 100/70 mmHg. As seen in Figure 1B, almost all LVEF values returned to normal after a median 3 months of ACE inhibitor therapy, and remained stable in the follow-up period of a median 33 months (15–60 months). Patients returned to NYHA class I ($n = 7$) to II ($n = 3$). On chest X-rays the lung fields and the cardiac silhouette normalized, except in one male case with persistent pronounced dilatation. Light microscopy of the heart in the patient who died of CHF showed a considerable fibrous thickening of the endocardium due to collagenous tissue, and severe interstitial fibrosis with a remarkable absence of inflammatory cells. The vessels all appeared normal without inflammation.

Figure 2B illustrates the actuarial probability of recovery with and without ACE inhibition. Included for this estimation were 33 patients (30 HCD and three LCD) who had a relative fall from pre-treatment LVEF values >20% after ending epirubicin therapy, who were without symptoms, and had a subsequent measurement of LVEF without ACE inhibition. A further 18 patients (16 HCD and two LCD) had a 20% reduction in cardiac function without a subsequent measurement, indicated by the black box at zero. An event of incomplete recovery was then arbitrarily registered as a relative increase of at least 15% from the 20% reduced value. Values at the last LVEF measurement were censored. Only one of the 33 patients without ACE inhibition had a late recovery 18 months after continued treatment with a calcium antagonist contrasting with seven of the eight patients with CHF evaluable after ACE inhibition ($P < 0.001$). In these patients, improvement occurred after a lag of a median 3 months (6 weeks to 8 months). The patient with a delay of 2 years before development of CHF needed 8 months of ACE inhibition to regain cardiac function, underlining the importance of prolonged therapy. The youngest patient (44 years at therapy) developed CHF after a delay of 5 years and regained cardiac function after 2 months of ACE inhibition, after which she obtained a better functional performance than in the preceding 3 years. Three patients discontinued ACE inhibitor therapy, after 21, 28 and 28 months, with a marked decline of 10–13 LVEF units after 4–5 months (Figure 1B). Only one patient with CHF survived from breast cancer for more than 5 years. Despite continued ACE inhibition with stable LVEF values she had a decline in LVEF from 50 to 30% after 5 years. The study was performed in the pre-taxane era. Extensive second-line therapy with HCDs of 40–60 g cyclophosphamide was used for treatment of recurrent disease in three patients treated with ACE inhibition for CHF without promoting cardiototoxicity.

In Figure 3, the time of first appearance of a decline in LVEF exceeding 15, 20, 25, 30 and 35% from baseline in the HCD group is plotted by means of Kaplan–Meier estimates. For the LCD group only the 25% decline curve is plotted, illustrating no events of this severity at this low dose level in the observation period contrasting an actuarial risk of 59% (28 of 85) in the HCD group ($P < 0.001$). As the LCD group of patients was otherwise comparable to the HCD group (Table 1), the cardiotoxicity could be ascribed to epirubicin and not the breast cancer disease state of the patient. The top curves show that a reduction of 15% from baseline occurred in 50% (40 of 85) of the patients during and 30% (19 of 85) following termination of chemotherapy, yielding an actuarial risk of 80% (59 of 85). Bars indicate the remaining 20% (26 of 85) of the patients who are still at risk, having sustained no changes in LVEF greater than or equal to 15%. The cumulative iso-cardiotoxic decline curves constructed at various levels only take one measurement from each patient into account, either the first time a given reduction was exceeded or the last measurement of LVEF in the patient at risk for such a reduction. The actuarial risk of a 20% iso-cardiotoxic decline in the HCD group was 78%, almost double that of 44% in the LCD group (curve not shown, $P = 0.0022$), indicating linearity between the degree of cardiotoxicity and the cumulative dose. The difference between the high- and low-dose groups was seen at all levels but was most manifest with increasing cardiotoxic affection. Both groups had a remarkable gap between the cumulative
Figure 2. Risk of epirubicin-induced congestive heart failure (CHF) and recovery after angiotensin-converting enzyme (ACE) inhibition. (A) Actuarial risk of developing CHF after 1000 mg/m² epirubicin (850–1000 mg/m²). Bars indicate patients at risk at latest follow-up or death without CHF. (B) Probability of recovery with and without ACE inhibition. The probability of recovering 15% in left ventricular ejection fraction (LVEF), after a relative decline from pre-treatment values of at least 20%. The filled square indicates 18 patients with a relative fall of 20% or more in LVEF without a subsequent measurement. Bars indicate patients with a relative fall of 20% in LVEF with a subsequent measurement ‘at risk’ for recovery (n = 34). The open circle indicates the one male patient who died of progressive CHF 10 months after 850 mg/m² epirubicin despite ACE inhibition.
iso-decline curves for a 20% and 25% reduction in cardiac function. The most susceptible HCD patients showed a 20% reduction in cardiac function 2–3 months after starting epirubicin therapy at a cumulative dose of 400 mg/m². The double time and dose was necessary for the first HCD patients to have a 25% decline in cardiac function. Thirty-five percent of the HCD patients (27 of 85) had a 20% reduction in cardiac function during chemotherapy, while this was the case for only 15% of patients with a 25% reduction (11 of 85). An increase in the cumulative iso-cardiotoxic decline level by 5% each time halved the number of declines occurring during chemotherapy. The more severe the functional cardiotoxic decline, the longer the interval before its expression. Even years after ending epirubicin administration, a few patients had a retarded deterioration of cardiac function exceeding a 20% reduction. Almost all events (11 of 12) of the most severe reduction in cardiac function (35% reduction) took place in the post-anthracycline period. Figure 3 also illustrates the wide variability among the individual patients in their susceptibility to the cardiotoxic effects of anthracyclines. Forty-one percent of the patients did not experience a 25% relative reduction from baseline, and 20% did not even experience a 15% reduction. This difference in susceptibility is also evident from the wide range around the median before, during and after epirubicin therapy in both the HCD and LCD groups, and in patients with or without CHF as illustrated in Figure 1A and B.

