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Perfusion Techniques of Profound Hypothermia and Circulatory Arrest for Pulmonary Thromboendarterectomy

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Abstract
One hundred ninety-five patients with the diagnosis of chronic pulmonary thromboembolic pulmonary hypertension have been operated on utilizing a standardized protocol involving profound hypothermia and circulatory arrest. A small subgroup, nine, were identified preoperatively as having heparin-associated thrombocytopenia (HAT). This challenging subgroup of patients was treated during heparin exposure with an investigational, "platelet disaggregating" agent, iloprost.

The surgical procedure of pulmonary thromboendarterectomy requires multiple periods of circulatory arrest under profound hypothermia. Perfusion management of this procedure involves cerebral and myocardial protection, cooling, reperfusion at hypothermia and rewarming, treatment with Iloprost when appropriate, and methods of hemodilution.

Introduction
Pulmonary embolism due to deep vein thromboembolism is a major source of morbidity and mortality. The incidence of pulmonary embolism in the United States likely exceeds 500,000 per year (1). Infrequently (0.5% to 4%), pulmonary embolism results in chronic pulmonary hypertension (2). Chronic pulmonary hypertension may be due to repeated embolic episodes or failure of resolution of the massive embolus, or a combination of both situations (3). Untreated, these patients have a poor prognosis (4).

The incidence of chronic thromboembolic pulmonary hypertension is unknown since many patients are treated under alternative diagnoses for many months to years. This may be due to the nonspecific nature of the two major symptoms, effort dyspnea and fatigue, and the complexity of diagnosis since the physical findings of pulmonary hypertension may be overlooked until evidence of severe right heart failure exists (5). Surgical intervention for chronic pulmonary embolism has been attempted by performing pulmonary thromboendarterectomies unilaterally or bilaterally via thoracotomy or median sternotomy with and without cardiopulmonary bypass (CPB) (3, 6). In our view, it is essential to utilize a median sternotomy and CPB with profound hypothermia and circulatory arrest in these patients. This approach is necessary since the surgery invariably involves bilateral pulmonary arteries, which may require distal arteriotomies, and control of the bronchial collateral flow by circulatory arrest for maximum visualization of the arteries.

Bilateral pulmonary thromboendarterectomy utilizing CPB with profound hypothermia and circulatory arrest has been performed at the University of California San Diego Medical Center, San Diego, California since 1970 on 208 patients. This paper will address the perfusion techniques utilized in the 195 patients who have undergone this procedure since 1983. The patients ranged in age from 15 to 81 years.

Materials and Methods
Intraoperative preparation for this procedure includes insertion of both a radial and a femoral artery monitoring line, a Swan Ganz thermodilution catheter, and a peripheral IV. ECG and EEG electrodes are attached as well as an oxygen saturation monitoring device. Temperatures are monitored by bladder, rectal, and nasopharyngeal devices. Once the patient has been anesthetized and his cardiovascular hemodynamics stabilized, one or two units of autologous blood may be removed for reinfusion post protamine administration.

Prior to anticoagulation, a baseline activated clotting time (ACT) and Sonoclot (a) are performed to assess the patients coagulation status. Beef lung heparin 400 U/kg is administered to anticoagulate the patient with a subsequent ACT and protamine titration test (b) performed to assure adequate anticoagulation prior to CPB. ACT levels are maintained > 480 seconds during CPB.

The CPB circuit consists of a heart lung machine, a hollow fiber membrane oxygenator with integral heat exchanger, a closed venous reservoir, an arterial filter, a filtered cardiomyocyte reservoir, an online blood gas monitor, a venous saturation

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monitor, a blood cardioplegia delivery device, and a myocardial cooling jacket. An autotransfusion device is also utilized. Bypass circuit prime consists of 1500-2000 ccs Plasmalyte, albumin sufficient to provide a 2.5% solution, 100 U/kg of beef lung heparin, 30 mg/kg of methylprednisolone, 30 meq of sodium bicarbonate, and 12.5 gms of mannitol.

The following parameters are monitored during CPB: arterial blood gases; venous saturations; water, blood, nasopharyngeal, bladder, rectal and myocardial temperatures; arterial, central venous and CPB arterial pressures; ECG and EEG; hematocrit, sodium, potassium, glucose, ionized calcium, and ACTs; and blood flow rates with corresponding gas flow rates. The times of aortic cross clamping, cooling, circulatory arrest, reperfusion intervals, and rewarming are recorded.

Conduct of Perfusion

The perfusion circuit is prepared prior to the patient's admission to the OR suite. During line placement, the albumin containing prime is recirculated for as long as possible until the CPB lines are connected to the cannulae. This coating of the tubing with albumin appears to afford a mild protective effect against platelet adherence to the perfusion circuit (7).

