Impairment of the Actin-Myosin Interaction in Permeabilized Cardiac Trabeculae after Chronic Doxorubicin Treatment

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ABSTRACT

The development of chronic cardiotoxicity in cancer patients treated with doxorubicin (DOX) and other anthracycline antineoplastic agents is a major dose-limiting factor. In a previous study, we demonstrated an acute effect of anthracyclines on the actin-myosin contractile system. Here, we report chronic effects of DOX both on the contractile system and on the function of the sarcoplasmic reticulum (SR). Male Wistar rats were treated with DOX (2 mg/kg, i.v., once a week for 4 weeks), whereas control rats received equal volumes of saline. Right ventricular trabeculae were isolated and skinned by exposure to Triton X-100 or saponin equal volumes of saline. Right ventricular trabeculae were isolated and skinned by exposure to Triton X-100 or saponin

INTRODUCTION

Cancer chemotherapy with anthracyclines is associated with the development of cardiomyopathy and congestive heart failure (1–3). The manifestations of anthracycline cardiotoxicity are characterized in humans (4–6) and in experimental animals (7–10). Several hypotheses have been proposed to explain this cardiotoxicity, including DNA intercalation (11), free-radical formation (12, 13), lipid peroxidation (14), the formation of C-13 hydroxyanthracycline metabolites (15), impairment of myocardial calcium homeostasis (16), and mitochondrial damage [see Singal et al. (17) for review]. Although acute and chronic effects of DOX on the contractile performance of human and animal hearts have been extensively studied, the complexity of the cellular effects precludes a single mechanism. Studies describing contractile effects as a result of DOX treatment most often do not provide insight into whether the observed contractile changes are caused by a direct alteration of the contractile system or by other mechanisms. In preparations that have intact membrane structures, it is difficult to separate membrane-related effects from direct effects on the contractile apparatus. To analyze the effects of DOX on the actin-myosin contractile system, we used trabeculae of the right ventricular wall of which both outer and inner membranes were permeabilized. This yields preparations in which the function of the contractile apparatus can be studied, because membrane-related effects do not interfere with the final tension response. Using this model, we found a strong positive inotropic effect in striated muscle preparations after incubation with DOX, indicating that DOX has an acute and direct effect on the actin-myosin interaction (18, 19).

The abbreviations used are: DOX, doxorubicin; SR, sarcoplasmic reticulum.

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The abbreviations used are: DOX, doxorubicin; SR, sarcoplasmic reticulum.
with DOX results in a progressive decrease of the maximal calcium-activated tension of the remaining functional muscle fibers without affecting the functionality of the SR.

**MATERIALS AND METHODS**

**Animals and Treatment.** Male Wistar rats with a starting weight of 320 ± 3 g (n = 83) were used in this study. Animals were allowed to acclimatize 1 week before drug administration. The experiments were approved by the Utrecht University Experimental Animal Committee. DOX was administered i.v. into a tail vein at a dose level of 2 mg/kg body weight once a week for 4 weeks (total cumulative dose, 8 mg/kg). DOX-treated rats (n = 44) and control rats (n = 32) were randomly divided in four groups. Each group was used in experiments after posttreatment periods of 1, 2, 4, or 6 weeks. For controls, age-matched rats were given i.v. injections with equal volumes of saline following the same treatment protocol as the DOX group. Control rats and DOX-treated rats were given water and standard chow ad libitum. To exclude possible effects of a reduced food intake, a group of rats was held on restricted food intake to induce a body weight loss similar to that of the DOX group. These rats were fed an average of 83% of the food intake of the rats treated with DOX. These rats were used as the DOX group. Control rats and DOX-treated rats were anesthetized with Nembutal (60 mg/kg body weight, i.p.) and kept on a 12-h light/dark cycle.

**Isolation of Preparations.** At the designated time, rats were anesthetized with Nembutal (60 mg/kg body weight, i.p.). After tracheotomy, the thorax was opened, and the aorta was cannulated. The heart was rapidly removed and connected to a Langendorff perfusion system. The Tyrode’s solution had the following composition (in mM): NaCl 130, KCl 4.7, Na2HPO4 0.42, NaHCO3 20.2, glucose 10.1, MgCl2 1.0, and CaCl2 2.0; the solution was continuously gassed with a mixture of 95% O2 and 5% CO2 to maintain pH at 7.4 at 30°C. 2,3-Butanedione-monoxime (15 mM) was added to the Tyrode’s solution to make sarcolemma and inner membrane structures permeable for small ions and molecules, whereas saponin disrupts only the sarcolemma, leaving inner membranes such as the SR membrane intact. The skimming solution was removed by washing with relaxation solution (see Table 1). The skinned preparations were mounted in the experimental setup using aluminum T clips (23).

