Heart transplantation in children with mitochondrial cardiomyopathy

Genetic defects of mitochondrial energy supply can give rise to a variety of symptoms and virtually any organ or tissue can be involved.1 In particular, cardiomyopathy can be the presenting symptom of a respiratory enzyme deficiency in infancy. Alternatively, cardiomyopathy frequently occurs in the course of these diseases.2 Multi-organ involvement is usually regarded as a contraindication for heart transplantation in metabolic disorders. Yet, since the clinical expression of respiratory enzyme deficiency can be limited to the myocardium, it is reasonable to consider heart transplantation in mitochondrial cardiomyopathy.3 Here, we report on successful orthotopic heart transplantation in seven children (four girls, three boys) with severe mitochondrial cardiomyopathy. Mean (SD) age at time of diagnosis was 7.5 (6.1) years (range 1 month to 16 years). All had dilated cardiomyopathy with hypertrophied walls. Six had a positive family history of cardiomyopathy or unexplained sudden death. All patients were screened for skeletal muscle, ocular myopathy, pigmentary retinopathy, and renal and liver dysfunction. Respiratory enzyme activities (cytochrome c oxidase, succinate cytochrome c reductase, and rotenone sensitive reduced nicotinamide adenine dinucleotide cytochrome c reductase) were spectrophotometrically measured in homogenates from frozen endomyocardial biopsy specimens according to previously published procedures.4 Skeletal muscle biopsy was performed in 6/7 patients. In addition, enzyme studies were performed in fibroblasts in 2/7 patients. Finally, one patient had a mild proteinuria and raised liver enzymes. She underwent a liver and kidney biopsy before heart transplantation.

A complex I (NADH-ubiquinone reductase) defect was diagnosed in two patients. This defect was confirmed to the myocardium in one patient, while another patient, with no evidence of clinical myopathy, expressed the defect in skeletal muscle as well. One patient had a complex III deficiency (ubiquinol cytochrome c reductase) in the myocardium but also in the kidney and liver. Four patients had a multiple defect limited to the myocardium: complex I + IV (cytochrome oxidase) in two patients, generalised defect in two twin sisters (table 1). Mitochondrial DNA deletions or point mutations previously reported in cardiomyopathy were not observed in these patients. Patient 7 had a mutation in the md2 helix of the mitochondrial cytochrome b gene.

One patient died while on the waiting list (patient 6). Orthotopic heart transplantation was performed in six children at our institution. Immunosuppressive prophylaxis included cyclosporine, methylprednisolone, and prednisone. Patient 7 died one month after heart transplantation because of dysfunction of the graft. Another patient died seven years after successful heart transplantation following aortic valve replacement for infective endocarditis with right coronary artery septic aneurysm (patient 2). Finally, patient 4 died of subacute rejection with severe coronary lesions after seven years. The remaining three patients are doing well after a mean follow up of 55.6 (9) months (range 2.6–6.5 years). The frequency of acute rejection episodes were identical in this series as compared to the population of transplanted children followed up in our institution. Extracardiac expression of the mitochondrial disorder was not observed during the follow up. Patient 2 (follow up 62 months) in whom the mitochondrial respiratory chain (MRC) defect was also present in skeletal muscle maintains normal muscular testing.

The issue of whether alterations in oxidative phosphorylation play a primary role in causing cardiomyopathy, or whether they occur as a secondary effect of oxidative damage in cardiac tissue remains to be determined. Remes and colleagues demonstrated that the occurrence of mitochondrial DNA deletions in the hearts of patients with idiopathic dilated cardiomyopathy was quantitatively similar to the control hearts and concluded that these deletions have no causal relation with the development of the cardiomyopathy.5 In our series, we have, however, strong evidence for a causal relation between the alteration of MRC function and the cardiomyopathy. Firstly, enzyme studies performed by using endomyocardial biopsy provided evidence of MRC dysfunction and values for protein indicated no detectable proteolytic breakdown, which can be potentially problematic when studying explanted hearts. Secondly, there was a familial history of cardiomyopathy or of acute cardiac events in 6/7 of our patients with dilated cardiomyopathy. The MRC disorder in siblings was proven in 3/4 of these families. In patient 1, the complex I defect was found in the myocardium but also in skeletal muscle. Finally, the remaining patient had a complex III-IV quinones deficiency both in endomyocardial biopsy samples and in microvessels from the explanted heart. Additionally, she had a multiorgan expression of the defect that was found in the kidneys, liver, and skeletal muscle. Finally, she was the only patient in whom we identified a mutation.

