Aortic arch repair using hypothermic circulatory arrest technique associated with pharmacological brain protection

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Abstract

Objective: Hypothermic circulatory arrest is a standard procedure for the treatment of aortic arch. However, there is a time limit for this procedure. There is now an urgent need to develop prophylactic measures to extend the time limit. We have used a pharmacological mixture of thiopental, nicardipine and mannitol for all patients undergoing circulatory arrest since 1991 to extend the safe limit. The purpose of this study was to analyze the neurological complications demonstrated by these patients and to evaluate the brain-protective effects of our measure. Methods: The clinical records of 75 consecutive patients undergoing an aortic arch repair using a hypothermic circulatory arrest technique during the past 8 years were retrospectively reviewed. Systemic cooling was continued until a total disappearance of EEG activity. Prior to circulatory arrest, 15 or 30 mg/kg of thiopental, 20 mg of nicardipine and 300 ml of mannitol were infused into the venous reservoir of a cardiopulmonary bypass circuit. Graft replacement was performed in all patients and the extent of replacement was a total aortic arch in 43 patients, a distal aortic arch in 17, a hemiarch in 13 and a total descending aorta in two. Results: The duration of circulatory arrest ranged from 16 to 80 min (mean 41.5 min), and it exceeded 45 min in 37 patients. Operative mortality was 10.7% and two patients died of stroke. Three patients had permanent and three other patients had transient neural deficits. The incidence of stroke was 8.0% as a whole, and no correlation between the incidence of neurological complications and the duration of circulatory arrest was found. A multivariate analysis showed that the duration of circulatory arrest was determined as a predictor of neither operative mortality nor postoperative stroke. Conclusions: The findings of the present study suggest that our pharmacological brain protection appears to be effective for safely extending hypothermic circulatory arrest. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Circulatory arrest; Brain protection; Thiopental; Nicardipine; Mannitol; Neurological complication

1. Introduction

In 1950, Bigelow and colleagues first introduced profound hypothermia [1] to facilitate surgery under conditions such as congenital cardiac malformation [2], aortic arch replacement [3], and neurosurgical procedures [4]. The hypothermic circulatory arrest technique is currently the standard method for aortic arch repair. However, some problems remain regarding the limited time that this technique can be performed, although some methods such as the retrograde cerebral perfusion technique have been introduced. To extend the safe limits of circulatory arrest, we have been using pharmacological mixtures of thiopental sodium, nicardipine and mannitol as prophylactic agents to protect the brain against ischemia in all patients requiring the circulatory arrest technique for aortic arch repairs since 1991. We demonstrated the protective effect of thiopental against cerebral ischemia during circulatory arrest in a previous study [5], in which we indicated the cerebral metabolic rate during circulatory arrest to be lower in patients receiving a high dose (30 mg/kg) of thiopental than a low dose (15 mg/kg) of thiopental prior to undergoing circulatory arrest. The purpose of this study was to analyze the incidence of neurological complications in 75 consecutive patients who underwent surgery using a hypothermic circulatory arrest technique in combination with the above pharmacological brain-protective agents and to investigate the likelihood that these agents can really extend the safe time limits of circulatory arrest.

2. Patients and methods

From November 1991 to November 1999, 75 consecutive patients underwent an aortic arch repair using the hypothermic circulatory arrest technique associated with pharmacological brain protection. The clinical records of these patients were retrospectively reviewed.
They ranged in age from 21 to 83 years, and 64% of them were men. In 37 patients (49%), the operation was performed on an emergency basis; 33 for an acute type A aortic dissection and four for ruptured aortic aneurysms. An aortic arch lesion was an aortic dissection in 50, an atherosclerotic aneurysm in 18, and a pseudoaneurysm in seven.

