Induced hypothermia as salvage treatment for refractory cardiac failure following paediatric cardiac surgery


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Received 21 September 1998; received in revised form 26 January 1999; accepted 2 February 1999

Abstract

Objective: Following corrective cardiac surgery in infants and children for congenital heart disease, a persistent low cardiac output refractory to conventional modes of treatment is associated with a mortality approaching 100%. We advocate the use of whole body hypothermia to reduce tissue oxygen demand and provide a degree of cellular protection against ischaemia allowing time for recovery. We describe our experience. Methods: Between July 1986 and December 1995, 1885 infants and children underwent surgery (operative mortality, 6%), 1302 requiring cardiopulmonary bypass. Fifty-seven patients had a persistent low cardiac output, impaired respiratory function, decreased urine output and acidosis despite maximal intensive care treatment. Cooling to 32–33°C was therefore started using a thermostatically controlled water filled cooling blanket. Results: Following cooling, there was a fall in heart rate (P < 0.001), a rise in mean arterial pressure (P < 0.001) and a fall in mean atrial pressure (P < 0.001). Significant (P < 0.001) increases in pH and urine output were also recorded. Thirty-one (54%) of the 57 patients treated with cooling survived to leave hospital. No long-term sequelae have been noted in these patients. Conclusion: Induced hypothermia is a useful salvage treatment, in children following corrective cardiac surgery when all conventional treatment has been tried and failed. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Cooling; Hypothermia; Cardiac failure; Paediatrics; Cardiac surgery

1. Introduction

Despite optimal myocardial protection, low cardiac output states following corrective cardiac surgery in infants and children still occur. Exclusion of a potential correctable surgical problem is essential, the low output states are then treated by optimizing ventricular pre- and after load, manipulating myocardial contractility and correcting anaemia, hypoxia and acidosis. When these low output states persist despite maximal therapy, cellular ischaemia worsens and they are associated with a mortality approaching 100%.

Induced hypothermia is a well established technique used primarily during operations involving cardiopulmonary bypass to reduce tissue oxygen demand and provide a degree of cellular protection against ischaemia [1–6]. We initially reported our postoperative experience with induced hypothermia in 1980 [7] and subsequently in 20 patients between 1986 and 1990, in 1992 [5]. We now report our cumulative experience with the use of induced hypothermia for the treatment of intractable heart failure unresponsive to conventional therapy in 57 patients following surgery for congenital heart disease.

2. Methods

Between July 1986 and December 1995, 1885 infants and children underwent surgery, 1302 requiring cardiopulmonary bypass for congenital defects in this unit. There were 114 early deaths for an overall mortality of 6%.

Data was taken retrospectively from ITU charts. Only patients formally cooled to 32–33°C for a persistent low
cardiac output state in the postoperative period were included in the review. Patients cooled for a SVT (four) and those who returned to theatre for further corrective surgery (eight) were excluded.

A low cardiac output state was diagnosed by continuing non-responsive hypotension, poor peripheral perfusion, a widening core-peripheral temperature, oliguria in the presence of normal (or raised) right atrial pressure and a developing base deficit, despite optimization of pharmacological support, biochemical and haematological parameters.

Inotropic support was instituted in all patients and included the use of infusions of adrenaline, dobutamine, noradrenaline, dopamine and nitrates as thought necessary. Metabolic abnormalities such as acidosis, electrolyte imbalance and anaemia were also corrected as far as possible.

All patients were intubated and mechanically ventilated and their blood gases optimized, the FiO₂ being kept to a minimum level to ensure an adequate PaO₂. Positive end-expiratory pressure (PEEP) and inverse ratio ventilation were used if appropriate. Patients were sedated with infusions of midazolam (10–100 μg/kg per h) and morphine (10–100 μg/kg per h) and paralyzed with an infusion of vecuronium (20–100 μg/kg per h).

Patients in a rhythm other than sinus were paced using sequential atrioventricular pacing through epicardial pacing wires.

Regular post-operative echocardiography was performed to exclude any potentially correctable mechanical defect and to exclude the presence of cardiac tamponade. Oliguria (<0.5 ml/kg per h) unresponsive to both adequate atrial pressure and diuretics was treated by peritoneal dialysis.

