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ANAESTHESIA MANAGEMENT WITH DEEP HYPOTHERMIA AND CIRCULATORY ARREST DURING SURGERY FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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Chronic thromboembolic pulmonary hypertension (CTEPH) occurs in 1 to 4% after acute pulmonary embolism. CTEPH can be cured by pulmonary endarterectomy (PEA), which is approved golden standard in chronic condition. There were performed three cases of PEA in Latvian Cardiology Centre during 2013–2014. General anaesthesia under cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrests was provided. The core issue is correct patient selection (in terms of central PA obstruction by thrombus) as well as pulmonary circulation recovery capacity. Neuroprotection was provided by deep hypothermia, topical cooling of the head, Trendelenburg position, mild hypocapnia, Hb 9–10 g/L and pharmacological agents. For screening postoperative cognitive function the mini mental state examination (MMSE) was used before and after the surgery. Postoperative pulmonary vascular resistance index decreased by 56.3% (right ventricular systolic pressure decreased from 93.3 ± 25.7 to 44.5 ± 11.2 mmHg). Before the surgery three patients had NYHA functional class III or IV, at the time of discharge — I or II. In one case moderate (MMSE 18) cognitive disorders was observed at discharge from the ICU. No one died neither in the hospital nor within 30 days of discharge. The surgery improved RV function and pulmonary perfusion with no considerable organ failure, except mild cognitive disorders.

Key words: *pulmonary endarterectomy, neuroprotection, cardiac bypass, pulmonary hypertension, neurocognitive dysfunction.*

INTRODUCTION

Pulmonary hypertension (PH) is a rare and progressive disease that is associated with poor prognosis. According to the clinical classification of pulmonary hypertension, there are five clinical groups of PH (Piazza and Goldhaber, 2011). Specific drug therapy is available for only two of these groups — Group 1 Pulmonary arterial hypertension (PAH) and Group 4 Chronic thromboembolic pulmonary hypertension (CTEPH) (Becatini *et al,* 2006).

CTEPH is defined as mean pulmonary artery pressure higher than 25 mm Hg that persists for six months after pulmonary embolism (PE) is diagnosed (Piazza and Goldhaber, 2011). It is caused by organised thrombi in the pulmonary arteries as the result of non-resolving thromboemboli, formation of fibrosis and remodeling of pulmonary blood vessels (Galie *et al.,* 2009)

Currently, the following specific drug therapy is used for the treatment of PAH: calcium channel blockers, prostanoids, endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and soluble guanylatecyclase stimulators (Galie *et al.,* 2009; Ghofrani *et al.,* 2013). For treatment of CTEPH only one specific drug therapy is available — soluble guanylatecyclase stimulators (Ghofrani *et al.,* 2013). Although results vary, it has been established that CTEPH occurs in 1 to 4% of patients after acute PE (Pengo *et al.,* 2004; Becattini *et al.,* 2006; Tapson and Humbert, 2006). It is almost impossible to determine the overall prevalence of CTEPH, since not all patients with CTEPH have a history of acute PE (Galie *et al.,* 2009). Even though PE may be asymptomatic, there is accumulating evidence that CTEPH may also develop in the absence of previous pulmonary embolism (Hoeper *et al.,* 2006).

Even nowadays, with good diagnostic feasibility, as the symptoms are not disease-specific, CTEPH is under-diagnosed and under-treated, which is shown by statistical studies (Blauwet *et al.,* 2003).

CTEPH can be sub-classified into operable and inoperable forms. Inoperability can be caused by occlusion of distal vessels, patient comorbidities, refusal to undergo surgery, and also inaccessibility of expert surgical centres (Mayer *et al.,* 2011). Surgical pulmonary endarterectomy (PEA) is the therapy of choice and is the only potentially curative treatment for patients with surgically accessible CTEPH, as it leads to a profound improvement in haemodynamics, functional class and survival. (Mayer *et al.*, 2011). The first successful bilateral PEA was performed in 1963 by Houk et al. (Houk *et al.,* 1963).

PEA is a complex procedure. It is performed by experienced specialists, and post-operation mortality can be as high as 5% (Mayer *et al.,* 2011). Patient selection is of great importance. It is necessary to evaluate haemodynamic improvement, which can be achieved post-operatively. Some authors believe that the PEA should only be performed if predicted decrease of pulmonary vascular resistance after performing PEA is greater than 50% (Dartevelle *et al.,* 2004; Keogh *et al.,* 2009).

The aim of the study was to demonstrate anaesthesia management with deep hypothermia and circulatory arrest for pulmonal endarterectomy.