Once the patient has been draped, a median sternotomy is performed. The inferior and superior vena cavae are cannulated for venous return. Separate caval cannulae and complete bypass are used to decrease the amount of systemic venous blood returning to the right atrium and thus rewarming the heart. The aorta is cannulated in the standard fashion. A vent is inserted into the pulmonary artery and left atrium (LA) to retrieve the often massive bronchial collateral flow.

Once the perfusion lines are attached, CPB is instituted and cooling begins by maintaining a 10°C gradient between arterial blood and bladder/rectal temperature. At this time, ice bags are placed around the patient's head and the cooling blanket turned on. As the core temperature decreases, the venous saturations increase. We have found that a venous saturation of 80% at 25°C and 90% at 20°C. appear normal due to the decreased metabolic rate. Blood flow rates are maintained at 2.4 l/min/m² throughout the cooling phase to maximize even distribution of cold perfusate to the organs. In the event systemic vascular resistance (SVR) increases during cooling, nitroprusside is administered. Phenytoin 15 mg/kg up to a maximum dose of 1 gm. is administered during cooling. (1)

As the nasopharyngeal and bladder temperatures approach 20°C, a cooling jacket is placed around the heart. Sterile cold saline is recirculated through the jacket utilizing a roller pump. The jacket temperature is maintained at 5-8°C. Immediately prior to circulatory arrest, the aorta is cross-clamped and blood cardioplegia is administered to produce a myocardial temperature of 6-10°C. Generally, additional dosages of cardioplegia are not required and the myocardial temperature remains well below 10°C with the cooling jacket. In the rare event the myocardial temperature increases to 20°C, additional dosages of cardioplegia are administered.

When the bladder/rectal temperatures approach 20°C, thiopental is administered until the EEG becomes isoelectric. At 20°C, all monitoring lines are turned off toward the patient to eliminate the possibility of pulling air into the patient during exsanguination. The arterial pump is turned off and the line clamped. The venous line remains open to exsanguinate the patient into the venous reservoir. Once it is determined that the majority of blood has been removed, the venous line is clamped. Blood is recirculated within the circuit through the arterial purge line attached to the arterial filter and cardiotomy reservoir.

Circulatory arrest is limited to 20 minute intervals and the operation may require from two to five intervals of arrest. Reperfusion at 18°C is instituted until the venous saturation returns to 90% or a minimum of 10 minutes has ensued; then circulatory arrest or very low flow perfusion can be resumed. If the EEG displays any activity, additional thiopental will be administered during the reperfusion intervals. In the event a metabolic acidosis exists, sodium bicarbonate is administered to maintain a normal acid base balance.

Once the endarterectomy is completed, the myocardial jacket is removed and rewarming begins at a blood temperature of 30°C; the aortic cross clamp is removed; ice bags around the head are removed; and 500 mg methylprednisolone is administered. A 10°C gradient is maintained during rewarming. Should the SVR be increased at this time, a nitroprusside drip is started to aid in rewarming. The length of CPB time required to rewarm a patient to a rectal/bladder temperature of 36°C appears to be proportional to the length of time at 20°C and the muscle mass of the patient. Rewarming generally requires 80 to 120 minutes. The heart usually begins a bradycardic rhythm when the blood temperature is 32°C. Also, slow activity returns on the EEG at around 25°C nasopharyngeal, and amplitude increases proportionally to temperature. Mannitol may be given at this point to promote diuresis and, therefore, increase the hematocrit.

During rewarming additional surgery if not performed during cooling, can be completed such as coronary artery bypass grafting or closure of a patent foramen ovale. At the conclusion of CPB, 1 gm calcium chloride is administered prior to termination of bypass. An autotransfusion device is aggressively utilized to retrieve blood loss and process any remaining blood in the bypass circuit.

Cerebral Protection

Post-operative delirium with an increased incidence at 72 hours after surgery has been observed in PTE patients and appears to be directly related to the length of circulatory arrest and profound hypothermia. Cumulative times exceeding 55 minutes of circulatory arrest results in a higher incidence of varying degrees of delirium (8). The clinical impression of an increased incidence of delirium exists when the singular circulatory arrest time exceeds 20 minutes. Therefore, singular arrest time is limited to 20 minutes, at which time the patient is reperfused at 18°C for a minimum of 10 minutes or until venous saturations have returned to pre-arrest levels. Restricting
cumulative circulatory arrest times is limited by the extensive surgical endarterectomies often required in multiple pulmonary arteries to remove the fibrotic emboli.

Multiple pharmacological and management strategies have been implemented to minimize or obliterate cerebral dysfunction due to circulatory arrest and prolonged CPB duration. Due to our low incidence of nontransient neurological deficit or stroke, less than 2%, these approaches may be beneficial. While there are newer approaches to cerebral protection, there is little clinical evidence to support their efficacy.