Figure 4 illustrates the influence of aging on cardiotoxic outcome by displaying only the 25% iso-cardiotoxic decline...
curve (dashed line). The HCD group of patients was subdivided by their median age of 50 years at therapy (solid lines). Patients above 50 years had an actuarial 68% risk of developing such a severe reduction in cardiac function compared with 36% for patients under 50 years of age ($P < 0.001$), demonstrating a dramatic increase in cardiotoxic susceptibility with advancing age. For the patients above 50 years, only 22% of the cardiotoxic events took place during chemotherapy while the majority occurred in the post-anthracycline period, with a median onset after 3–4 months. In both age groups some late declines occurred after 3–4 years.

Figure 5 displays the 30% and 35% cardiotoxic decline levels among the 10 patients eventually developing CHF (dashed line) and the 75 HCD group of patients not developing clinical symptoms of cardiotoxicity (solid lines). The 10 patients who eventually developed CHF had a total of 92 measurements of LVEF, with 32 obtained during chemotherapy and 60 in the follow-up period. Both groups had a peak onset of cardiotoxic decline 3–4 months after terminating epirubicin therapy. As proposed in the guidelines mentioned in the Introduction, a predefined degree of reduction in cardiac function is often used for discontinuing further anthracycline therapy. Eight of the 10 patients who eventually developed CHF underwent a measurement of LVEF just before 1000 mg/m² of epirubicin, but only three of these had a decline of 30%. In the subclinical group, only three of the 11 patients who eventually had a 30% decline had a peak onset of cardiotoxic decline 3–4 months after terminating epirubicin therapy. As proposed in the guidelines mentioned in the Introduction, a predefined degree of reduction in cardiac function is often used for discontinuing further anthracycline therapy. Eight of the 10 patients who eventually developed CHF underwent a measurement of LVEF just before 1000 mg/m² of epirubicin, but only three of these had a decline of 30%. In the subclinical group, only three of the 11 patients who eventually had a 30% decline had a peak onset of cardiotoxic decline 3–4 months after terminating epirubicin therapy.

**Figure 4.** Age and cumulative dose-dependent epirubicin cardiotoxicity. The actuarial cumulative 25% iso-cardiotoxic decline curves are indicated for all patients (dashed lines) and above and below a median age of 50 years (solid lines). HCD, high cumulative dose; LCD, low cumulative dose.
decline in cardiac function developed this during chemotherapy, while the majority (8 of 11) deteriorated in the post-anthracycline period. The figures illustrate the low predictive value of functional monitoring for developing CHF in close connection with anthracycline administration.

Discussion

Epirubicin cardiotoxicity was closely coupled to the cumulative dose, with a dramatic increase with advancing age and a striking variation in individual susceptibility, possibly reflecting inherent differences. Epirubicin induced a threatening, slowly progressive deterioration of cardiac function with a displaced onset of 3 months or more after drug administration. Cardiotoxicity was primarily unmasked in the post-anthracycline period, continuing years after treatment. The more severe the cardiotoxicity, the longer time for its expression. At a cumulative dose of 850–1000 mg/m² epirubicin an actuarial estimation of 15% of the patients experienced a 25% relative reduction in LVEF 3 weeks after terminating therapy, increasing to 59% after 3 years. One year after terminating epirubicin therapy, 11% of the patients deteriorated into a severely dilated CHF, increasing to 20% after 5 years. Although alarmingly high these estimates are probably still too low, since the numbers might have been even higher with longer observation time had the patients not died from breast cancer. Retrospective observations support the findings of a displaced and retarded functional effect of anthracyclines. The increased survival among children and young adults after anthracycline therapy has shown that long-term cardiotoxicity may appear years to

![Figure 5](http://annonc.oxfordjournals.org/)
decades after treatment [3, 11, 17, 18]. An alarming fraction of more than 65% of survivors of leukemia in childhood has shown progressive cardiac abnormalities 6 years after completing anthracycline therapy [3, 15, 17].

In two major consensus guidelines for monitoring anthracycline cardiotoxicity [12, 13], radionuclide LVEF estimations were proposed as prognostically valuable during therapy, with long-term progression recorded at least 10–14 days after the last anthracycline dose [13].

