Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: is deep hypothermia required?

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Abstract

Objective: To investigate whether deep (\textless -20 \textdegree C) hypothermia is necessary in patients undergoing pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Methods: Between January 2004 and February 2005, 30 patients (New York Heart Association (NYHA) class III or IV) were randomly assigned to increasing (1 \textdegree C) levels of moderate (28—32 \textdegree C) hypothermic cardiopulmonary bypass (CPB), each study group including six patients. Primary study endpoint was adverse neurological outcome. Overall preoperative total pulmonary vascular resistance was 1110 \pm 192 dyne s cm \textsuperscript{-5}. Results: Mean CPB and cross-clamp times, and core temperature at the time of circulatory arrests were 129 \pm 39 min and 92 \pm 24 min, and 30.1 \pm 1.5 \textdegree C, respectively. Circulatory arrest was induced 2 \pm 0.7 times and its mean total duration was 10.3 \pm 5.2 min (range, 2—19 min). Postoperatively, three patients (10\%) belonging to the 31 \textdegree C (\textit{n} = 1) and 32 \textdegree C (\textit{n} = 2) groups suffered from temporary neurological dysfunction. Postoperative mechanical ventilatory support and ICU stay were 26.3 \pm 18.9 h and 6.6 \pm 8.5 days, respectively, and uninfluenced by degree of hypothermia. There were no lung reperfusion injuries or any other major complications. All patients had a significant hemodynamic improvement. Conclusion: Results suggest that pulmonary endarterectomy can be safely performed with moderate hypothermia and short periods of circulatory arrests without the need of profound hypothermia.

Keywords: Chronic pulmonary embolism; Pulmonary hypertension; Pulmonary endarterectomy; Moderate hypothermia

1. Introduction

Pulmonary endarterectomy (PEA) is an established curative surgical therapy for patients with chronic thromboembolic pulmonary hypertension (CTEPH). It includes a bilateral endarterectomy made via a median sternotomy under total cardiopulmonary bypass and deep hypothermia (\textless -19 \textdegree C) with intermittent periods of circulatory arrest (CA) of in average 35 min, indispensable to interrupt temporarily the troubling back bleeding from the systemic-to-pulmonary artery circulation (Fig. 1) [1—3].

However, deep hypothermic circulatory arrests (DHCA) are still associated with a relatively high mortality and a disturbing incidence of neurologic complications [4—7]. We previously provided evidence that an alternative method of brain protection while equally minimizing the backflow can be obtained with similar outcome in patients undergoing PEA using antegrade cerebral perfusion under moderate hypothermia [8]. Stimulated by this past experience, we prospectively investigated whether PEA could be performed under moderate hypothermic circulatory arrest (MHCA) without any additional brain protection.

2. Patients and methods

Between January 2004 and February 2005, 30 consecutive patients with chronic thromboembolic pulmonary hypertension underwent PTE at the Hannover (\textit{n} = 24) and Barcelona (\textit{n} = 6) Medical Schools. Their preoperative profile is listed in Table 1. Overall, the diagnosis of CTEPH was made 35 \pm 21 months before surgery, and all patients were in New York Heart Association (NYHA) functional class III (\textit{n} = 21) or IV (\textit{n} = 9). Seventeen patients had a history of deep venous thrombosis and 13 patients had some coagulation disorders.
2.1. Study design

Patients were randomly assigned to increasing (1 °C each study group) degrees of hypothermia starting from 28 °C, including in each study group five patients, the primary endpoint being the occurrence of neurological adverse event [9]. Written informed consent was obtained. Because of our previous experience [8], no internal review board (IRB) permission was needed.

2.2. Preoperative evaluation

All patients underwent transthoracic echocardiography and contrast echocardiography to determine a patent foramen ovale, radioisotopic ventilation—perfusion scanning, and helical computed tomography scanning. Biplane pulmonary angiography was performed to establish whether pulmonary thromboembolic obstruction was present, to determine its location and extension and to calculate the number of the involved segmental vessels. All patients underwent preoperatively right heart catheterizations with measurements of the right atrial, pulmonary artery and pulmonary wedge pressures, at rest and under vasoactive stimulation. Cardiac output (CO) was determined by thermodilution, and pulmonary vascular resistance was calculated. Other non-invasive examinations included duplex scanning of both, lower and upper extremities, blood gas analysis to detect partial or severe hypoxia and pulmonary functional testing. Absolute surgical contraindications were severe underlying obstructive or restrictive lung disease, renal failure requiring dialysis and malignancy or other end-stage non-cardiac diseases. Coronary angiography was performed in all patients with risks of coronary

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Numbers</th>
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<tr>
<td>Gender (male vs female)</td>
<td>19 versus 11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 12</td>
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<tr>
<td>First diagnosis (months)</td>
<td>35 ± 21</td>
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<tr>
<td>Deterioration (months)</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>21 versus 9</td>
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<tr>
<td>Occluded segments</td>
<td>9.8 ± 1.9</td>
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Table 1: Preoperative profile of patients undergoing pulmonary endarterectomy for chronic postembolic pulmonary hypertension
atherosclerotic disease. All patients received an inferior cava filter before surgery.