Heart transplantation is usually contraindicated in metabolic diseases when the enzyme defect is ubiquitous and the expression of the disease multisystemic. Consequently, one may argue that transplanting the heart of patients with the MRC defect does not prevent extracardiac complications related to this defect. In our series, the MRC disorder was apparently heart specific in all patients but two, and it would have remained undetected if endomyocardial biopsy was not routinely performed in the metabolic screening of severe cardiomyopathies. Without data concerning the biochemical expression in other tissues except skeletal muscle, we cannot exclude the possibility that the defect is latent in these tissues. Nevertheless, we did not observe clinically patent extracardiac expression of the mitochondrial disorder following heart transplantation. Therefore, we believe that MRC disorders causing isolated severe cardiomyopathy in children do not contraindicate heart transplantation.

Extensive metabolic investigations including endomyocardial biopsy for enzyme investigations in adolescents or adults with isolated and apparently idiopathic cardiomyopathy is probably unreasonable. Most of the multisystemic MRC defects are diagnosed during infancy or early childhood. We believe, conversely, that extensive clinical and metabolic investigations are necessary when heart transplantation is indicated in young infants. Indeed, cardiomyopathy may reveal the mitochondrial disease while extracardiac involvement may still be absent. Consequently, the diagnosis of an MRC disorder causing the cardiomyopathy appears reasonable to guide extracardiac investigations and potentially predict delayed multisystemic expression of the defect.

Table 1 Spectrophotometric dosage of the respiratory chain complexes in myocardium

<table>
<thead>
<tr>
<th>Complex</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
</table>

The values in square brackets are the range of the values of the controls. They are different because the measures were done at different moments for each patient with a set of controls in which the spectrophotometric dosage of the MRC complexes was performed during the same experiment. The unit for the absolute values is nmol/min/mg of proteins. The figures in bold represent abnormal values.
Effect of circadian rhythm on response to carotid sinus massage

Carotid sinus massage (CSM) is commonly performed as a bedside test for determining the type and sometimes also the mechanism of different rhythm disturbances, or for routine investigation of older patients who experience syncope, dizziness, or unexplained falls. Recently, it has been reported that the response to CSM is affected by the patient’s position, and in patients with unexplained syncope or drop attacks, upright CSM may be used if initial supine CSM is not diagnostic. On the other hand, time of day at which massage is performed is usually not taken into consideration.

Circadian rhythm, which is the variability of physiology and biochemistry of humans in a predictable fashion during a 24 hour period, may also have an effect on response to CSM as well as the patient’s position. There has been no study, to our knowledge, that has explained the relation between circadian rhythm and response to CSM. For this reason, we conducted such a study.

A total of 120 consecutive patients (mean (SD) age 56.9 (12.4) years, 76 men and 44 women) who were in sinus rhythm were included in the study. Patients with a history or clinical findings consistent with cerebrovascular disease and who had murmurs on cardiac auscultation were excluded. Also, patients who suffered from serious arrhythmia or ischaemia and had symptoms suggestive of carotid sinus syncope were not included. Clinical characteristics of the patients were: hypertension in 60 (50%) patients; diabetes mellitus in 12 (10%); valvular heart disease in six (5%); ischaemic heart disease in 46 (38.3%); and compensated heart failure in 11 (9.1%) patients. Two thirds of the study population were not taking any drugs at the time of CSM. In multiple comparison test. This means that the absolute changes and the maximal changes in RR interval were measured for each time (table 1). The basal RR value (ms) among the four different time points did not differ, although there was a tendency for an increase over the 24 hour period from 0600 to 2400 (mean (SD) 820.4 (150.1) ms, 829.3 (146.3) ms, 836.8 (150.1) ms, 857.6 (214.4) ms, respectively for the four time points). There were significant differences among the four different times with respect to the maximal changes and absolute changes in RR interval (p < 0.001 for both). The significant differences were found between 0600 and 1800, and between 0600 and 2400 (p < 0.05 and p < 0.001 for both absolute changes and maximal changes in RR interval, respectively) in multiple comparison test. This means that the absolute changes and the maximal changes in RR interval were at their minimum at 0600 and at their maximum at 2400. There were no significant differences between 0600 and 1200, 1200 and 1800, and 2400 and 2400 (p > 0.05). Despite the ubiquitous influence of diurnal cycles on the cardiovascular system, we know relatively little of the clinical relevance of the circadian rhythm. Through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of a number of clinical disorders have a pattern associated with the body’s inherent clock set according to the circadian rhythm.

