Thrombosis Research 135 (2015) 410–414

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Retrograde lung perfusion in the treatment of massive pulmonary embolism. A randomised porcine study

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ARTICLE INFO

Article history:
Received 15 September 2014
Received in revised form 23 November 2014
Accepted 1 December 2014
Available online 6 December 2014

Keywords:
Pulmonary embolism
Retrograde perfusion
Cardiopulmonary support

ABSTRACT

Introduction: The treatment of massive pulmonary embolisms with an associated cardiac arrest is controversial; however, surgical thrombectomy with extracorporeal circulation (ECC) is an option for treatment. It is difficult to remove all thromboembolic material. Theoretically, retrograde blood perfusion through the lungs may be beneficial.
Objectives: To investigate whether retrograde blood perfusion through the lungs during a thrombectomy is beneficial.
Methods: Twelve pigs were prepared for ECC. Repetitive injections of preformed blood thrombi into the right atrium resulted in cardiac arrests. ECC was established after 10 minutes of cardiac arrest, and after a sternotomy, the main pulmonary artery was incised and as much thrombotic material as possible was removed from the pulmonary arteries. The pigs were randomised to ECC for one hour either with or without retrograde perfusion in the pulmonary circulation. After one hour, the released material was removed from the pulmonary arteries, and the incision was sutured. The pigs were weaned from the ECC. After sacrificing the pigs, they were autopsied with special attention to the amount of remaining thrombi. Additional histological analyses were performed with special attention to microembolisms, atelectases, and signs of tissue damage.
Results: All of the pigs were weaned from the ECC. The amount of the embolic material removed varied considerably, as did the amount removed after the retrograde or antegrade perfusion, and there was no significant difference between the two treatment modalities. There were no signs of tissue damage in the lungs.
Conclusions: Retrograde lung perfusion was not generally beneficial in the treatment of massive pulmonary embolism in this setup; however, it may be an option if only a modest amount of material is accessible in the pulmonary artery.

Introduction

A massive pulmonary embolism (PE) is a potentially lethal condition. Although evidence for an optimal treatment is scarce, European guidelines recommend thrombolysis for high-risk PE patients as the primary treatment because several studies have shown its beneficial effects on haemodynamic parameters. Surgical embolectomy is another valuable therapeutic option, which should be considered for patients in whom thrombolysis is contraindicated [1]. Because high-risk patients with PE may deteriorate quickly and surgical embolectomy has been shown to be potentially life-saving in some newer studies [2–4], increased therapeutic aggression has been suggested for the most severe cases [5]. We recently suggested using cardiopulmonary support (CPS) as an early option to save a patient's life [6]. CPS using a mobile extracorporeal setup keeps the patient alive while diagnostic procedures are performed, and CPS can be continued when starting treatment despite a cardiac arrest [7]. In our previous porcine model of PE, the use of thrombolysis did not actually dissolve much of the embolic material but did allow the return of spontaneous circulation (ROSC). Although ROSC is the first step in surviving a cardiac arrest caused by a PE, the remaining embolic material may strain or overload the right side of the

Abbreviations: PE, pulmonary embolism; CPS, cardiopulmonary support; ROSC, return of spontaneous circulation; BP, blood pressure; ECC, extra corporeal circulation; HE, haematoxylin-eosin; SD, standard deviation

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http://dx.doi.org/10.1016/j.thromres.2014.12.003
0049-3848/

heart, and removal of the embolic material may be necessary as an additional therapeutic intervention.

Therefore, if surgical removal of the embolic material is selected, it may be simple to remove the material present in the main pulmonary artery and the primary branches, but part of this material, or even most of it, may have passed into the smaller arterial branches in the lung circulation, resulting in difficulties in removing it surgically. After an operation, the circulation may often be impaired, with greater or lesser degrees of right ventricular heart failure. It is possible that this impairment may be due to remaining material or trapped air in vessels or to an overworked right ventricle prior to the operation.

Theoretically, retrograde lung perfusion during an operation with a heart lung machine may be an option in removing material and air from the pulmonary blood vessels. To the best of our knowledge, retrograde lung perfusion has been described in only a few cases, and no randomised trials have been published using retrograde blood perfusion through the lungs to reduce the remaining material in the pulmonary vessels [8,9].

The aim of this study was to test the efficacy of retrograde lung perfusion in a porcine model with induced massive PE, as previously described [6], but with a standard open embolectomy using a heart lung machine combined with retrograde perfusion. Our hypothesis was that a surgical pulmonary embolectomy using extracorporeal circulation with retrograde lung perfusion for one hour would result in a more complete removal of thrombotic material than antegrade lung perfusion.

Material and Methods

The experiments were performed on 12 female Danish Landrace pigs (~80 kg). The study was approved by the Danish Animal Experiments Inspectorate no 2011/561-6 and was in line with the Utstein recommendation for uniformity in animal experiments [10].