2.3. Anesthesiological management

Routine monitoring included five-lead ECG, a triple lumen central venous catheter, a Swan—Ganz thermomonitor catheter via the right jugular vein, radial artery catheters in both radial arteries, pulse oxymetry, capnography as well as blood- and urine-bladder temperature. Online neuromonitoring was with bilateral cerebral oxygen saturation (INVOS®, Cerebral Oximeter, Somanetics, Troy, MI, USA), and EEG (Bis Monitor A-2000, Aspect Medical Systems, MA, USA). Anesthesia was induced in all patients with etomidate (0.3 mg/kg) and fentanyl (0.8 μg/kg); 0.1 mg/kg Pancuronium bromide was used for neuromuscular blockade. During induction of anesthesia, all patients received 500 ml of lactated Ringer’s solution and 500 ml of hydroxyethyl starch (6% HES 200/0.5). Artificial ventilation was performed with low tidal volumes without positive end-expiratory pressure using a standard tracheal tube, because these patients were at high risk for acute right heart failure. For maintenance of anesthesia, all patients received sevoflurane at an end-tidal concentration of 0.5—2%. Repetitive boli of 0.25 mg fentanyl were given every 30 min. During cardiopulmonary bypass (CPB), a second bolus of pancuronium (0.1 mg/kg BW) was injected. According to our institutional standard, to limit ischemic injury a combined drug approach was given (9). Thiopental was infused at an infusion rate of 20 mg/(kg h) to maintain a deep level of anesthesia in the EEG (burst suppression during CA). The head was packed in ice to achieve topical cooling during CA. Additionally as potentially neuroprotective drug 1 g cortisol and 2 ml/kg mannitol (20%) were given.

2.4. Cardiopulmonary bypass management

CPB materials and methods were the same in all patients, including single aortic and bivacal cannulation technique, care being taken to place the superior vena cava (SVC) cannula right at the convergence of the innominate vein. Stoëckert™ roller pumps (Stoëckert Instruments, Munich, Germany) and membrane oxygenators (HiLite® 7000, Medos, Stolberg, Germany) primed with 1500 ml of Ringer’s lactate and 40 ml Natrium bicarbonat 8.4% were used. α-Stat management was applied for interpretation of the arterial blood gas analysis and treatment of the patients during cardiac bypass. Hematocrit was maintained at 25%. To minimize blood loss, all patients received 2,000,000 IU of the kallikrein inhibitor aprotinin applied through the CPB circuit. Initial heparinization was accomplished with 400 IU/kg and further on adapted to the activated clotting time (ACT) greater than 480 s. Anticoagulation was antagonized with protamine sulphate after weaning from CPB.

2.5. Surgical technique

All patients were basically operated using the technical recommendations described previously [8], with few modifications. Cooling was performed to reach the desired temperature, monitored by bladder and nasopharyngeal temperature. After induction of ventricular fibrillation, a cardiac sump was inserted through the right upper lobe vein and directed into the left ventricle to minimize its distension and further decrease the excessive bronchial artery flow. The aorta was then cross-clamped and cold cardioplegia administrated in the aortic root with additional doses being given every 30 min to allow optimal heart protection. After being on total CPB, the SVC was fully transected (after retraction of Swan—Ganz catheter) and using head- and intraoperative-lights, the arteriotomy was started and the endarterectomy made in an usual fashion starting generally on the right side (Fig. 1). The CAs were started only after maximal endarterectomy, usually during lower lobe or segmental endarterectomy and limited to 10 min maximally. During closure of the right arteriotomy, cardioplegia was given again and the left pulmonary artery transected 1.5 cm from its origin on its anterolateral aspects (Fig. 2). After completing the endarterectomy, extracorporeal circulation was resumed, and the patient rewarmed.

2.6. Postoperative management

All patients were placed in volume-controlled mechanical ventilation during the early postoperative period with a PEEP level of 6—8 and a tidal volume of 10 ml/kg BW. Inhaled nitric oxide at doses of 15—20 ppm were given for the first 4 h postoperatively and gradually withdrawn. The postoperative cardiac index was held as preoperative and a positive end-expiratory pressure of 8—10 was set. Low-dose inotropic support was usually necessary in the majority of patients. Continuous intravenous heparin was given as soon as (usually 6 h postoperatively) patient’s stabilization and minimal chest tube bleeding. Oral coumadin was usually started after 48—72 h targeting an international normalized ratio (INR) of 2.5—3.5.