MATERIALS AND METHODS

During 2013–2014, we performed three PEA in Pauls Stradins Clinical University Hospital, Latvian Cardiology Centre. Perioperative routinely collected patient data were analyzed, after the permission by the Ethics Committee for the publication of the medical research had been obtained. Clinically suspected diagnosis was confirmed by pulmonary artery CT angiography with contrast, cardiac catheterisation and transthoracic echocardiography. All the data were collected prospectively. Preoperative pulmonary artery pressure, cardiac index and pulmonary vascular resistance were measured prior to surgical incision. In the postoperative period the same values were compared after 24 h. Standard perioperative monitoring included invasive arterial blood pressure measurements, *Swan-Ganz* catheter for pulmonary artery pressures, once daily chest X-ray, 2D-ECHO and arterial blood gases. The surgery was performed with extracorporeal circulation, deep hypothermia 18 °C, with several periods of total circulatory arrest, in order to facilitate the extraction of the thrombi from pulmonary artery branches. The patients main diagnosis was CTEPH III functional class. Heart failure was the NYHAIII-IV functional class. The mini mental state examination (MMSE) was used for screening postoperative cognitive function. Neurocognitive status was assessed before and after the surgery (tl — first postoperative day, t2 — time of discharge from the ICU).

Surgical technique. PTEAE was performed from the pericardium and the pleural space was not entered in standard cardiac surgical approach via median sternotomy. Dissection was made within the superficial layer of the vessel wall, mobilising the inner part of the vessel containing thrombi and scar tissue. The right pulmonary artery was exposed between aorta and the *vena cava superior,* and an incision was made starting medially and extending beneath the mobilised vena cava superior, but not extending outside the pericardium. Very good visibility is required in a bloodless field to define an adequate endarterectomy plane, and periods of circulatory arrest are necessary because of excessive bronchial blood flow that is usually present. During the episodes of circulatory arrests, dendritically organised thrombi from the right and left pulmonary arteries and their branches were removed (Fig. 1). After surgery patients were referred to the Intensive Care Unit of Cardiac Surgery for successful recovery.

Anaesthesia management. General anaesthesia under CPB with deep hypothermic circulatory arrests for the safe surgical approach was provided (Fig. 2). Perioperative monitoring included: invasive arterial and central venous pressures measurement, measurements of continuous cardiac output (CCO), pulmonary and systemic vascular resistances (PVRI, SVRI) and mixed venous oxygen saturation (SvO_2). Arterial blood gas analysis was performed every 10–30 minutes to estimate glucose, lactate, sodium and potassium levels as well as to monitor mild hypocapnic ventilation. Bilateral constant measurements of regional cerebral oxygen saturation (SrO_2) were provided. Urine output in ml per hour and the difference of core body temperature (Celsius, °C) was measured in rectum and oesophagus. Transoesophageal echocardiography was performed to evaluate anatomical structures of the heart and blood flow in aorta.

Anaesthesia was induced by ketamine 0.75 mg/kg, fentanyl 3 mkg/kg and etomidate 0.2 mg/kg intravenously (i.v.).

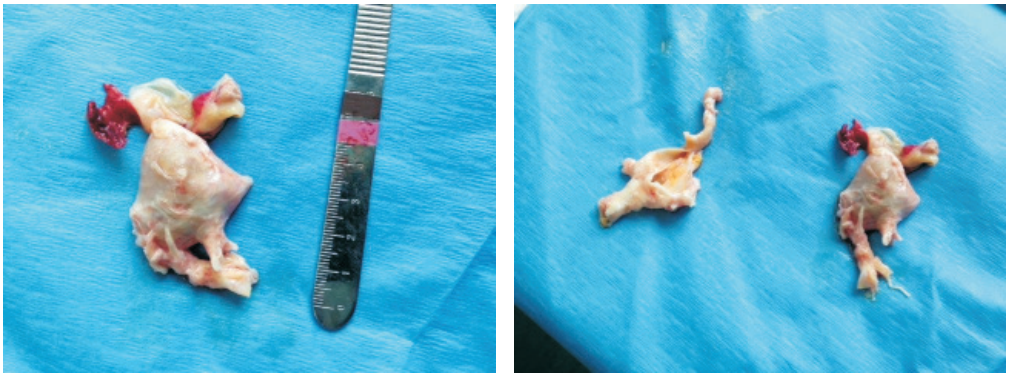

Fig. 1. Thrombus removed from left and right pulmonary arteries.

