hypertension and connective tissue disease. No definite risk factors were identified in our patient, except for mild hypertension controlled with drugs.

The pathological hallmark of arterial dissection is represented by a separation of layers of the vessel wall usually caused by an intimal tear that connects the arterial lumen with the wall of the artery, forming an intramural haematoma. SAHs are not rare in intracranial artery dissections because they lack an external elastic membrane and have a thinner adventitia and fewer elastic fibres in the media as compared to extracranial vertebral and carotid arteries.

Diagnosis of intracranial artery dissection relies on DSA, but MRI and MRA have found a role in establishing the initial diagnosis and in the follow-up. DSA signs of arterial dissections include irregular narrowing (‘pearl and string sign’), fusiform aneurysm (‘pseudoaneurysm’ or dissecting aneurysm) and venous mural pooling of contrast medium, although the only pathognomonic DSA finding is the identification of a double lumen—that is, the passage of the contrast medium into a true and false lumen. MRI is an ideal complement to DSA, as it can directly enable assessment of the vessel wall and demonstration of the intramural haematoma. The intramural haematoma typically has a crescent shape showing hyperintensity to isointensity in T1-weighted image and hyperintensity in proton density and T2-weighted images in the subacute stage.

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The natural history and optimal treatment of mitoxantrone-induced cardiotoxicity in secondary progressive multiple sclerosis

Mitoxantrone is an anthrancenedione antineoplastic agent approved as an escalating immunotherapy for multiple sclerosis. Owing to structural similarity with other anthracyclines, cardiotoxicity is a severe side effect of mitoxantrone. Cardiotoxicity from anthracyclines, cardiotoxicity is a severe side effect of mitoxantrone. Cardiographic findings of diastolic dysfunction were detected (prolonged DT and IVRT, E/A ratio with E/CA), although the patient did not show clinical signs of cardiac failure, the second infusion was cancelled in line with our treatment protocol. Two months later LVEF was 60%, but diastolic parameters had not returned to normal values. The patient discontinued mitoxantrone treatment because his Expanded Disability Status Scale had progressed to >6, which rules out further use of mitoxantrone in Germany. A follow-up echocardiogram 10 months later confirmed a normal LVEF of 60% but persistence of prolonged DT, suggesting incomplete remission of diastolic dysfunction.

In patient 2, the LVEF before treatment was 66% and the first mitoxantrone dose was well tolerated. After 3 months, before application of the second dose, LVEF was found to be 48% and additional signs of diastolic dysfunction were detected (prolonged DT and IVRT, E/A ratio with E/CA). Although the patient did not show clinical signs of cardiac failure, the second infusion was cancelled in line with our treatment protocol. Two months later LVEF was 60%, but diastolic parameters had not returned to normal values. The patient discontinued mitoxantrone treatment because his Expanded Disability Status Scale had progressed to >6, which rules out further use of mitoxantrone in Germany. A follow-up echocardiogram 10 months later confirmed a normal LVEF of 60% but persistence of prolonged DT, suggesting incomplete remission of diastolic dysfunction.

In patient 3, the LVEF before treatment was 65%. Follow-up echocardiogram 3 months later was normal, and both the second infusions were well tolerated. Follow-up echocardiogram before the third scheduled infusion showed a decrease in LVEF to 52%, as well as prolonged DT and IVRT, as a result, the

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Early mitoxantrone-induced cardiotoxicity in secondary progressive multiple sclerosis

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treatment was temporarily discontinued. The patient did not have any signs of cardiac dysfunction. Within several weeks LVEF had recovered to 63%, but diastolic dysfunction persisted. After consultation with our cardiologists we decided to continue mitoxantrone treatment, and the third and fourth doses have since been applied. Echocardiogram performed immediately before the fourth dose showed an LVEF of 61% with persisting diastolic changes. So far, no clinical signs of cardiac dysfunction have been reported by the patient or detected on physical examination.

Patient 4 had an LVEF of 64% before treatment, and the first dose was well tolerated. The LVEF after 3 months was 55%, with prolonged DT, but treatment was continued, as the difference in LVEF was <10% and the patient had no clinical signs of cardiac failure. The second infusion was well tolerated. Before the third infusion LVEF had decreased to 49%, with persistent prolongation of DT, but again without clinical signs of cardiac dysfunction. Mitoxantrone was discontinued until a control echocardiogram after several weeks of ramipril treatment showed a normal LVEF of 64%, and diastolic parameters also returned to normal values. The third and fourth doses have since been applied. LVEF was 60% and diastolic parameters were normal immediately before the fourth infusion.

Four other patients had subtle signs of diastolic dysfunction (prolonged DT, IVRT or an E/A ratio with E<CA) without any detectable decrease in LVEF and without clinical signs of cardiac dysfunction after their first or second mitoxantrone infusion.