On the other hand, circadian rhythm may also have an important effect on response to CSM as well as the activity of a number of disorders. Therefore, time of day at which massage is performed should be taken into consideration while assessing the response. A normal response to CSM is a transient decrease of the sinus rate and slowing of atrioventricular nodal conduction. However, the present study showed that this response could not be the same if it is performed at different times within a day. In this small prospective series of patients, the response to CSM assessed by the maximal change in RR intervals (%) was found to be at a minimum at 0600 and at a maximum at 2400. The reasons for this differing response are not yet understood. One explanation may be that the efferent limb of the reflex arcus, which reaches the sympathetic and parasympathetic nervous system of the heart and the peripheral vasculature, is affected by the sympathetic activity of the body. The plasma concentrations of adrenaline and noradrenaline (epinephrine and norepinephrine) in man, which reflect the sympathetic tone, display significant daily variations which are greatest in the morning hours and least at night. Therefore, decreased activity of the sympathetic tone at night may be responsible for the enhancement of the CSM gain and may heighten the response to CSM.

In summary, our findings support the proposal that the diagnostic and therapeutic value of CSM in patients with unexplained syncope or different rhythm disturbances may vary according to the time interval when that massage is performed.

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Table 1 Mean (SD) of the basal RR value, the absolute changes, and maximal changes in RR intervals

<table>
<thead>
<tr>
<th>Hours</th>
<th>*RR basal (ms)</th>
<th>RR basal (ms)</th>
<th>RR basal (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0600</td>
<td>820.4 (150.1)</td>
<td>818.6 (107.5)</td>
<td>820.4 (150.1)</td>
</tr>
<tr>
<td>1200</td>
<td>829.3 (146.3)</td>
<td>826.4 (105.6)</td>
<td>829.3 (146.3)</td>
</tr>
<tr>
<td>1800</td>
<td>836.8 (150.1)</td>
<td>834.9 (108.2)</td>
<td>836.8 (150.1)</td>
</tr>
<tr>
<td>2400</td>
<td>857.6 (214.4)</td>
<td>855.7 (130.5)</td>
<td>857.6 (214.4)</td>
</tr>
</tbody>
</table>

*p < 0.05.

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administration of conscious sedation during electrophysiology studies, and pacemaker and cardioverter-defibrillator implantations.1

We describe the use of intravenous midazolam in the setting of external electrical cardioversion for atrial flutter/fibrillation without the direct supervision of an anesthetist.

One hundred and forty nine consecutive unselected patients (112 men and 37 women), mean (SD) age 67 (11.8) years, with haemodynamically stable persistent AF were included in this study (December 1998 to June 2000). These included patients from cardiology and general medical/geriatric outpatient departments. The 149 patients underwent a total of 169 cardioversions with 20 patients requiring more than one cardioversion on separate occasions because of recurrence of AF.

The protocol involved obtaining informed consent, ensuring adequate antiocoagulation (international normalised ratio (INR) of 2.0–3.0) for at least four weeks before cardioversion. Patients were asked to fast from midnight before the procedure. Cardioversions were performed in an endoscopy suite equipped with a full resuscitation trolley. The procedure was carried out under the direct supervision of the cardiologist (consultant or specialist registrar) with the assistance of a specialist cardiology nurse. Continuous pulse oximetry monitoring was used to measure oxygen saturation and cardiac rhythm which was continuously monitored on a cardiac monitor. Patients routinely received low flow (2 l/min) oxygen by nasal cannula before and after the procedure. Midazolam was administered intravenously by the physician, 2.5 mg over 30 seconds, and repeated if necessary in 1 mg increments (maximum 12 mg) until the patient developed slurred speech and was not able to move his or her head. When adequate sedation was achieved, the procedure was discontinued if a patient failed to revert to sinus rhythm after at least three synchronised shocks, the latter two shocks being 360 J.

