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The effect of deep hypothermia on the human pulmonary circulation

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ABSTRACT

Objective: Acute rises in pulmonary artery pressures following complex cardiac surgery are associated with high morbidity and mortality. We hypothesised that periods of deep hypothermia predispose to elevated pulmonary pressures upon rewarming. We investigated the effect of this hypothermic preconditioning on isolated human pulmonary arteries and isolated perfused lungs.

Methods: Isometric tension was measured in human pulmonary artery rings ($n=24$). We assessed the constriction and dilation of these arteries at 37 °C and 17 °C. Isolated perfused human lung models consisted of lobes ventilated via a bronchial cannula and perfused with Krebs via a pulmonary artery cannula. Bronchial and pulmonary artery pressures were recorded. We investigated the effect of temperature using a heat exchanger.

Results: Rewarming from 17 °C to 37 °C caused a 1.3 fold increase in resting tension ($p<0.05$). Arteries constricted 8.6 times greater to 30 nM KCl, constricted 17 times greater to 1 nM Endothelin-1 and dilated 30.3 times greater to 100 μM SNP at 37 °C than at 17 °C ($p<0.005$). No difference was observed in the responses of arteries originally maintained at 37 °C compared to those arteries maintained at 17 °C and rewarmed to 37 °C. Hypothermia blunted the increase in pulmonary artery pressures to stimulants such as potassium chloride as well as to H-R but did not precondition arteries to higher pulmonary artery pressures upon re-warming.

Conclusions: Deep hypothermia reduces the responsiveness of human pulmonary arteries but does not, however, precondition an exaggerated response to vasoactive agents upon re-warming.

1. Introduction

Complex cardiac surgery, adult or congenital, may be associated with an acute pulmonary hypertension post-operatively. Such cases are often associated with a high morbidity (Bauer et al., 1997).

Deep hypothermia employed during such operations has many beneficial effects, not least the protection from ischaemic damage it conveys to the brain and peripheral organs whilst circulatory arrest can safely be utilised to undertake complex surgical anastomoses. However, its use has been known to cause complications upon rewarming (Morimoto et al., 2008; Shah et al., 2010; Vionnet et al., 2004).

Little is known about the effects of deep hypothermia directly on human pulmonary arteries. We wanted to see if deep hypothermia may precondition pulmonary arteries to heighten tones upon return to normothermia.

We investigated the effects of constrictors and dilators of pulmonary arteries in a dose-dependent manner at deep hypothermia temperatures and at normothermic conditions separately and in combination. Potassium chloride was used to assess constriction dependent on membrane potential mechanisms whilst Endothelin-1 was used to assess constriction dependent on receptor–ligand mediated mechanisms. We used sodium nitroprusside as it is one of the most potent vasodilators known and is routinely used in cardiac surgery to manage systemic and pulmonary hypertension.

2. Methods

2.1. Isolated human pulmonary artery rings

2.1.1. Ethics and harvesting

Ethical approval for this project was obtained from the Regional Ethics Committee (12/LO/1233). Informed written consent was obtained from each patient to use surplus tissue from lung resection surgery for research.

Extralobar (mean internal diameter 4 mm) and medium sized intralobar (mean internal diameter 3 mm) pulmonary arteries were dissected from healthy areas of lung resections from patients with lung cancer. Arteries were cut into 5 mm thick rings.

Abbreviations: KCl, Potassium chloride; SNP, Sodium nitroprusside

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Vessels were mounted on stainless steel wires connected to an isometric force transducer (Dynamometer UFI Devices, UK). The rings were immersed in a 25 ml water jacketed organ bath (Radnoti, USA) containing Krebs–Henseleit (Krebs) solution at either 17 °C for deep hypothermia or at 37 °C for normothermia. The temperature was maintained at either 17 °C or at 37 °C by a heat exchanger (Sorin Biomedica). Vessels were maintained under normoxic conditions using a carbogen based gas (21% O_2, 5% CO_2 and balance N_2) (British Oxygen Company).

2.1.2. Experimental protocols

A resting tension of 1 g was applied and the vessels were allowed to equilibrate for 60 min. Arteries were pre-constricted with 30 nM KCl prior to the experiment. Any arteries not responding to potassium chloride (KCl) were excluded from the analysis.

2.1.3. Effect of Endothelin-1, KCl and SNP on vessels maintained at 37 °C

Endothelin-1. Vessels ($n=4$) were left to equilibrate for 60 min under normoxic conditions at 37 °C and resting tension was recorded. 100 pM–1 nM Endothelin-1 was added to the organ baths and allowed to reach maximum tension.

KCl. Vessels ($n=4$) were left to equilibrate for 60 min under normoxic conditions at 37 °C and resting tension was recorded. 300 μM–30 mM of KCl was added to the organ baths and allowed to reach maximum tension.

SNP. Vessels ($n=4$) were left to equilibrate for 60 min under normoxic conditions at 37 °C and resting tension was recorded. 30 mM of KCl was added to the organ baths and allowed to reach maximum tension. 1–100 μM SNP was then added to the organ bath and allowed to reach maximum tensions.