### 2.1. Surgical technique

For all patients, electroencephalogram (EEG) electrodes were attached as usual. Surgery was performed through a median sternotomy in 54 patients, and through a posterolateral thoracotomy in 21 patients. The femoral artery, which had the stronger pulsation when the patient had an aortic dissection, was cannulated for arterial access in all patients. The right axillary arterial cannulation was added in patients with an aortic dissection in order to avoid a blind pocket phenomenon which has been known to be caused by retrograde perfusion through the femoral artery. A venous drainage cannula was placed through the right atrium, unless the left thoracotomy or the thoraco-retroperitoneal approach was chosen, in which case the main pulmonary artery was cannulated for venous drainage and the left atrium was vented. All patients were placed on cardiopulmonary bypass (CPB) and cooled to achieve profound hypothermia. The whole body was systemically cooled by using a heat exchanger in a pump-oxygenator. Usually, sodium nitroprusside was infused continuously intravenously at a dose of 1 μg/kg per min to cool the body effectively and quickly. To regulate the blood pH during CPB, the alpha-stat strategy was used. In 43 patients who required repairs of both ascending and transverse aorta, the ascending aortic repair, involving an aortic valve repair or replacement, was performed while systemic cooling was progressed. Systemic cooling was continued until the nasopharyngeal temperature reaching 8°C below that at which attendant neurologists confirmed a total disappearance of EEG activity. After the temperature had become constant, 15 or 30 mg/kg of thiopental sodium, 20 mg of nicardipine and 300 ml of mannitol were infused into the venous reservoir of a CPB circuit. Circulatory arrest was established at 5 min after the infusion of these pharmacological agents. After the patients had been placed in the Trendelenburg position, the aortic arch was opened. The aortic arch repair was performed during circulatory arrest and CPB was resumed after aortic arch reconstruction was completed. Graft replacement was performed in all patients and the extent of the replacement in these patients is shown in Table 1. Thirteen patients underwent a resuspension of the aortic valve, seven patients underwent concomitant aortic valve and ascending aorta replacement, and five patients underwent coronary artery bypass grafting. After 5 min passed from the resumption of CPB and the circulatory arrest was deemed to have been sufficiently tolerated, the patients were rewarmed. CPB was terminated after normothermia had been achieved.

### 2.2. Statistical analysis

Quantitative variables that approximated a normal distribution were presented as the mean ± SD. Nominal variables were analyzed non-parametrically using the χ² test. The correlation between the incidence of neurological complications and the duration of circulatory arrest was analyzed using the Spearman rank correlation test. The predictors of operative mortality and those of postoperative stroke were determined by the multivariate logistic regression analysis. Significance was defined as P < 0.05.

### 3. Results

#### 3.1. CPB

The duration of circulatory arrest ranged from 16 to 80 min (mean 41.5 ± 15.5 min). There were 37 patients whose circulatory arrest duration exceeded 45 min and among them, nine patients had a circulatory arrest duration of over 60 min due to the fact that they had either complicated lesions or anatomical abnormalities. The nasopharyngeal temperature at which circulatory arrest was established ranged from 10 to 22°C (mean 14.1 ± 2.1°C).

#### 3.2. Mortality

Operative mortality was 10.7% (8/75). The causes of death are listed in Table 2. Among these eight patients, five patients were ensured to have no neurological complications postoperatively by attendant neurologists. Three patients, who died of an aortic rupture at the anastomotic site, a myocardial infarction and a ventricular arrhythmia, Table 2

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number</th>
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<tr>
<td>Stroke</td>
<td>2</td>
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<tr>
<td>Respiratory failure</td>
<td>2</td>
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<tr>
<td>Graft versus host disease</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Rupture of the anastomotic site</td>
<td>1</td>
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</table>
respectively, died either during or soon after the operation and therefore were not able to undergo a neurological evaluation. Two patients died of stroke. One of these two patients was a 73-year-old man who went into shock due to an acute aortic dissection which ruptured into the left hemithorax and thus he had to undergo an emergency operation. He had preexisting cerebrovascular disease (atherosclerotic occlusion of the basilar artery). Since this patient was not clearly conscious when the emergency operation was started, the stroke may have occurred preoperatively. He died on postoperative day 12 due to cerebral herniation. The other patient was a 59-year-old man with an acute type A aortic dissection who underwent an emergency graft replacement of the ascending and transverse aorta. The duration of circulatory arrest was 46 min. A couple of hours after coming back to the intensive care unit, he suddenly fell into shock because of massive bleeding at the anastomotic site and cardiac tamponade. The severe shock continued even though an emergency reopening was performed and he did not regain consciousness until death. We judged the cause of death in this case to be whole brain ischemia. However, his stroke may not have occurred during circulatory arrest.

3.3. Neurological complications

All patients except for the three patients who died either during or soon after the operation were able to undergo a neurological evaluation. All of them underwent computed tomography (CT) and careful neurological examinations conducted by attendant neurologists after operations. Six patients had neurological complications and three of them suffered permanent neural deficits, and two of these three patients died of stroke (Table 3). The three remaining patients had transient neural deficits and recovered completely prior to discharge.