**Apparatus.** Isometric tension was measured with a Scientific Instruments (Heidelberg, Germany) force transducer. Isometric tension of rigor contractions was measured using a SensoNor AE801 (Horten, Norway) force transducer. Sarcomere length was determined by helium-neon laser diffraction. The output of the force transducer was recorded on a flatbed recorder and a voltmeter and was digitized by a computer with an analog-to-digital card (Keithley DAS 1602). The width and depth of the muscles were measured immediately after the experiments using an eyepiece graticule fitted in the dissecting microscope. The cross-sectional area was calculated on the assumption that the cross-sections were ellipsoid. The experimental solutions were carried in a series of wells (1.25 ml each) in a temperature-controlled stainless steel block. The sides of the wells were made of glass, allowing laser diffraction measurement at any moment during the experiment. Solutions were changed by lifting the muscle out of the solution and sliding the block horizontally to bring the next solution under the muscle.

**Experimental Protocols.** Table 1 summarizes the solutions used in the experiments. All experiments were performed at 22°C and pH 7.0. The Triton X-100-skinned preparations were placed in relaxation solution for stabilization. Sarcomere length was set at 2.15 μm and controlled throughout the experiment. Before activation, the trabecula was placed in a low-EGTA preactivating “jump” solution. After test activations, the calcium sensitivity was measured by immersing the preparation in solutions with increasing Ca2+ concentrations resulting in a gradual increase of the force response. The pCa values of these activation solutions ranged from 6.17 to 4.00, which was obtained by mixing relaxation and activation stock solutions. After these activations, two rigor contractions were measured using the same preparation. Rigor was forced by immersing the fiber in a solution without ATP and calcium and had a duration of 3 min, after which a stable rigor tension level was obtained. At the end of the protocol, maximal tension and calcium sensitivity was again measured.

The protocol followed to study the function of the SR was slightly modified from that of Stienen et al. (24). The SR of saponin-skinned trabeculae was loaded with calcium by im-

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**Table 1 Composition of solutions (in mM)**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Relaxation</th>
<th>Preactivation</th>
<th>Activation</th>
<th>Rigor</th>
<th>&quot;Low&quot; preactivation</th>
<th>Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPS^a</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>EGTA</td>
<td>7.0</td>
<td>6.8</td>
<td>7.0</td>
<td>7.0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>EDTA</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td>CP</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>MgATP</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>pCa</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>MgATP</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

* Ionic strength is 160 mM at pH 7.0 (22°C). All solutions, except rigor, contain 50 units/ml creatine kinase.

^a MOPS, 4-morpholine propane sulfonic acid.
Table 2  Body weight and heart weighta

<table>
<thead>
<tr>
<th>PTP</th>
<th>Terminal body weight (g)</th>
<th>Terminal heart weight (g)</th>
<th>Relative heart weight (% of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DOXb</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>410 ± 9</td>
<td>253 ± 11</td>
<td>1.52 ± 0.04</td>
</tr>
<tr>
<td>2</td>
<td>449 ± 8</td>
<td>259 ± 15</td>
<td>1.68 ± 0.05</td>
</tr>
<tr>
<td>4</td>
<td>469 ± 9</td>
<td>258 ± 22</td>
<td>1.68 ± 0.06</td>
</tr>
<tr>
<td>6</td>
<td>471 ± 11</td>
<td>303 ± 28</td>
<td>1.64 ± 0.07</td>
</tr>
<tr>
<td>Stv</td>
<td>255 ± 2</td>
<td></td>
<td>1.06 ± 0.02</td>
</tr>
</tbody>
</table>

a Terminal body weight, terminal heart weight, and the ratio between terminal body weight and terminal heart weight of control rats and DOX-treated rats at 1, 2, 4, and 6 weeks posttreatment. The starting body weight was 321 ± 5 (n = 32) for control animals and 320 ± 3 (n = 24) for DOX-treated animals. Data are means ± SE for n = 24).

P < 0.01 (ANOVA).

Fig. 1 Experimental trace of part of the protocol used to study active tension in a Triton X-100-skinned trabecula. Shown are a calcium activation curve and a rigor contraction. Partial activations were performed at pCa 6.35, 6.17, and 5.96, respectively. To allow comparison between trabeculae, the amplitude of each caffeine contraction was expressed as a percentage of the maximal calcium-activated tension.