2.7. Statistics

Results were expressed as mean ± standard deviation. Comparisons of pre- and postoperative results were made via the Wilcoxon sign rank test. Simple linear regression was used to analyze the relationship between the ratio of regional cerebral oxygen saturation from pre-MHCA and the duration of circulatory arrest. Mortality was defined as early (before hospital discharge or <30 days after operation) or late. Statistical analysis was performed using SPSS 10.0 software.

3. Results

Mean core temperature at the time of CA was 30.1 ± 1.5 °C (range, 28—32 °C). CA was induced 2 ± 0.7 times (range, 1—3 times). The maximal duration of one CA was 6.2 ± 2.4 min (range, 2—11 min), and total duration of CAs was 10.3 ± 5.2 min (range, 2—19 min). CPB and cross-clamp times were 129 ± 39 min and 92 ± 24 min, respectively. Regional cerebral oxygen saturation (rSO2) decreased from 60.6 ± 6.3% to 32.9 ± 8.8% (rSO2 ratio, 0.54 ± 0.15) at the first CA, and from 59.2 ± 8.6% to 32.6 ± 8.5% (rSO2 ratio, 0.55 ± 0.13) at the second CA. There was a significant correlation between rSO2 ratio and duration of CA at both the first (p = 0.002) and second CA (p = 0.001).
Table 2
Comparison of pre- and postoperative hemodynamic in surviving patients

<table>
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<tr>
<th>Parameters</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>p-value</th>
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<tr>
<td>PAP (mmHg)</td>
<td>57 ± 18</td>
<td>25 ± 7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CI (l/min m²)</td>
<td>1.7 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR (dyne s cm⁻⁵)</td>
<td>1110 ± 192</td>
<td>279 ± 98</td>
<td>&lt;0.0001</td>
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</table>

There were no intraoperative deaths or any major intraoperative complications. One patient (3%) died during hospital stay, he underwent two CAs at 29 °C of 4 and 3 min, with normalization of his preoperative hemodynamics but developed postoperatively while on mechanical ventilation a liver and renal insufficiency and finally multigorgan failure. The duration of postoperative mechanical ventilatory support and ICU stay was 26.3 ± 18.9 h and 6.6 ± 8.5 days, respectively. Three (10%) patients suffered from transient neurological dysfunction (two delayed awakening and one delirium). The former received CAs at 32 °C for 10 and 12 min and 9 and 8 min, respectively, and the latter at 31 °C for 3 and 9 min. No late death occurred.

There was a significant postoperative hemodynamic improvement (Table 2). All surviving patients achieved NYHA class I (p < 0.01) status 4 weeks after discharge and remained in this functional class during the median follow-up time of 18 months (range, 7–19 months) postoperatively.

4. Discussion

Hypothermic circulatory arrest (HCA) has been used for brain protection mainly for thoracic aortic surgery [10,11] but the question which temperature should be achieved remains controversial. There are experimental and clinical evidences that lower temperatures are safer for cerebral protection. Mezrow et al. [12] demonstrated in a canine model that oxygen consumption became progressively lower as temperature was reduced. McCullough et al. [13] showed in a clinical study that the predicted safe duration of HCA at 13 °C was only 29 min, concluding that shorter intervals and lower temperatures than those currently used may be necessary to provide adequate cerebral protection during HCA. However, profound hypothermia is associated with prolonged CPB times, activation of the inflammatory system, and coagulation disorders predisposing to postoperative bleeding and multi-system organ failure [7,11].

Until now, only a few reports have been published regarding MHCA. Yli-Hankala et al. [14] studied neurological outcome after 11 min circulatory arrest at cranial temperatures of 37, 30, 27, 24, and 22 °C in a rat model, and they demonstrated that moderate (30 °C) cooling improved neurological outcome and there was no additional benefit from more extreme hypothermia. Although rats were used, this study indicated that MHCA of short duration may be as possible as an alternative tool for brain protection. Moreover, Safar et al. [15] demonstrated that combination treatments including hypothermia (34 °C) and cerebral blood flow promotion with induced moderate hypertension, mild hemodilution, and normocapnia achieved complete functional and near-complete histologic recovery of the dog brain after 11 min of normothermic ventricular fibrillation cardiac arrest. Before our previous experience [8], the incidence of transient neurological events attributed only to profound hypothermia was less than 9%. In the previous study [8], moderate hypothermia was induced after normothermic circulatory arrest, and the concept is different from our study investigating moderate hypothermic circulatory arrest as the only form of brain protection.