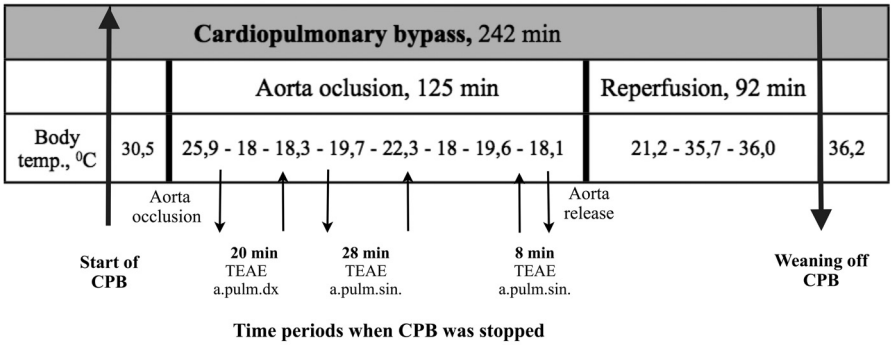

Fig. 2. Cardiopulmonary bypass with deep hypothermic circulatory arrests.

Cisatracurium 0.15 mg/kg was used for muscle relaxation. Mechanical lung ventilation was provided in pressure regulated volume control mode. Anaesthesia was maintained with sevoflurane administered at MAC 0.8–1.0. During CPB, anaesthesia was maintained with fentanyl 0.05 μg/kg/min, propofol 75 μg/kg/min and cisatracurium 1 μg/kg/min i.v. Standard pulsatile CPB with an extracorporeal circuit consisting of a polypropylene membrane oxygenator with deep hypothermia (rectal temp. 18 °C) was used. Before the start of CPB, heparin was administered in a dose of 25 000 units to achieve and maintain activated clotting time above 480 seconds during CPB. The blood was cooled by a pump-oxygenator. During cooling, a 10 °C gradient between blood and bladder or rectal temperature was maintained. Cooling in total took nl — 45, n2 — 55, n3 — 48 minutes. After completion of endarterectomy, CBP was resumed and warming was commenced. During warming a 10 °C temperature gradient was maintained between the perfusate and body temperature. The rewarming period in total took approximately nl — 84, n2 — 94, n3 — 89 min, but varied according to the body mass of the patient. When the patient had been rewarmed to a rectal temperature of at least 36 °C, the CPB was discontinued. After weaning from CPB, protamine was administered i/v in a dose of 1 mg per 100 units of heparin. Despite the duration of CPB, haemostasis was readily achieved, and the administration of platelets or coagulation factors was generally unnecessary. During the surgery normovolemic haemodilution was maintained. Much efforts was applied to provide cerebral protection during the surgery. Therefore, deep hypothermia, local ice applications on the head, Trendelenburg position, mild hypocapnia (arterial blood pCO_2 29–32 mmHg) and haemoglobin around 9–10 g/L were maintained. To reduce cerebral blood flow, i. e. to reduce cerebral oxygen consumption, Thiopental 500 mg × 3 i.v. was administered before each circulatory arrest. Methylprednisolone 250 mg i.v. was given after aortic occlusion and before reperfusion to decrease systemic inflammatory response, which can aggravate ischemia-reperfusion injury. Additionally, 250 ml 15% mannitol solution was added in the CPB system during reperfusion to reduce cerebral oedema.

Postoperative care. The postoperative course was characterised by a marked increase in cardiac output, with a concomitant decrease in pulmonary artery pressures and PVR both immediate and sustained. (Blauwet *et al.,* 2003) Patients were generally mechanically ventilated for at least 24 hours with a maximal inspiratory pressure maintained below 30 cm of water. The fractional inspired oxygen level was kept as low as possible, ensuring an oxygen saturation of over 90%, and the haematocrit level was kept about 27–30–33%. To prevent rethrombosis and reocclusion of the pulmonary arteries after surgery, intravenous heparin infusion was started within eight hours, followed by subcutaneous low molecular weight heparin on the evening of surgery, then by anticoagulation with warfarin as soon as the pacing wires and mediastinal drainage tubes were removed.

RESULTS

The mean patient age was 46 years, with a range of 31 to 67. The mean total cardiopulmonary bypass time was 251 ± 40 min; in one case circulation was stopped twice (24/20 min), and in two cases three times (20/28/8 and 26/17/29 min). The mean aortic cross clamp time was 114 ± 21 min and mean intermittent circulatory arrest time was 21.5 ± 6.9 min. Average rectal temperature during deep hypothermia was 19.1 ± 2.1 °C. The mean preoperative right ventricular systolic pressure was 93.3 ± 25.7 mmHg, and postoperative 44.5 ± 11.2 mmHg. Total cardiopulmonary bypass time correlated with body mass and cooling-rewarming intervals. After surgery a reduction in PA pressures and PVRI to normal levels, corresponding improvement in pulmonary blood flow and CO were generally immediate and sustained (PVRI reduction from 541 ± 33.9 to 236.5 ± 81.3, by 56.3%).