If the patient continued to deteriorate in the presence of maximal intensive care support, moderate hypothermia (32–33°C) was induced using a thermostatically controlled water-filled cooling blanket placed under the child. This usually took about 1 h to achieve but could be speeded up by placing a wet sheet over the patient and fanning. It is important not to overshoot, cooling should not go below 33°C. Core temperature was measured using a rectal theremistor and peripheral temperature using a skin theremistor placed on the big toe.

Haemodynamic parameters were measured for a 4-h period before cooling and compared with another 4-h period 6 h after the start of cooling. This 6-h period was chosen to allow adequate cooling of all tissues and the attainment of a physiological steady state. Parameters measured were heart rate, right atrial pressure, left atrial pressure (in patients with a left atrial catheter placed during surgery), systemic arterial blood pressure, urine output and core-peripheral temperature difference. The blood gases and acid-base status were also measured. Platelet count and white blood cell count were measured pre-cooling and at 48 h post cooling (or prior to rewarming if this occurred earlier) and were compared with the pre-cooling values.

Operative mortality was defined as death within 30 days or in hospital.

3. Statistical analysis

Statistical analysis was performed using a paired two-way t-test for analysis of changes in parameters following cooling, and an unpaired two-way t-test for comparison between surviving and non-surviving groups. Values were compared pre- and post cooling and thus the patients acted as their own controls. Significance was taken as P = 0.05. Unless otherwise stated, results are given as mean values ± 1 standard deviation.

4. Results

Fifty-seven (4.3%) patients were cooled, mean weight 7.3 kg (range 2.5–33). Table 1 shows the spectrum of the disease in which patients developed low output state. Cooling was commenced 0–118 h postoperatively (mean 20 h) and was continued for mean 65 h (range 1.5–216).

4.1. Changes in measured parameters are shown in Table 2.

Following cooling, mean arterial blood pressure rose significantly from 50 ± 14 to 63 ± 7 mmHg, (P < 0.001). There was a significant drop in heart rate from 174 ± 31 to 142 ± 19 beats/min (P < 0.001), and mean right atrial pressure from 14 ± 4 to 10 ± 2 mmHg, (P < 0.001). There was no significant change in pre-cooling (6.7 ± 3.4°C) and post-cooling (6.1 ± 2.6°C) toe-core temperature differential.

Table 1

<table>
<thead>
<tr>
<th>Anatomical defect</th>
<th>No. patients</th>
<th>Anatomical defect</th>
<th>No. patients</th>
</tr>
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<tbody>
<tr>
<td>VSD</td>
<td>2</td>
<td>RVOTO</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>2</td>
<td>DORV (repair)</td>
<td>1</td>
</tr>
<tr>
<td>VSD</td>
<td>8</td>
<td>DORV (PA banding)</td>
<td>1</td>
</tr>
<tr>
<td>AVSD</td>
<td>7</td>
<td>DORV + TGA</td>
<td>1</td>
</tr>
<tr>
<td>Fallots tetralogy</td>
<td>2</td>
<td>Truncus arteriosus</td>
<td>5</td>
</tr>
<tr>
<td>(repair)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>(Fontan)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TGA (switch)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation + VSD</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA VSD (switch)</td>
<td>2</td>
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</tr>
</tbody>
</table>

VSD, ventricular septal defect; RVOTO, right ventricular outflow tract obstruction; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; B–T shunt, Blalock–Taussig shunt; TGA, transposition of the great arteries; TAPVD, total anomalous pulmonary venous drainage.
A significant increase in pH from 7.37 ± 0.16 to 7.48 ± 0.06 occurred following cooling (P < 0.001). Bicarbonate increased from 20.1 ± 6.2 to 22.7 ± 3.1 mmol/l (P < 0.03). No marked rebound metabolic acidosis was observed during subsequent gradual rewarming.