Discussion

The therapeutic benefit of mitoxantrone for patients with worsening multiple sclerosis has been proved in clinical trials. Because of rare but serious cardiotoxicity, its cumulative lifetime dose is limited in patients with multiple sclerosis. A retrospective analysis of 1578 patients with multiple sclerosis showed an asymptomatic decrease of LVEF to <50% in 1.8% of patients below a cumulative dose of 100 mg/m2, compared with 5% above 100 mg/m2, without continuous monitoring of cardiac function from the beginning of treatment. By performing regular echocardiography before each infusion, we detected 4 of 18 prospectively assessed patients (22%) who transiently experienced a notable decrease in LVEF of between 13% and 16% after their first or second mitoxantrone infusion. All four patients had additional diastolic changes (prolonged DT, IVRT or E/A ratio of E<CA), which remitted in two patients along with normalization of LVEF. Two patients experienced a drop in LVEF to a value below 50%, which prohibited continuation of treatment. Four further patients (another 22%) showed diastolic changes without marked changes in LVEF. The following points argue against technical artefacts: (1) primary and follow-up investigations were performed by the same experienced echocardiographer in 90% of the examinations, using the same equipment, and with full access to prior imaging sequences, allowing comparison of findings with previous results; (2) the dimension (difference between two measurements >10%) and time frame of changes in LVEF followed a similar pattern (normal value at baseline, decrease after the first or second infusion, and (partial) resolution) in all four patients; (3) the minor (5% maximum) differences in LVEF compared with preceding values in the remaining 14 patients; (4) a coefficient of variation of 8.6% for variability of LVEF in our entire group, which is comparable with the coefficients of variation in a previous study using Simpson’s rule; and (5) the quantification of LVEF by means of a well-established and broadly accepted algorithm that has shown good correlation with cardiac magnetic resonance imaging and better agreement with this technique than other echocardiographic assessments (ie, Teichholz method)."

We provide empirical data for early systolic and diastolic cardiac dysfunction after the first or second infusion of mitoxantrone. In line with a previous report on the rapid-onset cardiotoxicity of mitoxantrone, our findings indicate that early cardiac dysfunction under mitoxantrone seems to be more frequent than so far reported. Taking into account both systolic and diastolic parameters, we found a total of 8 of 18 (44%) patients with abnormal findings on follow-up echocardiograms compared with the pretreatment baseline.

The reasons for early decrease of LVEF remain unclear. None of our patients had a history of cardiac disease or had been treated with cardiotoxic substances before. The duration of infusion over 60 min makes peak plasma levels unlikely to cause transient cardiac dysfunction. Our data on early diastolic changes are in line with oncological studies on anthracycline-induced cardiotoxicity, which show that diastolic dysfunction may occur independently of left ventricular systolic function or precede disturbances there. A recent study which reported no marked early decrease of LVEF during treatment with mitoxantrone in multiple sclerosis did not measure functional diastolic parameters. Histopathological data on anthracycline cardiotoxicity suggest a possible change in diastolic performance as a result of increased myocardial stiffness. The clinical effect of early cardiotoxicity is unclear, and to date it is not known whether early subclinical changes are a risk factor for symptomatic cardiac dysfunction later in the course of mitoxantrone treatment or after its completion.

The increasing evidence for early cardiotoxicity calls for regular and frequent cardiac monitoring from the beginning of mitoxantrone treatment. A revision of the product labelling guidelines for mitoxantrone by the US Food and Drug Administration in April 2005 (http://www.fda.gov/medwatch/SAFETY/2005/Novantrone_pl may24.pdf) recommends that an echocardiogram or multi-gated radionuclide angiography be performed before each dose. The best method for assessment of cardiac function under mitoxantrone treatment in

![Figure 1](postscript199a.png)

**Figure 1** Time course of left ventricular ejection fraction (LVEF) in 18 patients during the early treatment phase including follow-up LVEF after recovery (*) or withdrawal of treatment (**).