These recommendations are based on mostly retrospective data with a substantial lack of data on dysfunction in the post-anthracycline period [3, 14, 17]. Before the present study, two retrospective studies from our institute had demonstrated that radionuclide measurements of LVEF during anthracycline therapy were unable to predict the development of CHF [5, 6]. Those and similar reports [3, 14, 15] provided the ethical basis for the present study. We serially recorded LVEF during and after anthracycline therapy but only made estimations in those cases where the patients manifested clinical signs of cardiotoxicity. Results were stored for analyses at least 6 months after terminating epirubicin therapy for the last included patient without premature interference from laboratory data. The present study is the first with blinded, observational, prospective collected data that demonstrate a displacement of the functional cardiotoxic effect. The lag-time necessary for anthracycline-induced subclinical processes to express functional cardiac manifestation makes the radionuclide method insensitive and unable to predict outcome when monitoring is performed in close connection to anthracycline administration. Recording of cardiotoxicity by LVEF months to years after anthracycline administration is a much more meaningful end point for a monitoring program. Current guidelines and recommendations should therefore be revised, as proposed by others [3, 6, 14].

The cardiotoxic effects of the anthracycline anthraquinone have been consistently associated with free radical generation [3, 4, 19, 20]. Patients treated with anthracyclines may serve as a model for studying the pathophysiological processes of anthraquinone free radical-induced damage in the healthy intact human heart, providing us with the rare opportunity to analyze the time windows for these functional damages. Anthracycline-induced cardiotoxicity resembles the cardiotoxicity caused by the burst of free radical formation after activated phagocytic activity following myocardial infarction, or after re-oxygenation and reperfusion of ischemic tissue following thrombolytic therapy or other revascularization procedures [21–28]. Smoking similarly causes a severe oxidative stress, with the principal radicals being anthraquinones held in the tarry matrix [29] that increase the risk of cardiovascular disease, especially in women [30]. Female sex is in general associated with a remarkable, about two-fold, increase in cardiac morbidity and mortality once a cardiac risk factor is established [9]. This increase in female susceptibility is observed after anthracycline therapy [11, 15] and thrombolytic therapy [26], in diabetes [10], with cigarette smoking [7, 30] and during aging [7]. In the present study of female patients we found age to be the most dominant factor, increasing anthracycline cardiotoxicity susceptibility. The same age-dependent increase in susceptibility to heart damage is seen in idiopathic, dilated cardiomyopathy [8], CHF of other causes [7, 10], and after thrombolytic therapy [26, 27]. The normal senescent heart is potentially a diseased heart [31]. It has been suggested that many of the aging processes themselves are the result of long-sustained tissue abuse by free radicals [23] with a reduced amount of protective antioxidants in the old and the sick [27].

The cardiac matrix is profoundly disrupted in patients with advanced heart failure [32], after reperfusion in the ‘stunned’ myocardium [33] or after anthracycline administration [34, 35], as also demonstrated by the histological section from our patient who died of a dilated CHF. Increased dilatation with decreased LVEF correlates well with adverse prognosis in idiopathic dilated cardiomyopathy, in CHF, after thrombolysis, after myocardial infarction, and in anthracycline cardiomyopathy [2, 7, 8, 10, 26, 36]. A common property of cardiac toxicity associated with cardiac matrix alterations, including anthracycline cardiotoxicity, is the salutary effect of prolonged ACE inhibition [3, 23–26, 37–39]. Without ACE inhibition the prognosis of anthracyline-induced CHF is grave [1, 2, 5, 6], resembling the general prognosis of CHF and idiopathic cardiomyopathy with a mortality rate of about 50% within 2 years of diagnosis [1, 7–10]. In our institute we have previously performed two retrospective studies on the incidence and outcome of CHF after therapy with 1000 mg/m² or more of epirubicin for advanced breast cancer [5, 6]. In one study of 135 patients, the incidence of CHF was 35% and four of seven patients died of CHF [6]. In another study of 469 patients, 15% developed CHF with a mortality of 40% within a median of 5 months [5]. Results from this study made us recommend a reduced maximum cumulative dose of epirubicin of 900 mg/m². In the present prospective study with ACE inhibition only 1 of 10 patients with severe heart failure (NYHA class III–IV) died of CHF. The patients with a decreased cardiac function did not spontaneously recover during the observation period but function could only be reversed by ACE inhibition for several months. We have now successfully treated a total of more than 60 patients with severe CHF after anthracyline therapy with ACE inhibition, with a remarkably long-lasting recovery evaluated clinically and by LVEF determination. All three patients in the present study who stopped ACE inhibition after years of stabilized cardiac function deteriorated. This corresponds to trials with ACE inhibition documenting the necessity of ACE inhibitor therapy lasting years in heart failure [38, 39], and this should probably also be the case after anthracycline-induced CHF.

The lag time before progressive cardiac deterioration with dilatation occurs may, however, open a therapeutic window for interventional strategies. We have performed and are awaiting results from a placebo-controlled blinded study for
prevention of cardiotoxicity in the post-anthracycline period by ACE inhibition.

References