A significant increase in urine output from 0.78 ± 0.9 to 3.07 ± 2.1 ml/kg per h occurred following cooling (P < 0.001). Cooling resulted in a significant drop in the platelet count from 202 ± 97 to 70 ± 63 (x10^9/l), (P < 0.001). Thrombocytopenia was treated with platelet transfusions although no fixed limit was used below which this transfusion was instituted. There was no evidence of disseminated intravascular coagulation in any child. The fall in platelet count was not associated with increased bleeding. There was no significant change in white blood cell count post-cooling.

There was only a significant difference in the increase in urine output between survivors and non-survivors (P < 0.01).

5. Discussion

Analysis of such a heterogeneous group of patients is always difficult and accepting the difficulties and pitfalls of a retrospective analysis, this series demonstrates that for selected infants and children with a low cardiac output following cardiac surgery which is refractory to conventional treatment, induced hypothermia is a useful salvage treatment. It was thought that all those treated were dying, yet 54% survived after cooling.

The protective effects of hypothermia are thought to be due to a fall in metabolic rate associated with a slowing of temperature-dependent enzymatic reactions [1]. Oxygen consumption falls by around 8% for each degree drop in temperature and at a core temperature of 33°C, oxygen demand falls to approximately 70% of basal rate [1,8]. The cytoprotection seen at moderate hypothermia (33–35°C) is however disproportionate to the degree of hypothermia. This additional protection is thought to result from other mechanisms including reduced anaerobic metabolism whose products are themselves cytotoxic, suppression of oxygen free radicals [9], preservation of a high-energy phosphate store [10] and a specific action on lipid peroxidation [11].

In addition to the possible beneficial metabolic effects, there is also evidence that moderate hypothermia may have a direct beneficial effect on myocardial function, particularly when there is pre-existing ventricular dysfunction [4,12–14]. There may also be some added beneficial direct effect on the failing myocardium, as a result of the decrease in heart rate caused by the direct effect of cold on the sinoatrial node [13,15].

As with any retrospective series spanning a decade that documents the effect of a treatment, there is wide scatter in the pre- and post treatment variables of patients that are subjected to that treatment. Statistically proving that any treatment is solely responsible for a change in outcome requires large numbers. Thankfully the scenario of a low cardiac output state refractory to all conventional treatment is rare and therefore sufficient numbers are not available, given the data scatter to achieve statistical significance in variables between survivors and non-survivors. Similarly it is impossible to scientifically demonstrate the different benefits between survivors and non-survivors. A proposed explanation of how we believe hypothermia increases cardiac output is however incumbent upon us.

The rise in mean arterial pressure is due to peripheral vasoconstriction causing an increase in peripheral vascular resistance. Any increase in afterload does not seem adversely to affect cardiac function because there is a reduction in atrial pressure. The decrease in heart rate following cooling is partly due to a direct effect of cold on the sinoatrial node. Usually both the blood pressure and urine output increase before the heart rate decreases, suggesting that mechanisms other than control of heart rate may be important. We believe this observation is due to the direct benefit of cooling on myocardial function. The improved urine output reflects quantitatively the additional benefit produced by cooling in those patients in whom cardiac function has been enhanced.

Moderate hypothermia has several potentially harmful effects. The oxygen dissociation curve is shifted to the left [2], resulting in an increased affinity of haemoglobin for oxygen at a given PaO2. This reduced oxygen delivery to tissues is partly offset by an increase in free dissolved oxygen by as much as 10% at 33°C [1,2]. Hypothermia increases muscle tone and at the degree of hypothermia used in these patients is usually sufficient to trigger shivering. This increase in muscle activity can increase oxygen consumption by several fold [16] but is prevented by the use of muscle relaxants. Despite known detrimental effects of cooling, this technique however appears safe. The only adverse change we noted was a falling platelet count which was treated by platelet transfusions and was not associated with increased mortality or morbidity from bleeding. Furthermore, cooling has been widely used in the treatment of persistent supraventricular tachycardia with no unwanted side effects.