Following the cardioversion, the patient was turned on his or her left side and sedation was immediately reversed in all patients with flumazenil, a competitive benzodiazepine receptor antagonist. The dosage schedule for flumazenil was 200 µg over 15 seconds, then 100 µg at 60 second intervals if required, to a maximum total dose of 1 mg. An anesthetist was always available on site for emergencies. Once the procedure was completed the patient recovered for two hours with vital signs (blood pressure/respiratory rate) assessed every 15 minutes for the first hour and every 30 minutes for the second hour. Patients were asked to walk for 30 minutes before discharge. All patients were reviewed by a specialist cardiac nurse before discharge by use of a questionnaire which asked: (1) Did you find the procedure: intolerable; very unpleasant; mildly unpleasant; not unpleasant? (2) Do you remember anything about the test being done?

### Table 1 Dose of midazolam versus age and number of synchronised shocks

<table>
<thead>
<tr>
<th>Number of synchronised shocks</th>
<th>Number of patients</th>
<th>Mean (SD) dose of midazolam (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106 (63%)</td>
<td>8.3 (2.1)</td>
</tr>
<tr>
<td>2</td>
<td>35 (21%)</td>
<td>8.5 (1.9)</td>
</tr>
<tr>
<td>3</td>
<td>28 (16%)</td>
<td>9.9 (1.7)</td>
</tr>
</tbody>
</table>

(3) Would you be prepared to have another cardioversion done: yes; no.

Multiple regression analysis and analysis of variance (ANOVA, three way) was used to compare dose of midazolam, age, and number of synchronised shocks. A probability value of p < 0.05 was considered significant.

The mean (SD) dose of intravenous midazolam was 8.6 (2.1) mg. The requirement of midazolam varied inversely with age (p < 0.001) (table 1).

The mean (SD) level of synchronised energy necessary for cardioversion was 263 (88) J.

The requirement of midazolam varied inversely with the number of synchronised shocks required for cardioversion (table 1). Four of the 35 patients (11.4%) who required three shocks needed additional midazolam for the second shock. Eight patients of 28 (28%) who required three shocks needed additional midazolam following the first shock.

Pethidine was administered to 54 (31.9%) patients in addition to midazolam to augment sedation. The requirement of pethidine varied inversely with age (q2 linear trend p = 0.001).

No procedure was abandoned because of failure to sedate the patient adequately. The mean (SD) dose of flumazenil was 223 (72.1) µg.

Cardioversion with reversion to sinus rhythm before discharge was achieved in 134 procedures (79%). No patient found the procedure intolerable and only five found it very unpleasant. All patients had total amnesia in regard to the procedure. All patients were prepared to have another cardioversion. One patient developed symptomatic hypotension post-procedure which responded well to intravenous fluids. This did not delay discharge. No patient required intubation, or hospital admission.

Our findings show that conscious sedation with midazolam can be safely administered to patients undergoing elective electrical cardioversion by physicians without the direct supervision of an anesthetist. The patients in our study were unselected and consecutive and a large number of elderly patients (31% > 75 years) were included. This is the largest study in the UK on conscious sedation in patients undergoing electrical cardioversion. Three previous smaller studies (n = 12–33) have shown safety and efficacy of conscious sedation in a similar setting.

Concern regarding the safety of conscious sedation in absence of an anesthetist is valid. In our study, all the attending physicians and the specialist cardiac nurse were trained in airway management and resuscitation. We consider close monitoring and a short sedation period with its immediate reversal following cardioversion contributed to the low complication rate. Flumazenil allowed patients to recover quickly and was associated with no adverse effects consistent with other studies. There was no evidence of a wearing off effect of flumazenil which could result in a recurrence of drowsiness following an initial recovery from sedation. In summary, conscious sedation is a safe and effective method and an alternative to general anaesthesia in patients undergoing electrical cardioversion.

