

## REVIEW

## Anthracyclines and the heart

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The anthracyclines are effective and widely used antineoplastic agents. They are used to treat many types of malignancy including acute lymphoblastic leukaemia.<sup>1</sup> Their introduction has considerably improved survival, especially in childhood cancers.

Signs of cardiac toxicity may develop during, soon after or many years after a course of treatment. Early toxicity is dependent principally on the cumulative anthracycline dose. Typically the patient presents with left ventricular or congestive heart failure and with clinical features of congestive cardiomyopathy. Less often an arrhythmia is the first manifestation of toxicity. The major differential diagnoses are malignant pericarditis, cardiac injury from concomitant radiotherapy, and coincidental heart muscle or coronary artery disease.

The two most widely used and studied anthracyclines are daunorubicin and its C-14 derivative, doxorubicin (adriamycin). They are glycoside antibiotics that owe their antineoplastic action to a complex effect that results in inhibition of nucleic acid synthesis by binding to both strands of the DNA helix, preventing the normal function of RNA and DNA polymerases.

### Pathogenesis of myocardial toxicity

Possible mechanisms of the myocyte damage include a disturbance of calcium and sodium exchange caused by an interaction with the inner mitochondrial membrane to form a complex that inactivates the electron transport chain<sup>2</sup> and the production of free oxygen radicals. Daunorubicin added to cultured myocardial cells from neonatal rats at concentrations similar to those used in chemotherapy is accompanied by rapid production of free radical derivatives.<sup>3,4</sup> An explanation for the myofibrillar loss is selective inhibition of gene expression in cardiac muscle cells. Doxorubicin causes a dose-dependent decrease in the concentrations of messenger RNA for  $\alpha$  actin, troponin I, myosin light chain 2, and the M isoform of creatine kinase in rat cardiac muscle. These changes in gene expression precede the classic changes of anthracycline toxicity both in myocyte cultures and cardiac muscle in vivo.<sup>5</sup> Doxorubicin induced automaticity in cultured chick heart aggregates by depolarising the cardiac membrane.<sup>6</sup>

### Effects on ventricular function

Dose-dependent myocardial toxicity is characterised by impairment of left ventricular diastolic function which is followed by reduced systolic function<sup>7-9</sup> with progressive left ventricular free wall thinning and dilatation.<sup>10</sup> Dysfunction confined to the right ventricle has also been described.<sup>11,12</sup> An upper limit to the cumulative dose of 450-550 mg/m<sup>2</sup> was recommended.<sup>13,14</sup>

Non-dose dependent electrocardiographic abnormalities including non-specific ST and T wave changes, low QRS voltage, and ventricular arrhythmias were described in a review of patients with evidence of early cardiotoxicity.<sup>15</sup> Steinberg *et al* observed arrhythmias in 3% of patients during the first hour of doxorubicin administration, increasing to 24% of subjects within the first 24 hours. The most common abnormality was an increase in the frequency of ventricular extrasystoles but a few patients developed non-sustained ventricular tachycardia. The appearance of arrhythmias was not associated with an adverse outcome in this group of patients<sup>16</sup> but sudden death has been reported by others.<sup>17</sup>

Early congestive cardiac failure developed in about 30% of patients receiving more than 550 mg/m<sup>2</sup> doxorubicin but in only 0.01-0.27% of patients receiving less than 550 mg/m<sup>2</sup>.<sup>18-20</sup> Smaller doses of anthracycline can lead to a reduction in myocardial function that is demonstrable only on exercise.<sup>21,22</sup> Cardiotoxicity can be enhanced when anthracyclines are used in combination with other agents such as cyclophosphamide, bleomycin, cisplatin, methotrexate, and mitomycin C<sup>23,24</sup> as well as with thoracic irradiation. Cumulative anthracycline doses below the "safe upper limit" of 450-550 mg/m<sup>2</sup> can be fatal in these circumstances.

Heart failure late after anthracycline therapy is increasingly recognised.<sup>25-29</sup>

In a prospective study of 201 children treated with anthracyclines, Steinherz and colleagues found that no patient assessed 4-6 years after treatment had a fractional shortening of less than 20%, whereas by 10 years one third had values of less than 20% and over half of less than 25%.<sup>30</sup> Limiting the dose of anthracycline does not eliminate the risk of long-term myocardial damage. Lipshultz *et al* identified abnormalities of cardiac function in 17% of patients who had received a single dose of only 45 mg/m<sup>2</sup> of doxorubicin.<sup>31</sup>

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### Treatment of cardiotoxicity

