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Induced hypernatraemia is protective in acute lung injury

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ABSTRACT

Background: Sucrose induced hyperosmolarity is lung protective but the safety of administering hyperosmolar sucrose in patients is unknown. Hypertonic saline is commonly used to produce hyperosmolarity aimed at reducing intra cranial pressure in patients with intracranial pathology. Therefore we studied the protective effects of 20% saline in a lipopolysaccharide lung injury rat model. 20% saline was also compared with other commonly used fluids.
Methods: Following lipopolysaccharide-induced acute lung injury, male Sprague Dawley rats received either 20% hypertonic saline, 0.9% saline, 4% albumin, 20% albumin, 5% glucose or 20% albumin with 5% glucose, i.v. During 2 h of non-injurious mechanical ventilation parameters of acute lung injury were assessed.
Results: Hypertonic saline resulted in hypernatraemia (160 (1) mmol/l, mean (SD)) maintained through 2 h of ventilation, and in amelioration of lung oedema, myeloperoxidase, bronchoalveolar cell infiltrate, total soluble protein and inflammatory cytokines, and lung histological injury score, compared with positive control and all other fluids ($p \leq 0.001$). Lung physiology was maintained (conserved PaO_2, elastance), associated with preservation of alveolar surfactant ($p \leq 0.0001$).
Conclusion: Independent of fluid or sodium load, induced hypernatraemia is lung protective in lipopolysaccharide-induced acute lung injury.

1. Introduction

Acute respiratory distress syndrome (ARDS) has a substantial impact on public health (Rubenfeld et al., 2005). ARDS incidence varies considerably across the world (Bersten et al., 2002; Luhr et al., 1999; Rubenfeld et al., 2005), ranging from 15.3–58.7 cases per 100,000 person-years (Arroliga et al., 2002; Rubenfeld et al., 2005). Attributable mortality also varies with reported ranges of 30–58% (Bersten et al., 2002; Mashonganyika et al., 2009; Rubenfeld et al., 2005; Zilberberg and Epstein, 1998). The difficulties in managing and treating ARDS patients were highlighted by the recent (2009) H1N1 influenza pandemic where intensive care units (ICU) treated an unprecedented number of cases of ARDS (Mashonganyika et al., 2009). However, lung protective ventilation remains the only accepted efficacious treatment strategy (ARDSN, 2000).

Induced hyperosmolarity, facilitates endothelial barrier integrity and is lung protective in lung injury in animal models of haemorrhagic shock and acid-induced lung injury (Quadri et al., 2003; Safdar et al., 2003, 2005; Shi et al., 2002; Wang et al., 2011) and presents a therapeutic option in patients with ARDS. Hyperosmolarity achieved with administration of hyperosmolar sucrose strengthens the lung endothelial barrier through increased E-selectin expression and actin polymerization in the endothelial periphery (Quadri et al., 2003; Safdar et al., 2003) and both protects against and ameliorates acid-induced lung injury mediated through enhanced alveolar type-1 epithelial cell repair, down regulation of inflammatory mediators and immune cell adhesion molecules (Quadri et al., 2003; Safdar et al., 2003; Shi et al., 2002; Wang et al., 2011).

Administration of intravenous resuscitation fluids is a common practice in patients with ARDS (Myburgh et al., 2012; Perner et al., 2012; Rivers et al., 2001); however, the safety of systemic administration of intravenous sucrose in humans is not known and there are major concerns with the use of synthetic colloids (Myburgh et al., 2012; Perner et al., 2012). Administration of hypertonic saline is common in management of patients with raised intracranial pressure (Cooper et al., 2004) and it leads to hypernatraemia and as a result increased osmolarity and hence could serve as an alternative

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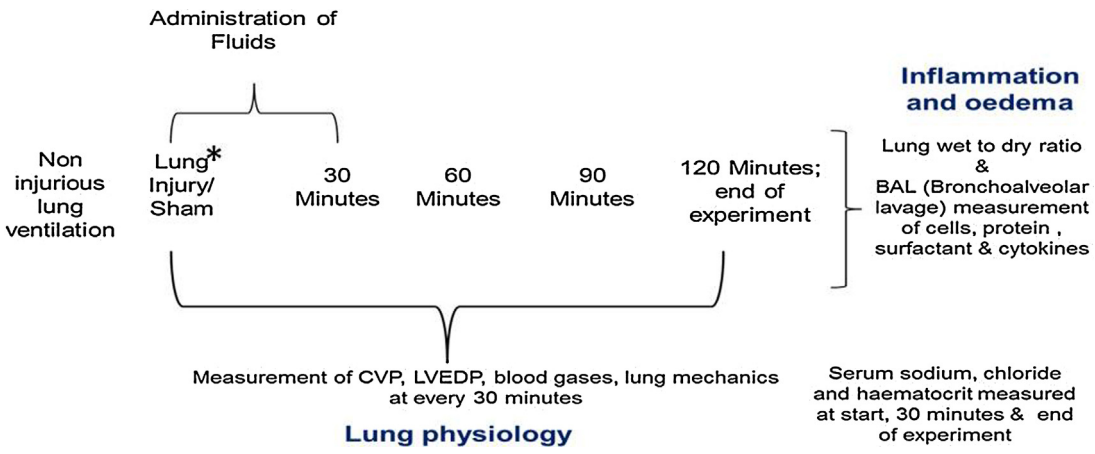