**Data Analysis.** The normalized calcium sensitivity curves, which were obtained by gradually increasing the calcium concentration surrounding the preparation, were fitted to the Hill equation:

\[
\frac{T([Ca^{2+}])}{T_{\text{max}}} = \frac{[Ca^{2+}]^n}{K^n + [Ca^{2+}]^n}
\]

In this Hill equation, \(T_{\text{max}}\) is the maximal isometric tension at saturated \(Ca^{2+}\) binding sites, \([Ca^{2+}]\) is the \(Ca^{2+}\) concentration, \(T([Ca^{2+}])\) is the isometric tension at \([Ca^{2+}]\), and \(K\) and \(n\) are constants to be fitted. \(K\) is the \(Ca^{2+}\) concentration necessary to develop half-maximal tension, and \(n\) represents the steepness in this point.

**Statistical Analyses.** Data are expressed as mean values ± SE for \(n\) observations. In our statistical analysis, we included data on the first Triton X-100 and saponin-skinned preparations of each individual animal. Subsequent preparations showed similar results. An ANOVA (two-tailed) was used to compare differences between control preparations and DOX-treated preparations. A trend test was used to analyze the decrease in tension as a function of time in preparations of DOX-treated animals. Differences with a \(P < 0.05\) were taken to be significant.

**RESULTS.** All DOX-treated rats started to lose weight during the treatment period, whereas control rats showed a normal weight gain (Table 2). In the posttreatment period, treatment-related deaths of animals in the DOX group increased in time. None of the control rats died during or after the treatment period. In the experimental protocols, each control posttreatment group consisted of eight rats, whereas DOX posttreatment groups consisted of seven, seven, six, and four rats (at 1, 2, 4, and 6 weeks posttreatment respectively). At sacrifice, 70% of the rats treated with DOX had ascites, and 42% of the rats treated with DOX suffered from diarrhea. In all posttreatment periods, the absolute heart weight of rats treated with DOX was significantly lower as compared to the heart weight of control rats. This decrease in heart weight was proportional to the decrease in body weight, so that the relative heart weight was unchanged. A group of seven rats was held on restricted food intake over a period of 3.5 weeks to induce a similar weight loss as occurred with DOX-treated rats. The mean body weight at the start of the starvation protocol was 316 ± 2 g and was 255 ± 2 g at the end of it. All rats in the starvation group appeared healthy and had none of the above-mentioned abnormalities as occurred in the DOX group. The terminal heart weight of rats in the starvation group (1.06 ± 0.02 g) was significantly decreased as compared to the heart weight of ad libitum-fed rats of the same starting weight (1.25 ± 0.03 g).

**Maximal Tension and Calcium Sensitivity.** Fig. 1 shows traces of a typical experiment using a Triton X-100-skinned trabecula. The maximal calcium-activated tension of trabeculae obtained from DOX-treated rats was significantly decreased starting from week 2 after the last DOX infusion. Tension parameters are summarized in Tables 3 and 4. At 2, 4, and 6 weeks posttreatment, maximal tension of DOX-treated
trabeculae was significantly decreased by 27, 32 and 37%, respectively, as compared with controls (P < 0.01). At 1 week after the last DOX infusion, the maximal tension was comparable for DOX-treated animals and saline-treated animals. The negative inotropic effect in the DOX groups gradually increased as a function of the posttreatment period (trend test; P < 0.05). In spite of the pronounced reduction of cardiac mass, the dimensions of right ventricular trabeculae were not affected by treatment with DOX. The mean diameter (mean of the width and the depth measurements) of the trabeculae used in each posttreatment period was similar for control preparations and DOX preparations. The overall mean diameter was 110 ± 5 μm for all control preparations (n = 32) and 115 ± 5 μm for all preparations of DOX-treated animals taken together (n = 24). DOX-treated trabeculae had an overall lower calcium sensitivity as compared to control preparations (5.59 ± 0.02 and 5.65 ± 0.01, respectively; P < 0.05). The Hill coefficient was similar between all groups, indicating that the cooperativity of the regulatory proteins involved in muscle contraction was not changed upon treatment with DOX. In the starvation group, active tension parameters of trabeculae were similar to control values.