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### Table 1 Dose of midazolam versus age and number of synchronised shocks

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Mean (SD) dose of midazolam (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>36 (21%)</td>
<td>10.4 (1.4)</td>
</tr>
<tr>
<td>60–74</td>
<td>80 (48%)</td>
<td>8.7 (1.8)</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>53 (31%)</td>
<td>7.3 (2.0)</td>
</tr>
</tbody>
</table>

1. Sedation by physician with dexamethasone for DC cardioversion of atrial arrhythmias

External DC cardioversion is a commonly used method of terminating atrial arrhythmias. The chance of procedural success is inversely related to the duration of the arrhythmia. Rapid patient turnover is therefore of importance in managing this condition. In many hospitals, the procedure is carried out under general anaesthesia, necessitating the presence of anaesthetic as well as medical staff. Frequently, it may be difficult to coordinate the availability of the two teams, causing delays to each patient, waste of staff time, and an inefficient service.

We report our experience with physician administered sedation using intravenous diazepam during DC cardioversion, without anaesthetic support. We assessed the safety, efficacy, and cost effectiveness of this approach.

One hundred and forty one patients (63% men, age (SD) 69 (11.3) years) undergoing DC cardioversion in our coronary care unit were studied over 15 months; 119 (84%) had atrial fibrillation (AF), 22 (16%) had atrial flutter. Underlying aetiology is shown in table 1. Sedation and cardioversion was carried out on each occasion by one physician and one nurse, both experienced at cardioversion and trained in advanced life support. Full resuscitation equipment, including facilities for assisted ventilation, was immediately available. Oxygen was administered continuously via a facemask.

Patients were initially given 5–10 mg diazepam intravenously, with further aliquots of 5–10 mg each minute, until adequate...
additional sedation or analgesia. One received midazolam 10 mg after 90 mg diazepam. Two received pethidine 50 mg; one requested additional analgesia, the other received 80 mg diazepam and required four cardioversion attempts. A 65 year old received diamorphine 5 mg in addition to diazepam 80 mg. Despite this, he later recalled a “thump” in his chest but no discomfort. None of these patients, nor the patient who received 100 mg diazepam, suffered any complications.

Respiratory depression occurred in two patients, both female, aged 66 years and 88 years, who each received 25 mg diazepam. In both cases, the arterial oxygen saturation dropped below 90% and responded rapidly to administration of flumazenil 500 µg intravenously. No patient required assisted ventilation. In no instance was the presence of an anesthetist required.

One patient suffered a transient ischaemic attack. This was a 54 year old man in atrial flutter for five days. He had undergone coronary bypass surgery three weeks before and was on aspirin but not anticoagulated.

There were no instances of sustained ventricular arrhythmia or hypotension requiring treatment.

A total of 131 patients (93%) fully completed the questionnaire. No patient recalled any pain. Two (1.5%) recalled a “thump” and a “sensation” in the chest but no discomfort. All patients were satisfied with the procedure and were discharged home the same day.

Our findings are comparable with those of studies reported in the early days of DC cardioversion, which suggested that diazepam produced effective sedation during DC cardioversion, with few adverse effects. 

Respiratory depression is far less common with diazepam than with general anaesthetic agents and occurred in only 1.4% of our patients. Diazepam has been found to produce no significant changes in the arterial P02 or PC02 during cardioversion.

Flumazenil, a benzodiazepine antagonist, is effective at reversing deep sedation in cardioversion patients.

An important advantage of physician administered sedation is the relative ease of organizing procedures. When general anaesthesia is employed, it is often a member of the on-call anaesthetic team who is required to be present. However, the commitments of on-call staff are often such that elective procedures, such as DC cardioversion, are unacceptably delayed or even cancelled. The impact of sedation on both staff and economic resources was recently studied prospectively in 59 patients undergoing DC cardioversion. Subjects were given either a general anaesthetic by an anesthetist or midazolam plus morphine by a physician. As well as proving equally safe and effective, sedation by physician was more convenient and considerably cheaper.

We calculated similar cost savings with our approach. At our hospital, the cost of DC cardioversion per procedure is contracted at £337 under general anaesthesia and £265 under sedation. With our current procedure rate of around 350 per year, this translates into an annual cost saving of over £25 000.

In summary, we have found that sedation by physician with diazepam for DC cardioversion is both safe and effective, providing excellent patient satisfaction and flexibility in arranging procedures. Staff efficiency and patient turnover are improved and costs greatly reduced. Sedation should be administered by staff experienced in its use, in an area where assisted ventilation may be carried out and full resuscitation facilities (including flumazenil) are available.

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