**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>SPMS course</th>
<th>Disease duration (years)</th>
<th>EDSS</th>
<th>Pre-treatment LVEF before treatment (%)</th>
<th>Dose per infusion (mg/m2)</th>
<th>Cumulative MITOX dose (mg)</th>
<th>LVEF after MITOX (%)</th>
<th>Follow-up LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>37</td>
<td>SPMS</td>
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<tr>
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<td>F</td>
<td>43</td>
<td>SPMS</td>
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<td>66</td>
<td>12</td>
<td>17.7</td>
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<td>71</td>
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<tr>
<td>3</td>
<td>M</td>
<td>30</td>
<td>SPMS</td>
<td>12</td>
<td>5.5</td>
<td>65</td>
<td>12</td>
<td>46.2</td>
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<tr>
<td>4</td>
<td>M</td>
<td>35</td>
<td>SPMS</td>
<td>3</td>
<td>5.5</td>
<td>64</td>
<td>12</td>
<td>51.4</td>
<td>49</td>
<td>64/60</td>
</tr>
</tbody>
</table>

EDSS, Expanded Disability Status Scale; F, female; LVEF, left ventricular ejection fraction; M, male; MITOX, mitoxantrone; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
patients with multiple sclerosis has not been evaluated, and there are no longitudinal studies comparing different techniques (ie, echocardiography, radionuclide ventriculography and magnetic resonance imaging). Therefore, prospective studies for monitoring cardiac function in patients with multiple sclerosis under mitoxantrone are urgently needed. Appropriate techniques should assess systolic and diastolic cardiac functions. Any decisions concerning the discontinuation of mitoxantrone owing to presumed cardiotoxicity should be based on a reliable and accurate method of assessment, as patients often have no therapeutic alternative.

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We thank Mr Andrew Mason for helpful comments and support as a native English speaker, and Dr Mirko Froehlich and Dr Sebastian Kubitz for valuable technical discussion on echocardiography.

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Rasmussen encephalitis with ipsilateral brain stem involvement in an adult patient

Rasmussen encephalitis is a rare unihemispheric inflammatory disease of the brain that leads to intractable seizures, cognitive decline and progressive neurological deficits associated with the affected hemisphere. It predominantly affects children, with the onset in adults having a milder course. Immunotherapy has been suggested to improve the outcome of Rasmussen encephalitis.1

Case report

In November 2000, a left-handed 37-year-old woman experienced a head trauma with brief loss of consciousness. Shortly after, she had prodromal weakness of her right leg and hand (due to the EPC), the neurological examination and electroencephalogram were normal at that time. Cerebrospinal fluid contained 10 cells/μl, had a normal protein level and showed occasional bands. Microbiological studies showed no sign of an infectious agent. MRI of the brain showed a mild left temporal atrophy. A steroid pulse treatment was given. However, the motor deficit progressed, accentuated in the right hand and leg, with central sensory deficit.

In December 2002, Jacksonian motor seizures of the patient’s right hemibody started evolving from the EPC. Brain MRI showed left-sided supratentorial atrophy (most pronounced around the Sylvian fissure) and increased fluid-attenuated inversion recovery or T2 signal of the white matter. The brain stem, however, was neither atrophic nor did it show an increased signal (fig 1A, D, G).

In April 2003, the patient presented to our department (Department of Epileptology, University of Bonn, Bonn, Germany). MRI scans showed progression of hemiatrophy of the left hemisphere and involvement of the left mesencephalon (fig 1B, E, H). Biopsy specimens of the brain biopsy, obtained from the left superior frontal gyrus, showed perivascular and parenchymatous CD3+ CD8+ T lymphocytes partly in close apposition to neuronal microglial activation and astroglisis. The patient received a total of 1.2 g intravenous immunoglobulins (IVlg) per kilogram body weight.

On discharge, the patient had a 4/5 right hemiparesis with hypoesthesia. Further, monthly courses of 0.4 g IVlg/kg were recommended. The patient’s compulsory health insurance, however, refused to cover the costs for this kind of treatment and hence, the patient’s hemiparesis had markedly progressed (arm, 2–3/5; leg, 4/5). Despite reinstitution of monthly IVlg by inpatient treatments in our department, the patient was hemiplegic by October 2003 and became seizure free at about the same time (onset of the “residual stage”). Fortunately, the patient’s language abilities were preserved, obviously owing to atypical dominance (functional MRI scan disclosed bilateral, predominantly right-sided activation of frontotemporal regions during language tasks). IVlg treatment was stopped.

In April 2004, the patient was admitted because of swallowing and speech problems. On cranial nerve examination, she had a newly observed deviation of the uvula to the left side and reduced soft-palate elevation; gag and cough reflexes were normal, and speech showed signs of a flaccid dysarthria. Neither oculomotor abnormalities nor signs of upper brain stem were affected. No cerebellar signs on the unaffected side were noted. The MRI scan showed an ongoing progression of the supratentorial left-sided hemiatrophy and an increase in signal extending subcortically to the left mesencephalon and pons, without contrast enhancement. This strictly unilateral signal increase in the left pons was newly observed (fig 1C, F, I). A high-dose long-term oral steroid treatment was started. One year later, swallowing and speech problems as well as the palatal velum paresis had resolved. MRI was unchanged. The patient is now 41 years old and remains seizure free.

Discussion

To the best of our knowledge, this is the first published biopsy-proven case of an adult-onset

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