Anthracycline-induced heart failure should be treated with the conventional combination of a diuretic and digoxin, and an angiotensin converting enzyme inhibitor may be indicated at an early stage.<sup>32-33</sup>

Progressive heart failure unresponsive to conventional therapy has been successfully treated by heart transplantation.<sup>34-35</sup>

### Prevention of cardiotoxicity

#### DOSE REDUCTION

Dose reduction reduces the incidence of early myocardial dysfunction but does not remove the risk of long-term problems. Low dose infusion reduced cardiotoxicity in some studies<sup>36-38</sup> as did a weekly low dose schedule,<sup>39</sup> possibly by avoiding high peak concentrations. Continuous infusions can however cause a progressive fall in resting left ventricular ejection fraction.<sup>40</sup>

#### NEW ANTHRACYCLINES

Anthracycline analogues such as epirubicin, idarubicin, esorubicin and pirarubicin have been reported to cause less early cardiotoxicity than daunorubicin or doxorubicin<sup>41-43</sup> but their long-term effects cannot yet be assessed.

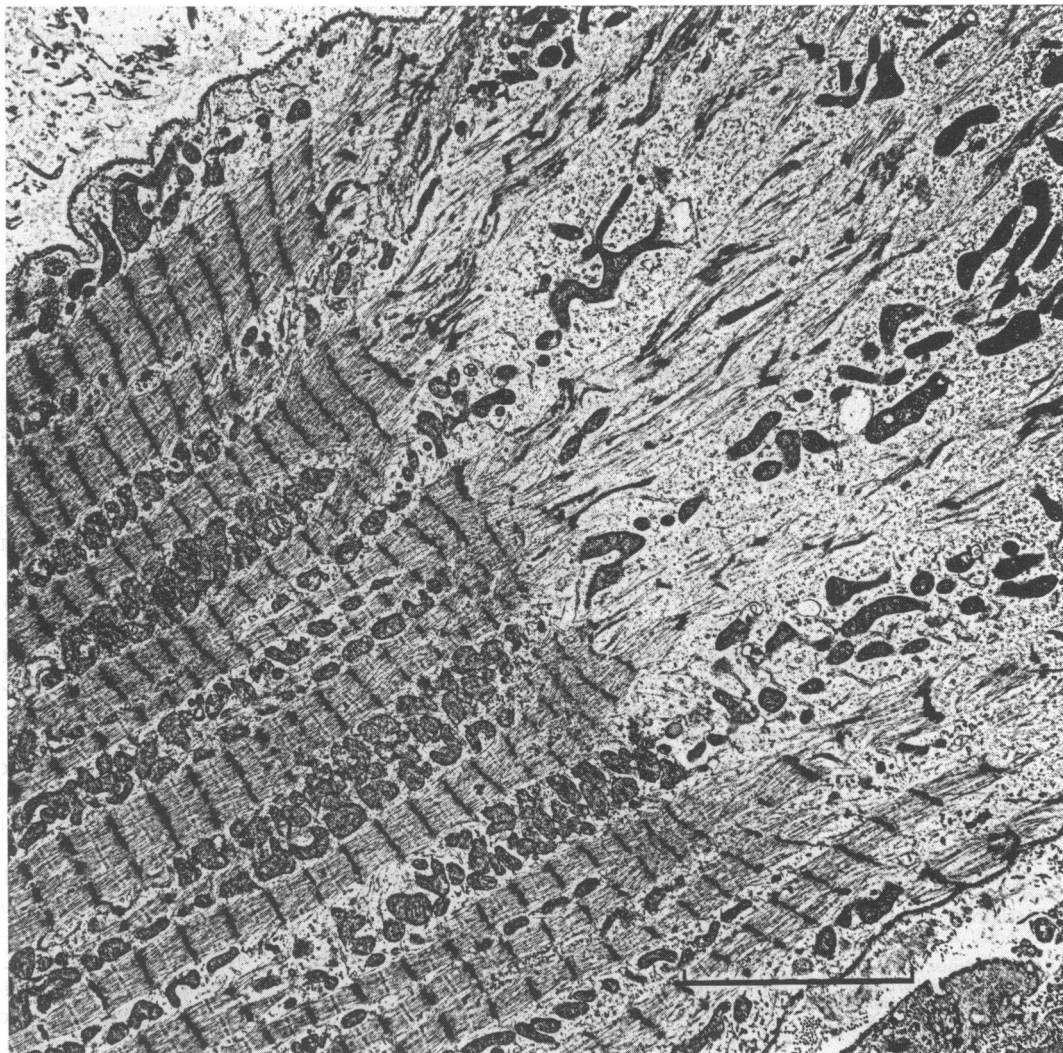
#### CARDIOPROTECTIVE AGENTS

The ICRF187, given with an anthracycline, seems to reduce cardiotoxicity without lessening its antineoplastic action.<sup>44-46</sup> The mechanism of action of ICRF187 is unknown. Niacin and isocitrate have both been shown to reduce cardiotoxicity in mice.<sup>47</sup>

