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. 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. 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. Here, we report on successful orthotopic heart transplantation in seven children (four girls, three boys) with severe mitochondrial cardiomyopathy. Mean (SD) age at 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. 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 proteomyopathy 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 cd2 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, azathioprine, 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. 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 biopsies 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 myocardium but also in skeletal muscle. Finally, the remaining patient had a complex III-quinones deficiency both in endomyocardial biopsy samples and in macrobiopsies 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 contra-indicated 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 myocytes or skin fibroblasts, however, 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 defect after 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 essential 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>Patient</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 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 absolute and maximal changes in RR interval (\( \Delta RR_{\text{abs}} \), \( \Delta RR_{\text{max}} \)) at different times within a 24-hour period. The RR interval decreases with increasing age, due to the decrease of the sinus rate and slowing of atrioventricular nodal conduction. However, the plasma concentrations of adrenaline and noradrenaline are higher at dawn than at dusk. The absolute changes in RR interval \( \Delta RR_{\text{abs}} \) have a predictable fashion during a 24-hour period. However, the results may vary among different individuals. Therefore, the response to CSM at different times of the day may influence the clinical significance of the test.

### Table 1

<table>
<thead>
<tr>
<th>Hours</th>
<th>( \Delta RR_{\text{abs}} ) (ms)</th>
<th>( \Delta RR_{\text{max}} ) (ms)</th>
<th>Maximal changes in RR interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0600</td>
<td>820.4 (151.0)</td>
<td>314.8 (507.1)</td>
<td>18.0 (17.31)</td>
</tr>
<tr>
<td>1200</td>
<td>829.3 (146.3)</td>
<td>436.7 (458.6)</td>
<td>19.8 (20.04)</td>
</tr>
<tr>
<td>1800</td>
<td>834.8 (150.1)</td>
<td>474.2 (485.2)</td>
<td>20.1 (21.59)</td>
</tr>
<tr>
<td>2400</td>
<td>857.6 (214.4)</td>
<td>610.2 (609.7)</td>
<td>22.4 (21.52)</td>
</tr>
</tbody>
</table>

The Friedman test was used for the comparison of the maximal change in RR interval at four different times within a 24-hour period. The absolute changes in RR interval \( \Delta RR_{\text{abs}} \) and the maximal change (%) in RR interval were measured for each time (Table 1). The basal RR interval, the absolute changes, and the maximal changes in RR interval were comparable at 0600 and 2400 (p > 0.05) and between 0600 and 2400 (p < 0.05 and \( p < 0.001 \)). The greatest decrease of the sinus rate and slowing of atrioventricular nodal conduction occurred between 0600 and 1200, when the RR interval increases compared to the maximal change in RR interval. As a result, the absolute changes in RR interval are less significant at 0600 and at midnight compared to 2400. The reasons for this differing response are not yet understood. On the other hand, all of the patients underwent CSM. No neurological complications or exaggerated response suggesting hypersensitive carotid sinus syncope were recorded during and after CSM. Standard deviation and mean of the basal RR interval, 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 an increase of the RR interval from 0600 to 2400. The basal RR value (ms) of the patients was comparable at 0600 and 2400 (p > 0.05) and between 0600 and 2400 (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 000 (p > 0.05). Despite the ubiquitous influence of diurnal cycles on the cardiovascular system, it is important to take the time of hospitalisation into account. The remainder of the study population were not taking any drugs at the time of hospitalisation. The preliminary results of this study population were not significant compared to the clinical trials and epidemiological studies, which have been done in multiple comparison test. This means that the CSM assessed by the maximal change in RR interval (%) is not diagnostic. The clinical characteristics of the patients were: hypertension in 58 (38.3%); and compensated heart failure in 11 (5%); ischaemic heart disease in 46 (32%); and short acting general anaesthetic. It is often difficult to schedule cardioversions at a mutually acceptable time for both the anaesthesiologist and cardiologist. Recently, cardioversion gists have become more accustomed to the.
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 anticoagulation (international normalised ratio (INR) of 2–3) 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 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 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 easily arousable by verbal and physical stimuli (Ramsay sedation score 5). Pethidine (25–50 mg) was given intravenously, at the discretion of the physician, to potentiate midazolam sedation. When adequate sedation was achieved, cardioversion was performed with 200–360 J (of synchronised energy used (100 J for atrial flutter). The defibrillator paddles were positioned over the ventricular apex and in the right infraclavicular area. At each cardioversion attempt, serial shocks using higher energy were used if necessary. 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 50 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 routinely assessed 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; no unpleasant; pleasant; very pleasant? (2) Do you remember anything about the test being done? (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 35 patients (11.4%) who required two 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 (r² 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 immediately 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 = 20–23) have shown safety and efficacy of conscious sedation in a similar setting.3-5

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.4-5 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.
sedation was achieved, characterised by somnolence and loss of the eyelid reflexes. Additional agents were used at the doctors’ discretion. DC shock was delivered in the anteroposterior position for patients undergoing DC cardioversion.

Table 1: Aetiology of arrhythmia in 141 patients undergoing DC cardioversion

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>53 (38)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (17)</td>
</tr>
<tr>
<td>VEB</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dressler’s syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

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 20 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 organising 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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