The relationship between the incidence of neurological complications and the duration of circulatory arrest is shown in Fig. 1. Here, three patients who were not able to undergo neurological evaluation because of death during or soon after the operation were also indicated. The incidence of stroke was 8.0% as a whole. In addition, according to the Spearman rank correlation test, no correlation between the incidence of neurological complications and the duration of circulatory arrest was found ($P = 0.46$).

3.4. Multivariate logistic regression analysis

To identify the independent risk factors of operative mortality and those of postoperative neurological complications, multivariate logistic regression analysis was used. The variables included age, sex, a duration of circulatory arrest, nasopharyngeal and rectal temperature at circulatory arrest, an extent of graft replacement, a method used to reconstruct the brachiocephalic vessels (individual or en bloc reconstruction), an etiology of the aortic disease, a surgical approach (median sternotomy or posterolateral thoracotomy), urgency of the operation, and a history of prior stroke and concomitant procedures (coronary artery bypass grafting, aortic valve replacement, aortic root replacement with coronary artery reimplantation). Regarding operative mortality, no variables were determined to be independent risk factors. On the other hand, regarding postoperative neurological complications, each variable of a posterolateral thoracotomy approach and a concomitant coronary artery bypass grafting was determined to be an independent risk factor (Table 4).

4. Discussion

It goes without saying that surgeons should naturally make all possible efforts to shorten the duration of circula-
tory arrest. However, it is possible that however skillful the surgeons may be, some patients may nevertheless require a longer period of circulatory arrest to repair aortic arch lesions due to either anatomical abnormalities or complex lesions. We therefore need to develop a way to extend the safe limits of circulatory arrest. We have used pharmacological brain-protecting agents consisting of thiopental sodium, nicardipine and mannitol to reduce cerebral metabolism and to extend the limited time allowable for circulatory arrest before cerebral ischemic damages occurs.

In general, profound hypothermia alone is considered to be effective for protecting the brain when circulatory arrest lasts less than 45 min [6,7]. According to the study of large series by Svensson and colleagues [6], an increased stroke rate was evident after 40 min of circulatory arrest, and the stroke rate after 45–59 min of circulatory arrest was 10.7% while that after 60–120 min of circulatory arrest was 14.6%. On the other hand in our series, the incidence of postoperative stroke was 8.0% as a whole and 5.4% in patients in which circulatory arrest duration was over 45 min. Svensson and colleagues warned about the possibility of underestimating the prevalence of strokes in patients with a prolonged circulatory arrest because of marked increase in mortality rate for this group of patients. However, in our study, even if the three patients who were not able to undergo a neurological evaluation because of early death after the operation were included in the stroke group, the postoperative stroke rate in patients with a circulatory arrest over 45 min was 8.1%, which is lower than that reported by Svensson and colleagues.

It remains controversial as to whether or not the brain-protecting agents, which were administered prior to circulatory arrest in our study, contributed to the fact that the prolonged circulatory arrest time did not result in a high prevalence of postoperative stroke. However, according to a multivariate logistic regression analysis, the duration of circulatory arrest was not determined to be an independent predictor of the postoperative stroke in our study, while Ergin and colleagues demonstrated that temporary neurological dysfunction correlated with the duration of hypothermic circulatory arrest [8].

Regarding brain-protective effects of thiopental, our previous study demonstrated that a higher dose (30 mg/kg) of thiopental reduced the cerebral metabolic rate to a greater extent than a lower dose (15 mg/kg) of thiopental even during profound hypothermic CPB. In addition, thiopental is also often used in aortic arch repair [9,10] based on the fact that it has a protective effect against global cerebral ischemia [11,12]. Furthermore, according to a study by Rung and colleagues [13], a high level of thiopental was demonstrated to reduce the cerebral metabolic requirements to the lowest possible level during circulatory arrest in infants. However, thiopental is known to be one of the cardiac depressants[11]. In fact, a small amount of inotropic agents were required during early postoperative hours in all patients. However, there was no significant difference in the amount of inotropic agents required between patients who received low- (15 mg/kg) and high-dose (30 mg/kg) thiopental.