Fig. 1. Study protocol.
*LPS/Sham (0.9% saline) was instilled through a tracheal catheter in three separate volumes. Rats received normal ventilation for 5 min after each instillation to stabilize. Fluid administration began after this.
Rt carotid artery: left ventricular end diastolic pressure (LVEDP); Rt femoral artery: blood pressure monitoring and blood sampling; Rt femoral vein: for administration of drugs and fluids; Lt femoral vein: central venous pressure (CVP); tracheostomy-lungs ventilated via a computer controlled small animal mechanical ventilator (flexiVent, SCIREQ) capable of measuring lung mechanics.

to sucrose in increasing osmolarity. We therefore hypothesised that induced hypernatraemia through administration of intravenous hypertonic saline would lead to an increase in serum osmolarity and the amelioration of LPS-induced lung injury. In this study we compared the effect of hypertonic saline with other commonly utilised fluids in the ICU, controlling for the amount of fluid and sodium load, in a rat model of lipopolysaccharide (LPS)-induced lung injury.

2. Methods

2.1. Animal model of acute lung injury

All experiments were approved by the Flinders University Animal Welfare Committee (approval number 812.12) and performed according to the National Health and Medical Research Council of Australia's code for the care and use of animals for scientific purposes, 8th edition 2013.

Pathogen-free male Sprague-Dawley rats (250–280 g) were used in all experiments. Briefly, rats were anaesthetised with 1% inhaled isoflurane (Forthrane, Abbott Australasia) and the right femoral vein and artery catheterised for maintenance via continuous intravenous infusion of thiopental (60 mg/kg/h; Abbott Australasia) and for arterial blood sampling and pressure monitoring, respectively. A tracheotomy was performed and the lungs ventilated via a computer controlled small animal mechanical ventilator (flexiVent, SCIREQ Scientific Respiratory Equipment, Montreal, Canada) with 100% oxygen for 15 min to stabilise at a tidal volume (Vt) of 6 ml/kg body weight, breathing frequency (f) of 120 min^{-1}, positive end expiratory pressure (PEEP) of 2 cmH_2O using a constant flow waveform where Ti/Ttot = 0.3. Rats were paralyzed with a bolus injection of pancuronium bromide (1 mg/kg i.v.; Astra Zeneca, Bedfordshire, UK) maintained by continuous infusion (0.2 mg/kg/h i.v.) and kept at 37 °C with a temperature-controlled heat pad. Central venous pressure—CVP was continuously monitored through cannulation of the left femoral vein. Similarly, continuous left heart pressure monitoring was achieved by cannulation of the right carotid artery with advancement of the cannula through to the left ventricle (left ventricular end diastolic pressure—LVEDP). Both were monitored using disposable pressure transducers (Sorenson Trans Pac; Abbott Critical Care Systems, Chicago, IL) connected to a MacLab system (AD Instruments, Sydney, Australia).

LPS (Escherichia coli O55:B5, 15 mg/kg in 0.9% saline, Sigma-Aldrich, St Louis, MO) was instilled through a tracheal catheter in 3 separate 0.1 ml volumes, each volume was followed by a 3 ml air bolus and a respiratory recruitment manoeuvre of 2.5 × Vt and PEEP of 10 cmH_2O for 15 s (Dixon et al., 2009). Sham treatment rats received 15 mg/kg 0.9% saline. Rats received normal ventilation as above for 5 min after each instillation to stabilize. Following LPS or saline instillation, rats were ventilated for 2 h, as above. Study plan with description of measurements and time intervals is shown in Fig. 1.

2.2. Fluid administration

Following intra-tracheal LPS administration animals was randomized into the following fluid groups: no fluid-positive control (*it lps/nf*), 20% saline (*it lps/20% saline*), 0.9% saline (*it lps/0.9% saline*), 4% albumin (*it lps/4% albumin*), 5% glucose (*it lps/5% glucose*), 20% albumin (*it lps/20% albumin*) and 20% albumin with 5% glucose (*it lps/20% albumin + 5% glucose*) (n = 6 for each group). Negative control animals (*it S/nf*) received no intra-tracheal LPS or intravenous fluids (n = 6). The fluids were chosen to compare 20% saline with the other commonly utilised fluids in the ICU, controlling for the amount of fluid and sodium load.

All fluids were administered at a constant rate over 30 min through the right femoral vein (Fig. 1). Dose rates and total sodium and albumin delivered for each of the treatment groups is described in Table 1

2.3. Measurement of respiratory mechanics

Respiratory mechanics (airway (Newtonian) resistance (Raw); tissue resistance (Gtis) and tissue elastance (Htis) were measured before instillation (baseline), 5 min after the last intra-tracheal instillation of either LPS or saline (start) and every 30 min thereafter for the duration of the experiment (Fig. 1), to determine lung impedance (Z) using the computer-controlled ventilator, as described previously (Davidson et al., 2002). Briefly, 2 min after a recruitment manoeuvre (2.5 × VT), impedance of the respiratory system was measured following a forced oscillation. The data were fitted to the constant phase model (Hantos et al., 1992) $Z = Raw + jI + (Gtis - jHtis)/(2\pi f)\alpha$, where I is inertance, j is the