Rigor Tension. At 1 week posttreatment, no effect was observed in the DOX group on the tension level of an established rigor contraction. However, rigor tension was significantly lower at 2, 4, and 6 weeks after the last DOX infusion as compared to control values (P < 0.01; Table 4). The ratio between rigor tension and maximal calcium-activated tension was significantly higher in DOX-treated trabeculae compared to control preparations (0.39 ± 0.01 and 0.36 ± 0.01 respectively; P < 0.05). In the starvation group, both the absolute rigor tension and the ratio between rigor tension and maximal tension of trabeculae were not different from control values.

Function of the SR. Saponin-skinned trabeculae were used to study effects on the SR function. After equilibration for 2 min in preactivating solution with 0.1 mM EGTA, exposure to 25 mM caffeine elicited a tension transient in preparations that were previously loaded with calcium (Fig. 2). To allow comparison between preparations of different experimental groups, the amplitudes of caffeine-induced contractions were normalized to the maximal calcium-activated tension. The normalized

Table 3 Active and rigor tension parameters in Triton X-100-skinned trabeculae of control rats and rats treated with DOX at 1, 2, 4, and 6 weeks posttreatment

<table>
<thead>
<tr>
<th>T&lt;sub&gt;max&lt;/sub&gt; (kilonewtons/m²)</th>
<th>pCa&lt;sub&gt;50&lt;/sub&gt;</th>
<th>n&lt;sub&gt;Hill&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>DOX&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Control</td>
</tr>
<tr>
<td>1 week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74.8 ± 4.9</td>
<td>5.70 ± 0.02</td>
<td>6.2 ± 0.6</td>
</tr>
<tr>
<td>2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88.2 ± 3.6</td>
<td>5.59 ± 0.03</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86.5 ± 4.8</td>
<td>5.66 ± 0.03</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>87.6 ± 4.8</td>
<td>5.63 ± 0.03</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>Stv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89.1 ± 3.8</td>
<td>5.66 ± 0.03</td>
<td>4.9 ± 0.7</td>
</tr>
</tbody>
</table>

Table 4 Rigor tension parameters in Triton X-100-skinned trabeculae in control rats and rats treated with DOX at 1, 2, 4, and 6 weeks posttreatment

<table>
<thead>
<tr>
<th>T&lt;sub&gt;rigor&lt;/sub&gt; (kilonewtons/m²)</th>
<th>Ratio T&lt;sub&gt;rigor&lt;/sub&gt;:T&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP</td>
<td>Control</td>
</tr>
<tr>
<td>1 week</td>
<td>28.0 ± 2.3</td>
</tr>
<tr>
<td>2 weeks</td>
<td>31.3 ± 2.3</td>
</tr>
<tr>
<td>4 weeks</td>
<td>29.6 ± 2.0</td>
</tr>
<tr>
<td>6 weeks</td>
<td>34.2 ± 1.5</td>
</tr>
<tr>
<td>Stv</td>
<td>34.0 ± 1.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> PTP: posttreatment period; Stv: starvation group. Data are means ± SE.
<sup>b</sup> P < 0.01 (ANOVA) and P < 0.05 for time-dependent tension decrease (trend test).
<sup>c</sup> P < 0.05 (ANOVA).

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amplitude of caffeine-induced contractions was similar for control preparations and preparations of DOX-treated animals under all Ca\textsuperscript{2+} loading conditions and at all posttreatment periods (Fig. 3). Spontaneous oscillatory contractions were typically observed at higher Ca\textsuperscript{2+} loading concentrations and occurred as often in control groups as in DOX groups.

DISCUSSION

Although many possible mechanisms of anthracycline cardiotoxicity have been reported (17), few focus on abnormalities that are caused directly by an impaired contractile machinery. We reported recently that DOX significantly increased both maximal tension and calcium sensitivity by direct interaction with the actin-myosin cross-bridges in skinned cardiac trabeculae after acute exposure to this drug (19). We showed that DOX acted during the transition to force generating cross-bridges as was reflected by an increase in rigor tension after preincubation of trabeculae with DOX. The present study describes a new mechanism for the development of heart failure after chronic DOX treatment: impairment of the actin-myosin interaction. The progressive impairment of the maximal tension (up to 37% of control tension) after chronic DOX treatment may lead to congestive heart failure and might therefore provide a relevant mechanism through which DOX exerts its cardiotoxic effects.

Anthracycline cardiotoxicity is commonly described by two differently timed cardiotoxic effects, i.e., an early effect that is characterized by an increased contractile performance and a delayed effect showing an attenuation of the contractile performance (25). Because DOX treatment was discontinued at least 2 weeks before the negative inotropic effect was manifested, the negative inotropic effect in the present study is likely to be the result of chronic damage to the myocardium, rather than acute effects of DOX. At 1 week posttreatment, however, it cannot be excluded that early effects did play a role in the tension response, because the maximal tension of DOX preparations was similar to the maximal tension of control preparations at that time. This might be caused by opposite-directed early and late cardiotoxic effects being active at the same time.