Glucose-containing solutions are not administered during the intraoperative phase unless blood glucose levels fall below normal values. During transient reversible ischemia, hyperglycemia with corresponding elevation of brain glucose levels will contribute to greater amounts of lactic acid production during anaerobic glycolysis. This cerebral acidosis and the resulting liberation of excess hydrogen ions may result in membrane damage and cellular catabolism (8, 9, 10).

Hematocrits are maintained between 18% to 25% during the periods of profound hypothermia and circulatory arrest.

Phenytoin, an anticonvulsant drug which may reduce calcium influx in the brain, is administered during cooling in dosages of 15 mg/kg to a maximal dose of 1 gm. Phenytoin is administered during CPB cooling. To avoid its myocardial depressant effects and to ensure adequate plasma concentrations during circulatory arrest, phenytoin is administered during CPB (10). Seizure activity has not been observed in the PTE patients postoperatively.

Ice bags are placed around the patient's head during cooling to provide an additional protective effort of hypothermia. The ice bags remain on the patient's head until rewarming.

Thiopental sodium, when administered prior to a cerebral ischemic episode, has been demonstrated to provide a protective effect on the area of hypoxemia by increasing the tolerance of the brain to global ischemia (11). All PTE patients presented receive thiopental when the bladder/rectal temperatures approach 20°C and circulatory arrest is eminent. Thiopental sodium is administered until the EEG suppression is complete. Dosages necessary for EEG suppression vary from 400 mg to 1 gm. Additional dosages of thiopental are rarely necessary for EEG suppression during the periods of circulatory arrest, but are administered if EEG activity resumes. Although we have not experienced the negative inotropic action as described by others (12, 13), this may be due to the lapse of time from administration until separation from CPB, which exceeds two hours.

**Heparin Associated Thrombocytopenia**

Nine patients with chronic thromboembolic pulmonary hypertension have been diagnosed preoperatively as having heparin-associated thrombocytopenia (HAT). The diagnosis of HAT was based on a positive in-vitro heparin-induced platelet aggregation study in the setting of a suggestive clinical history (thrombocytopenia following heparin exposure). This clearly presents a serious dilemma for the physician who must anticoagulate these patients for invasive studies and the PTE.

The mechanisms responsible for HAT remain poorly defined despite extensive investigation. The most recent data presents evidence for a complex interaction between immunoglobulins, platelets, heparin and endothelial cells that may lead to intravascular thrombosis (14). Clinically, severe thrombocytopenia due to aggregated platelets and resulting intravascular thrombosis can be observed (15).

PTE patients in whom HAT tests are positive preoperatively have their prophylactic heparin discontinued immediately and enter an investigational protocol in which treatment by Iloprost (c) is considered. Iloprost, a synthetic analog of PGI2, inhibits platelet activation and does not interfere with other clotting factors in the setting of HAT. Iloprost acts by increasing intracellular levels of CAMP, an important chemical messenger that interferes with all phases of platelet activation. Since the half life of Iloprost is relatively short (15-20 minutes), cessation of infusion results in rapid recovery of normal platelet function and effective hemostasis (16).

On the day of surgery, an Iloprost infusion is begun immediately after the induction of anesthesia. In-vitro platelet aggregating studies are repeated to assure adequate platelet inhibition with Iloprost. An appropriate dose infusion is maintained until protamine administration; after which, the infusion rate is dropped to a low dose for 48 hours postoperatively (17).

In our experience, Iloprost treated patients exhibited varying degrees of hypotension during administration. This hypotension is treated by administration of vasopressors, primarily phenylephrine (18).

Preliminary analysis comparing the postoperative platelet numbers of the HAT-PTE patients treated with Iloprost to the nonHAT patients undergoing similar surgery is comparable. This investigation is being continued at this time.

**Discussion**

Patients suffering from chronic pulmonary hypertension due to chronic pulmonary thromboemboli are afforded treatment for this severely debilitating disease by the operative procedure of pulmonary thromboendarterectomy. Pre-operatively, all patients were classified in the New York Heart Association (NYHA) classes III and IV. Postoperatively, over 95% of the survivors returned to NYHA classes I or II. Mortality, intraoperatively and postoperatively, is 14%.

As stated earlier in this paper, this disease entity is very difficult to diagnosis. The pre-operative assessment is extensive and requires an experienced pulmonologist to identify patients who will not only benefit from this procedure but who in fact have this disease.

Surgically, this procedure is challenging. It requires surgical expertise to identify the intimal layers and tediously dissect the fibrotic emboli from the pulmonary arteries without damage to those arteries.
Perfusion management during PTE surgery is very interesting and requires a fairly sophisticated approach. Monitoring and maintaining the various parameters within a precise spectrum is indeed challenging.

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