Our mean duration of CAs was 10.3 ± 5.2 min (range, 2–19 min) with no neurological morbidity in patients having hypothermic arrests between 28 and 30 °C. By contrast, patients having higher degree of temperature (>30°) experienced, by almost equal CA times, a significant higher incidence of temporary neurological dysfunction, suggesting a suboptimal brain protection during HCA. The almost 50 fall in the measured regional cerebral oxygen saturation (rSO₂) needs to be further explored. So far, how much decrease of rSO₂ can be clinically tolerated has not been investigated. Higami et al. [16] demonstrated in their comparative study between retrograde and selective cerebral perfusion during aortic surgery that an rSO₂ ratio less than 0.7 could represent a critical lower limit. Mille et al. [17] reported in patients undergoing carotid endarterectomy that an rSO₂ ratio less than 0.8 has a high but not certain negative predictive value. Our rSO₂ ratio 0.55 is extremely lower than that of the previous investigations but it was not associated with increased negative outcome, suggesting that low rSO₂ may be tolerated if the CA time is short under moderate hypothermia.

Whether PE can be achieved with CA only within 15 min is the other question. Jamieson et al. [1] reported their experience of PE in 1500 patients where the mean DHCA time was 35.7 ± 11.9 min. Similarly, Tscholl et al. [3] reported on a mean duration of circulatory arrest of 35 ± 13 min. We previously demonstrated that we could perform PE using antegrade cerebral perfusion instead of HCA, and the mean CA (except the brain) time was 21 ± 10 min [8]. Possible explanations is that we, like Zund et al. [18], transect the superior vena cava but also the anterolateral aspects of the proximal left pulmonary artery as well, minimize the contralateral backflow by occluding via tourniquets the contralateral pulmonary vessels, use maximally cardiac sumps intravascularly and tolerate back bleeding until starting the segmental endarterectomy at the lower lobar arteries. These maneuvers significantly reduce, in our experience, the need of long CA without interfering with the endarterectomy.

In conclusion, this study provides definitive evidence that pulmonary endarterectomy can be safely performed with moderate hypothermia and short periods of circulatory arrests without the need of profound hypothermia.

References

Appendix A. Conference discussion

Dr M. Turina (Zurich, Switzerland): This operation can be quite unpredictable. It can be fairly easy, but you can get into real difficulties. How many times do you have to go down with the temperature because you have a lot of backflow, bad visualization, and very distal disease? Do you have to sometimes change the technique?

Dr Macchiarini: In this last 4 years, when we started the operation we saw immediately that the backflow was unpredictable in very, very few patients. I can remember only two patients of about more than 100. As soon as you do the arteriotomy, you see that the backflow is not controllable, so you need to cool down. Another reason for cooling down was the fear at the beginning with patients who had renal insufficiency and so forth, but this doesn’t happen anymore. The fact is, if you open the pulmonary artery on the right or on the left side at first, at the beginning, and you see that the backflow is uncontrollable despite maximal sump usage, then you need to cool down more, because otherwise you cannot do a good surgery.

Dr M. Zembala (Zabrze (Silesia), Poland): It’s a good message that we can do chronic pulmonary embolism operations in moderate hypothermia. There was a similar message 2 or 3 years ago from our Japanese colleagues. But based on my experience, 73 patients, and the last 28 with zero mortality, still it was previously higher. How many of those consecutive patients did you do in moderate hypothermia, and how did it affect the outcome, moderate versus the San Diego technique, which is the Jamieson technique?

Dr Macchiarini: If I understood the question correctly, how many patients.

Dr Zembala: How many consecutive patients with chronic pulmonary embolism did you do using deep hypothermia?

Dr Macchiarini: Since we stopped this study in February 2005, we are doing all the patients with 28 °C, and I think that we are trying to answer the question why patients who have a pulmonary vascular resistance of above 1300 are doing better under 28 °C than in the previous experience with less degrees.

Dr Zembala: Even type 3 of the Jamieson classification, you don’t find that difficulty with backflow?

Dr H. Ogino (Osaka, Japan): This is a very interesting study. My question is just about reperfusion injury. It’s very interesting that you did not find any reperfusion injury. Reperfusion injury is a very serious problem after the operation. Could you tell us the reason why there was no reperfusion injury? Was it due to hypothermia? Could you tell us?

Dr Macchiarini: Frankly speaking, probably because we are lucky. No, I think that there are several reasons. First, the circulatory arrests were very, very short, a mean of 10 min compared to the 35 min described in the literature. Second, the fact is, by doing 28 °C, I go from our Japanese colleagues. But based on my experience, 73 patients, and the last 28 with zero mortality, still it was previously higher. How many of those consecutive patients did you do in moderate hypothermia, and how did it affect the outcome, moderate versus the San Diego technique, which is the Jamieson technique?

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