#### SURVEILLANCE FOR SIGNS OF TOXICITY

Steinberg and Wasserman recommended that during treatment left ventricular function should be monitored by serial radionuclide ventriculography, and that doxorubicin should be stopped if the ejection fractions dropped to  $\leq 45\%$  at rest or failed to increase with exercise.<sup>48</sup> The results of serial radionuclide studies must, however, be interpreted with caution to avoid labelling spontaneous variations in the left ventricular ejection fraction as doxorubicin cardiotoxicity.<sup>49</sup> M Mode echocardiography can also be used to identify patients with asymptomatic ventricular dysfunction. Both these approaches require the clinician to wait until ventricular systolic function has been affected before altering treatment. Assessment of left ventricular diastolic performance by measurement of isovolumic relaxation time<sup>50</sup> and pulsed wave Doppler transmitral flow velocity<sup>51</sup> can give

*Electron micrograph of a myocardial fibre affected by anthracycline toxicity showing a relatively normal appearance on the left and extensive myofibrillar loss and degenerative elongated mitochondria on the right. (Original magnification,  $\times 7000$ ).*



an earlier indication of cardiotoxicity. Ideally methods of identifying patients at risk of cardiotoxicity, or of identifying cardiotoxicity before it causes irreversible depression of myocardial function need to be developed.

Monoclonal antimyosin antibody imaging has been proposed for the early diagnosis of anthracycline cardiotoxicity<sup>52,53</sup> because antibody uptake seems to predate other markers of myocardial damage. Evidence from <sup>123</sup>I. Methoxy-isobutyl isonitrile (MIBI) scanning suggests that doxorubicin-related cardiotoxicity involves myocardial adrenergic derangement,<sup>54</sup> pointing to the possibility that the study of cardiac autonomic function could be helpful for patient monitoring. One study showed a reduction in respiratory sinus arrhythmia that preceded the onset of clinical congestive cardiac failure by several months<sup>55</sup>; however, another study that identified abnormalities in cardiovascular responses to hand grip and standing found no correlation with ventricular function.<sup>56</sup>

The Cardiology Committee of the Children's Cancer Study Group recommends regular echocardiography and radionuclide ventriculography during treatment.<sup>57</sup> If initial investigations remain normal, long-term echocardiographic follow-up should be carried out three to six months, 12 months, and then on alternate years after completion of chemotherapy. Five-yearly radionuclide ventriculography and Holter monitoring are also recommended. Abnormal results should prompt shortening of the follow up interval.

If anthracycline toxicity is suspected or if further treatment is required for a patient who has already received a high dose of one of the agents, endomyocardial biopsy should be considered as a guide to the safety of further therapy.<sup>58</sup>

**Ultrastructural changes**

Light microscopy is unreliable for the early diagnosis of anthracycline cardiotoxicity. At least three biopsy specimens of the myocardium should be obtained and examined by electron microscopy. Two types of myocardial damage occur in anthracycline toxicity. One is sarcotubular dilatation which may progress to vacuolisation with the mito-

chondria remaining intact. The second is myofibrillar loss of actin and myosin, leaving an empty cell with small elongated mitochondria (figure) and peripheral Z-band remnants. For grading, both types of cell damage are counted equally<sup>58</sup> (table).

At grade 2-5 only one more dose of anthracycline should be administered without further evaluation. At grade 3-0 no more anthracycline should be given.

Some oncologists are reluctant to use endomyocardial biopsy but the procedure provides uniquely valuable information in planning further therapy.

*Morphological grading system for anthracycline cardiotoxicity*

Grade	Morphology
0	Normal myocardial ultrastructure
1	Isolated myocytes with distended sarcotubular system and/or early myofibrillar loss; damage to <5% of all cells in 10 plastic blocks
1.5	As grade 1 but with 6-15% of all cells affected in 10 plastic blocks
2	Clusters of myocytes affected by myofibrillar loss and/or vacuolisation, with damage to 16-25% of cells in 10 plastic blocks
2.5	Many myocytes, <26%-35% of all cells in 10 plastic blocks, affected by vacuolisation and/or myofibrillar loss
3	Severe and diffuse myocyte damage with >35% of all cells in 10 plastic blocks showing vacuolisation and/or myofibrillar loss

From Billingham and Bristow.<sup>58</sup>

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