Cerebral protection was monitored with cerebral oximeter INVOS monitoring (Fig. 3) of SrO_2, which had to be equal on the left and right sides. The lowest acceptable limit for SrO_2 is 40% (Fig. 2). Before starting CPB, SrO_2 was equal on both sides, right — 69 ± 5% and left side 70 ± 7%, respectively. The lowest values of SrO_2 during the first circulatory arrest were 38 ± 7% and 44 ± 8%, while in the second circulatory arrest — 30 ± 3% and 28 ± 4%. At those moments circulation was restored shortly until SrO_2 turned back to the baseline. In the third circulatory arrest SrO_2 values were within normal ranges — 70 ± 6% and 68 ± 7%. During weaning from CPB, SrO_2 values were within normal range at 74 ± 6% and 71 ± 5% in right and left sides. In one our case cognitive disorders was observed postoperatively at discharge from the ICU (MMSE 18 points — moderate cognitive impairment). Measurements of lactate, glucose,

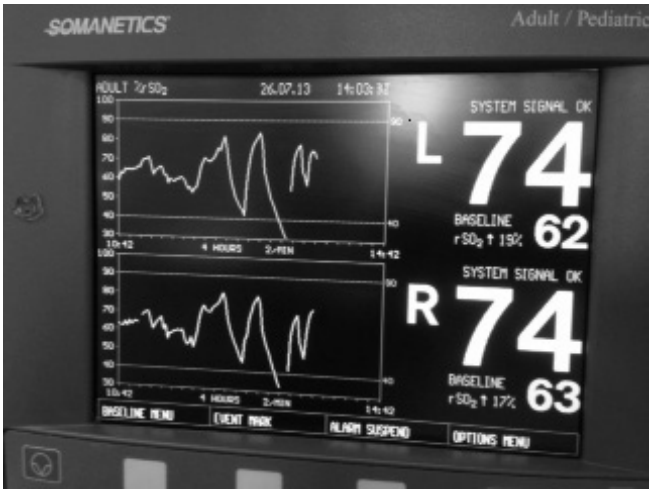

Fig. 3. INVOS cerebral oximetry monitoring during deep hypothermic circulatory arrests.

potassium and sodium levels are essential to evaluate tissue perfusion and acidosis. In the present case the maximum serum lactate level was 5.0 ± 1.3 mmol/L during the reperfusion period. In parallel, acidosis is accelerated in the presence of hyperglycaemia, which compounds ischemic cerebral injury. Therefore, the glucose level was maintained below 10 mmol/L. Before the surgery, three patients had NYHA functional class III or IV, at the time of discharge their NYHA functional class had turned to I or II. Echocardiographic studies have demonstrated that with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts to normal. In general, right atrial and right ventricular hypertrophy and dilation regressed after operation. The median stay in ICU for all patients was three days, and the median duration of intubation was 24 hours. The median length of hospital stay postoperatively was 16 days. No patient died, neither in the hospital nor within 30 days of discharge. The rates of perioperative neurcognitive dysfunction for PTE were similar to those seen with conventional open heart surgery. Successfully performed PTE led to significant reduction of right ventricular chamber size and improved RV systolic pressure. PVRI, SVRI, brain natriuretic peptide may be considered as good markers for efficacy of PEA.

DISCUSSION

The greatest challenge of general anaesthesia during CTEAE is to manage deep hypothermic circulatory arrest, which can lead to tissue hypoxia (Blauwet *et al.,* 2003; Pengo; *et al.,* 2004). Deep hypothermia during circulatory arrest significantly decreases brain metabolism (by 15%) and oxygen demand; the latter helps to reduce anaerobic glycolysis and accompanying acidosis (Dalen and Alpert, 1975; Corsico *et al.,* 2008).