Parallel to the effect on the maximal tension, the absolute rigor tension is significantly lower in the DOX group as compared to control values starting from 2 weeks posttreatment.
During a rigor contraction in which ATP is absent, myosin binds actin with high affinity forming rigor cross-bridges. This leads to a situation in which cross-bridges are arrested in a strongly bound stage, in which cycling of cross-bridges, which occurs during normal activations in the presence of ATP, no longer occurs. Recently, we showed that acute DOX exposure affects transitions to force-generating cross-bridges during a rigor contraction (19). This resulted in a higher rigor tension possibly by altering the coupling and/or the decoupling of cross-bridges and thus the distribution of cross-bridges during the activation cycle. In the present study, the ratio between rigor tension and maximal calcium-activated tension is significantly higher in the DOX-treated group, suggesting that the distribution of cross-bridges during rigor is changed upon chronic DOX treatment.

The cumulative DOX dose used in this study results in progressive morphological changes of heart cells, such as microvacuoles and edema, similar to those described previously (10). However, we did not observe cardiac cell loss and fibrosis, and the dimensions of the trabeculae did not differ between control and DOX preparations. The absence of fibrosis in our preparations is further supported by the observation that the passive stiffness of preparations of DOX-treated animals appeared normal. Because other processes besides muscle contraction do not play any role in our preparations, it is likely that the observed contractile effects are caused by changes on the level of the contractile apparatus. The exact origin of the attenuation of the contractile performance described here remains to be elucidated. Cappelli et al. (26) found that delayed DOX cardiotoxicity was accompanied by a marked reduction in the percentage of α-heavy chains and a shift from V1 to V3, resulting in a decreased contractile performance and a reduced myofibrillar ATPase activity. This same mechanism may explain the small but significant change in calcium sensitivity of DOX preparations in the present study. Papoian and Lewis (27) reported that DOX treatment leads to defects in the expression of cardiac genes coding for muscle-specific mRNAs, which may contribute to contractile abnormalities. Changes on the molecular level as are reported by others will affect the transition rates between cross-bridge states. This can be studied by analyzing tension transients after application of small-length steps. Preliminary results from our laboratory support this hypothesis.

All rats treated with DOX displayed a progressive decrease in body weight, which is most probably caused by gastrointestinal toxicity (28). Both the DOX-treated and starved rats showed a marked reduction in cardiac mass, which was related to the reduction in body weight. The reduction of cardiac mass could on the one hand be a consequence of a general, nonspecific impairment of protein synthesis induced by the treatment but could on the other hand be caused by the reduction of food intake in the DOX-treated rats. To assess the contribution of a reduced caloric intake to the contractile changes reported in this study, a group of rats was deprived of normal food intake to control and DOX preparations at all calcium-loading concentrations and at all posttreatment periods. It seems, therefore, that in our preparation, both the function and the volume of the SR remain in equilibrium with the contractile performance after chronic exposure to DOX. Our results seem to be inconsistent with previous studies reporting alteration of the SR function after both acute and chronic exposure to DOX (20, 21). In our protocol, we used thin trabeculae, in which diffusion problems are limited. This may also be concluded from the observation that caffeine induced fast and short-lasting tension transients (Fig. 2). We maintained a constant Ca2+ loading time of 3 min, which has proven to be sufficient to equilibrate the SR in control preparations. Although the capacity of the calcium pump, the storage capacity, and the calcium release by the SR seem to be functioning normally under our experimental conditions, we cannot exclude that the rate of Ca2+ uptake by the SR is altered. Because we maintained a constant loading time of 3 min, it might be that although the rate of Ca2+ uptake was diminished in the DOX groups, the capacity of the calcium pump was still sufficient to fill the SR. This may, at least partially, explain the apparent discrepancy between our data and those reported in previous studies.

In conclusion, long-term DOX administration in rats causes substantial impairment of the actin-myosin cross-bridge interaction without affecting the functionality of the SR in our preparations. The effect of chronic DOX treatment directly on the level of the contractile machinery provides an additional mechanism through which anthracyclines exert their debilitating cardiotoxic effects. Elucidation of this mechanism may open up new interventional pathways to prevent chronic DOX-induced cardiomyopathy.

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