2.1.4. Differential effect of Endothelin-1, KCl and SNP at 17 °C warmed to 37 °C

The above experiments (depicted in Sections 2.1.1 to 2.1.3, each with $n=4$) were repeated at 17 °C and then the arteries were washed out. They were then rewarmed to 37 °C for 30 min and the experiments were repeated at 37 °C.

2.2. Isolated perfused and ventilated lung models

Informed consent was obtained for human lung tissue obtained from patients undergoing surgery for bronchial carcinoma at Castle Hill Hospital, Cottingham, UK. Ethical approval for this project was obtained from the Regional Ethics Committee (13/NW/0042).

The set-up for the isolated lung is similar to that described by our group before (Bennett et al., 2004) and is illustrated in Fig. 1. The ex-vivo krebs perfused human lung system used in the present study is shown in Fig. 1. Briefly, the lung sample was suspended in a polycarbonate collection reservoir (Sorin Biomedica, Quedgeley, Gloucester, UK) from a force transducer (Thames Side Maywood Instruments Ltd., Tilehurst, Berkshire, UK) to allow continuous measurement of lung weight. The pulmonary arterial and bronchial systems were cannulated. The bronchial cannula was connected to a piston ventilator (Harvard Apparatus Ltd., Edenbridge, Kent, UK) to allow ventilation with room air. A respiration rate of 10 breaths/min and tidal volume of 100–300 ml were set according to the size and airway resistance of the lung sample and maintained for the duration of the experiment. The resultant mean airway pressure was 15 (4.7) mmHg. The pulmonary artery cannula was then connected to the perfusion circuit which consisted of connective PVC tubing (Cobe Laboratories, Quedgeley, Gloucester, UK), which had been primed with 1 l oxygenated Krebs bicarbonate solution to ensure that all air had been evacuated. The perfusate comprised Krebs bicarbonate solution aerated with 95% O_2/5% CO_2 and was circulated to the pulmonary arteries from a second polycarbonate perfusate reservoir (Baxter Healthcare, Compton, Berkshire, UK) via a peristaltic pump (Watson-Marlow, Falmouth, Cornwall, UK). The perfusate temperature and pH were continuously recorded using in line temperature (Terumo UK, Knowsley, Merseyside, UK) and pH (Philips Medical Systems, Leeds, West Yorkshire, UK) probes. The temperature was controlled by a heat exchanger (Sorin Biomedica) and the pH at 7.4 via a pH controller (Medical Physics, Hull Royal

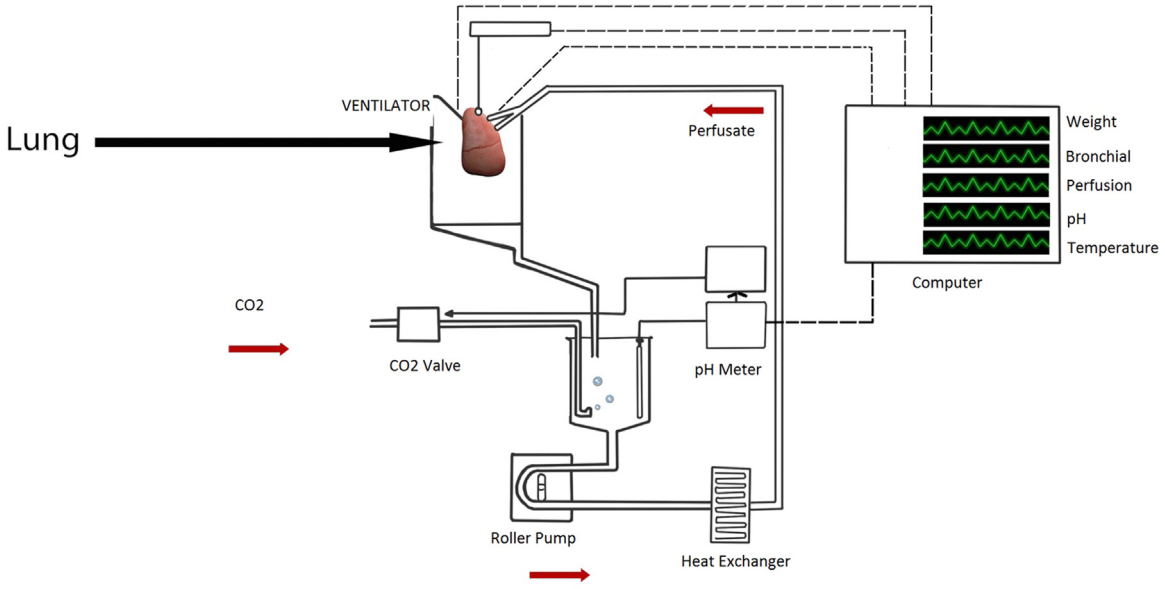

Fig. 1. Isolated perfused lung model: the lung is suspended in a perfusion system from which the weight is recorded. The pulmonary artery (which is perfused mechanically with a roller pump) and bronchus (which is ventilated with an artificial mechanical ventilator) are cannulated and the pressures are continuously monitored on a screen. Carbon dioxide is added to the system to maintain pH as this isolated lung system does not have a renal system to normally maintain pH. Temperature is maintained with a heat exchanger and the temperature of the perfusate is continually monitored.