Other than thiopental, we used nicardipine and mannitol to protect the brain against ischemic injury. Nicardipine is one of the well-known calcium antagonists. Cerebral ischemia causes a rapid shift of Ca$^{2+}$ from the extracellular spaces into cells. Nicardipine directly reduces Ca$^{2+}$ entry into ischemic cells [14] and interrupts the posts ischemic cerebral hypoperfusion phenomenon [15] which exacerbates cerebral damage. Mannitol is well known to reduce cerebral edema after ischemia. Mannitol can also scavenge free radicals [16] and thus reduce the degree of tissue damage caused by superoxide radicals. Based on these facts, we used nicardipine and mannitol as brain-protective agents prior to circulatory arrest. However, these drugs have not been demonstrated to be effective under profound hypothermia by any comparative studies. It will be the task of future assignments to prove these drugs to be effective in protecting the brain against ischemic injury when these drugs are administered prior to circulatory arrest.

Many authors have reported the safe limit of circulatory arrest to be from 45 to 60 min [6–9]. Nevertheless, in our study, the duration of circulatory arrest was not found to be related to the incidence of neurological complications while the stroke rate in 37 patients with a circulatory arrest of over 45 min was only 5.4%. The only difference between these reports and ours is the use of brain-protecting agents. Our pharmacological combination of thiopental, nicardipine and mannitol therefore appears to extend the time allowable for aortic arch repairs, although effects of nicardipine and mannitol remain speculative.

The retrograde cerebral perfusion technique appears to be an effective adjunct of hypothermic circulatory arrest technique based on the outcomes described in a recent report [17], although it is unknown as to whether or not retrograde cerebral perfusion actually perfuses the brain because of the interference of component valves at the level of the internal jugular vein [18] and multiple venovenous anastomoses between the deep and superficial cerebral venous drainage systems of the head [19]. Our method of pharmacological brain protection appears to be a simpler way than the retrograde cerebral perfusion technique to extend safe limits of hypothermic circulatory arrest.

On the other hand, according to our multivariate logistic regression analysis, each variable of a posterolateral approach and concomitant coronary artery bypass grafting was determined to be an independent predictor of the postoperative stroke. When the posterolateral approach is

<table>
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<th>Variable</th>
<th>p</th>
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<tbody>
<tr>
<td>Surgical approach (posterolateral thoracotomy)</td>
<td>0.0056</td>
</tr>
<tr>
<td>Concomitant coronary artery bypass grafting</td>
<td>0.0198</td>
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Table 4
Multiple logistic regression analysis with regard to postoperative neurological complications
chosen because of the site of aneurysm and its distal extension, the orifices of the brachiophalic vessels are located at the bottom of the incised aorta and atherosclerotic debris may easily fall into these orifices. In addition, under the lateral decubitus position, de-airing the ascending and transverse aorta is difficult. We connect the vent to the arterial line and flush blood through the left ventricle and the proximal aorta to remove air. Nevertheless, air embolism may occur more frequently in a posterolateral approach than in an anterior approach. To exclude the prevalence of postoperative stroke in a posterolateral approach, we limited the use to the patients with an anterior approach and analyzed the correlation between the incidence of neurological complications and the duration of circulatory arrest. Then, two of 54 patients had neurological complications (3.7%) and the duration of circulatory arrest of these two patients was 46 and 61 min, respectively. Although both patients had circulatory arrest longer than 45 min duration, no statistically significant correlation between the incidence of neurological complications and the duration of circulatory arrest was found. A concomitant coronary artery bypass grafting is required when severe atherosclerosis exists at the coronary arteries, and in such patients, atherosclerosis of the aorta also usually tends to be severe. As a result, it was considered that concomitant coronary artery bypass grafting was determined to be an independent risk factor of postoperative stroke.

5. Conclusions

Our experience is still insufficient to draw any definitive conclusions. In addition, drugs other than thiopental have not been demonstrated to protect the brain against ischemia in any comparative studies. Also, our results may be biased by the small numbers of episodes and the prevalence of episodes in a posterolateral approach. However, about half of all subjects (49%) in this study required over 45 min of circulatory arrest and the majority (95%) of them did not have any neurological complications. The postoperative stroke rate in patients who required a circulatory arrest of over 45 min duration in our study is lower than that recently reported by other authors using the circulatory arrest technique alone. The present study thus appears to suggest that our pharmacological combination of thiopental, nicardipine and mannitol appears to extend the safe time limits of hypothermic circulatory arrest although absolute statistical proof would require a larger prospective study including the control group. Further improvements regarding the composition and dose of the brain-protective agents are expected. The ultimate objective of our study is the development of cerebroplegia which can provide sufficient time to repair complicated aortic arch lesions.

References