Therefore, deep hypothermia is essential during PTEAE, as it prolongs brain tolerance to ischemia up to 60 minutes (Ishida *et al,* 2012). In the present cases, both pharmacological and non-pharmacological methods for brain protection were used. Additionally, low-flow CPB between circulatory arrests was used to augment brain protection (Kumral *et al.,* 2001; Keogh *et al.,* 2009). Pharmacological protection was achieved by using barbiturates, propofol, steroids and mannitol. Although steroids might lead to glucose metabolism alterations, their role in decreasing proinflammatory cytokines, which are thought to play a role in brain ischemic injury, is pivotal. Disadvantages of deep hypothermic circulatory arrests are prolonged CPB time, which increases risk of coagulopathy, and reperfusion syndrome inducing oedema. Therefore, relative hypovolemia was maintained (Piazza and Goldhaber, 2011; Ozsu and Cinarka, 2013)

Neurological disorders caused by imperfect cerebral protection during CPB with deep hypothermic circulatory arrest may be present in the postoperative period. In the early days of PTE there was a substantial incidence of postoperative delirium with incidence of 3–12%. This can significantly affect patient outcome (Becattini *et al,* 2006; Mayer *et al,* 2011). Studying the cognitive disorders after surgery is one of the pressing issues nowadays. Cognitive and psychoemotional disorders are associated with presence of general pathogenetic factors (phenomenon of isolation and frontal dysfunction) and directly influence each other. Only combined neurocognitive and neuropsychological testing makes it possible to define the presence and degree of the disorder's intensity. MMSE examination is not suitable for making a diagnosis, but can be used to indicate the presence of cognitive impairment. MMSE is far more sensitive in detecting cognitive impairment than the use of informal questioning or overall impression of a patient's orientation.

Cerebral oximetry with the INVOS (IN Vivo Optical Spectroscopy) system provides the possibility of non-invasive, continuous measurement of regional cerebral oxygen saturation (rSO_2), which can improve patient outcome (Ozsu and Cinarka, 2013; Tian *et al.,* 2013).

The cooling was done gradually, long enough to achieve homogenous cooling of all organs. Ice packing on the head enhanced cerebral hypothermia via conduction across the skull. Moreover, it also helped to prevent an undesirable rewarming of the brain during surgery. The rewarming phase was longer than the cooling to avoid brain hyperthermia. Rewarming was stopped when core body temperature reached 36 ^{o}C (Svyatets *et al,* 2010).

Life-long anti-coagulation is mandatory. The administration of iloprost six to eight times a day, with a single dose up to 25 mkg, has been described as more potent selective pulmonary vasodilation, compared to NO inhalation, with superior improvement in gas exchange (Kumral *et al,* 2001; Ozsu and Cinarka, 2013). Recruitment manoeuvres and high positive end-expiratory pressure have been used to prevent reperfusion pulmonary oedema, which develops in the majority of patients, but of variable degrees of severity. In some rare cases extracorporeal membrane oxygenation has been used to overcome this period of life-threatening pulmonary oedema.

In conclusion, our experience in three cases of providing general anaesthesia for PTEAE with deep hypothermic circulatory arrests showed that it was relatively safe, without cognitive disorders and hypoxemia-related complications in the perioperative period. Moreover, it provided good conditions for full extent surgical treatment.

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ANESTĒZIJA PIE PLAUŠU ARTĒRIJAS ENDARTEREKTOMIJAS DZIĻĀ HIPOTERMIJĀ AR CIRKULĀCIJAS APTURĒŠANU

Hroniska trombemboliska plaušu hipertensija (HTPH) ir plaušu hipertensijas forma ko sastop 1–4% pacientu pēc akūtas plaušu artēriju trombembolijas. HTPH „zelta standarta" ārstēšanas metode ir plaušu endarterektomija (PEA). Latvijas Kardioloģijas centrā 2013.–2014. gadā ir veiktas trīs PEA ar vispārējo anestēziju mākslīgajā asinsritē (MAR) dziļā hipotermijā ar cirkulācijas apturēšanu. Labvēlīgu operatīvo iznākumu nosaka pareiza pacientu atlase (pēc centrāla tipa plaušu artēriju obstrukcijas ar trombiem). Intraoperatīvi neiroprotekciju nodrošināja ar nefarmakoloģiskām (dziļā hipotermijā, lokāla galvas dzesēšana, Trendelenburga pozīcija, viegla hipokapnija, Hb 9–10 g/L) un farmakoloģiskām metodēm. Pacientu neirokognitīvo funkciju pirms un pēc operācijas izvērtēja pēc MMSE skalas. Pēcoperācijas pulmonālās vaskulārās rezistences indekss samazinājās par 56,3% (labā kambara sistoliskais spiediens samazinājās no 93,3 ± 25,7 uz 44,5 ± 11,2 mm Hg). Pirms operācijas NYHA FK bija III un IV, pēc — I un II. Izvērtējot neirokognitīvo funkciju, vienam pacientam konstatēja vidēji smagu neirokognitīvu disfunkciju (MMSE 18 punkti). PEA ievērojami uzlaboja labā kambara funkciju un plaušu asinsriti, bez orgānu mazspējas pēcoperācijas periodā, izņemot vidējas pakāpes neirokognitīvu disfunkciju vienam slimniekam.