Instrumentation and Measurements

The experiments were performed essentially as described before [6]. In brief, anaesthesia was induced with etomidate 40 mg iv. and maintained with infusions of Fentanyl and Midazolam. Mechanical ventilation was accomplished via an endotracheal tube with a tidal volume of 6 ml/kg, a respiratory rate 16 breaths/minutes (adjusted to achieve an arterial pH of 7.4), and a fraction of inspired oxygen of 0.6. The positive end-expiratory pressure was set at 5 cm H_2O. A Swan-Ganz catheter (Baxter Health Care Corporation. Irvine, CA, USA) was introduced into the pulmonary artery via the left jugular vein, and the cardiac output, pulmonary artery blood pressure and core temperature were measured continuously (Vigilance, Edwards Lifesciences, Irvine, CA, USA) and maintained using intravenous fluid etc., as described before [6]. A large bore catheter (Portex tube, ID 8.0 endotracheal tube with the cuff removed, Smiths Medical, London, England) was inserted via the right external jugular vein into the cranial caval vein with the end placed approximately at the right atrium to be used for injections of preformed blood clots. These clots were formed from fifty ml of autologous blood withdrawn in each of six 60 ml syringes, into which 1.5 ml bovine thrombin solution (100 NIH units/ml from Biofac A/S, Copenhagen, Denmark) was added. After 1 hour, the serum was discarded, and the thrombus was placed in a 20 ml syringe, where the outer end was cut; this syringe was put into a conical device placed in a 60 ml syringe connected to the large bore catheter. The thrombi were pressed through the catheter into the right atrium followed by an infusion of approximately 20 ml saline to force all of the material into the heart, where the blood flow carried it to the pulmonary artery. A new thrombus was infused every 10 minutes until circulatory arrest was achieved (after 3 to 6 injections). Circulatory arrest was defined as a systolic blood pressure (BP) below 25 mm Hg, as in the Utstein recommendations [10]. After cardiac arrest, the large bore venous catheters that were to be used for the extracorporeal circulation (ECC) were placed into the jugular vein and into a femoral vein. A 17 French catheter in a femoral artery was used for returning the blood from the heart lung machine, which was a roller pump (Stöckert Shirley, Munich, Germany) with a quadrox oxygenator (Maquet Hirrlingen, Germany). Using the heat exchanger in the Quadrox oxygenator, the blood temperature was kept at a constant temperature of 38–39 °C, the normal temperature for pigs. For further details see reference [6].

Experimental Protocol

Just before the injections of the blood clots, all of the animals were heparinised to an activated clotting time exceeding 800 s. (Haemochrom 301, International Technidyne Corporation, Piscataway, New Jersey, USA). Ten minutes after cardiac arrest, ECC was established using the inserted catheters and the heart lung machine. After the start of ECC, a sternotomy was performed, and a supplementary venous drain was inserted into the apex of the right ventricle, and a 10 French catheter was inserted into the left atrium for retrograde blood infusion in case it was required subsequent randomisation. The retrograde catheter was connected to the arterial side from the heart lung machine via a y-connector to be opened if the pig was randomised to a retrograde flow. The main pulmonary artery was incised, making it possible to extract the thrombus material from the pulmonary artery using a 3 ml Fogerty catheter (Edwards Lifesciences, Irvine, CA, USA).

To avoid bias, randomisation to either the retrograde or antegrade lung perfusion was performed after 15 minutes of removing as much of the thrombus material as possible. ECC was continued for 60 minutes with or without retrograde perfusion for both groups with an open incision in the common pulmonary artery with drainage into the ECC system. All 12 of the pigs were treated in the same manner, except that the retrograde group had the catheter in the left atrium connected to the arterial side of the heart lung machine. This resulted in a retrograde flow of 2–300 ml/minute measured on the pump and a corresponding increase in the amount of aspirated blood from the incision in the main pulmonary artery. After 60 minutes, a new attempt to remove the remaining thrombus material was performed, the opening in the pulmonary artery was sutured, and ECC was continued for 30 minutes before weaning.

The pigs were weaned from the ECC, demonstrating that the animals could survive after the completion of the procedure, and then the pigs were sacrificed. A post mortem autopsy was conducted in all of the animals with special attention to the amount of thrombi in the pulmonary arteries, which were carefully dissected. The thrombi removed surgically before the perfusion, after the perfusion and from the lungs post mortem were weighed. Lung biopsies from the upper and lower parts of both of the lungs were further examined microscopically for tissue damage, intravascular thrombotic material and micro atelectasis.

During the experiments, echocardiography was performed intermittently to demonstrate that the cause of cardiac arrest was due to PE. Due to the porcine cardiac anatomy, a skin incision was performed over the upper part of the rectus abdominis muscles to improve the picture (Fig. 1).

Histological Analysis

After euthanasia, the lung tissue samples were collected, with a sample from the apex and the bases of both the right and left lungs. The specimens were initially immersion fixed in 4 % buffered formalin and subsequently embedded in paraffin. A histopathological examination was performed on 4 μm tissue sections cut from the lung samples. The samples were stained with HE (Haematoxylin-Eosin), Masson´s Trichrome and Fraser Lendrum staining methods using the standard protocols.

To investigate for atelectasis, we used the sections stained with Masson´s Trichrome. Pictures of each section were taken using a