Table 2
Change in measured parameters (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-cool</th>
<th>Post-cool</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mmHg)</td>
<td>50 ± 14</td>
<td>63 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>14 ± 4</td>
<td>10 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>174 ± 31</td>
<td>142 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Core temp difference (°C)</td>
<td>6.7 ± 3.4</td>
<td>6.1 ± 2.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.37 ± 0.16</td>
<td>7.48 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol/l)</td>
<td>20.1 ± 6.2</td>
<td>22.7 ± 3.1</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Urine output (ml/kg per h)</td>
<td>0.78 ± 0.9</td>
<td>3.07 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count (x10^9/l)</td>
<td>202 ± 97</td>
<td>70 ± 63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White cell count (x10^9/l)</td>
<td>12.0 ± 3.9</td>
<td>10.9 ± 3.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
There are certain points which we have learned following our experience. It is important not to overshoot on cooling, we avoid going below 32°C. Once cool, complete paralysis is essential, the increased oxygen consumption produced by shivering is detrimental. It is sometimes tempting to rewarm early, when the haemodynamics appear more favourable, we now usually avoid rewarming for at least 48 h.

We acknowledge that proving that cooling affected the outcome in these cases is impossible, for the reasons stated, however, subjecting patients to a cheap non-interventional technique, when the outlook is appalling, think of cooling in our experience, it has reduced mortality by over 50%.

It is our belief that the use of moderate hypothermia has played a significant part in reducing the mortality in this extremely ill group of patients.

References


Appendix A. Conference discussion

Dr G. Sarris (Athens, Greece): In your management protocol, when do you decide to use induced hypothermia rather than extra corporeal membrane oxygenation (ECMO)? Conversely, when do you give up hypothermia and switch to ECMO? Presumably, you have ruled out a surgical lesion that would dictate taking the patient back to the operating room.

Mr Dalrymple-Hay: We’ve used ECMO when we failed to get the patient off cardiopulmonary bypass and taken them to ITU on ECMO. However, in the scenario where we have a persistent low cardiac output state that we can’t correct in ITU, we wouldn’t use ECMO, we’d induce hypothermia.

Dr G. Stellin (Padua, Italy): As Dr. Jim Monro gave us the idea of the surface cooling to treat severe low output syndrome in the postoperative period about 8 years ago, we have treated over 40 patients with such a technique and we are sharing similar clinical results. However, it is still not clear to us why surface cooling improves cardiac output, renal function reversing arterial blood gases acidosis. We are undertaking experimental studies in animals at our University in order to scientifically validate these data. I wonder if you have any answer to all my questions?

Mr Dalrymple-Hay: I don’t have any experimental animal data. I can however offer an opinion, because we’ve clearly all thought about it. Aside from the benefit of reducing the metabolic rate with hypothermia due to changes in temperature-dependent enzymatic reactions, I think there is now quite a lot of evidence showing that you get a disproportionate benefit from the reduction in temperature. This is thought to result from other mechanisms, because you get reduced anaerobic metabolism, preservation of high energy phosphate stores, less free radical production. In addition, I think from the myocardial point of view, there is quite good evidence in dogs that you see improvements in myocardial function with cooling if they had abnormal myocardial function precooling. Furthermore, I think the cooling directly slows the heart rate via a direct effect on the sinoatrial node. Therefore, the disproportionate balance of improvement in myocardial function, while raising the peripheral resistance by cooling, allows us to get away with the cooling to 32°C.

Dr M. Wojtalek (Poznan, Poland): Did you use any vasodilators to control rising systemic vascular resistance? That those patients with better urine output survived, don’t you think it means that those with better cardiac output survive and those with worse do not?

Mr Dalrymple-Hay: We don’t have to use any vasodilators for the rising arterial pressure. I’m sure you’re correct that the increase in urine output is a manifestation of better residual myocardial function with cooling.

Dr C. Knott-Craig (Oklahoma City, OK, USA): I noticed that your mean blood pressure prior to cooling was 50 and your mean age of the patients was 8 months, which is probably not a really bad blood pressure if one can equate blood pressure with cardiac output. Does this presuppose that your patients are on a number of inotropes before you decide to cool them? If so, what do you do with your inotropic support once you introduce cooling?

Mr Dalrymple-Hay: Each case clearly is treated on its own merit. Yes, they’re on a lot of inotropes when they’re cooled. We’ve persisted with maximum medical therapy before we cool. Once they are cooled, we would manipulate the inotropes as we felt the haemodynamic parameters permitted through the cooling process and once they were cooled.