Characterisation of lipopolysaccharide induced pulmonary oedema in rats by MRI

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INTRODUCTION

Lipopolysaccharide (LPS) is an ubiquitous endotoxin and is well known to induce pulmonary inflammation associated with neutrophil infiltration. It produces many of the pathophysiological features of acute respiratory distress syndrome (ARDS) including rapid pulmonary oedema development, causing airflow obstruction, and neutrophil influx to the lungs which is associated with tissue damage. ARDS has three main phases; oedemic, proliferative and repair, and fibrotic. Before proliferation and repair can take place, the inflammatory process and injury must diminish. The earlier the repair process begins, the less damage is likely to be done to the alveolar membranes and so the reduced chance of fibrosis and permanent lung damage in addition to the benefits of earlier lung clearance. It is therefore important to understand the processes and mechanisms in early phase ARDS in order to develop therapeutic intervention.

Magnetic resonance imaging (MRI) has been used for *in vivo* animal imaging of lung disease[1]. MRI has been used as a tool to evaluate the oedemic regional distribution[2], and its appearance[3] at time-points extending to several days after LPS challenge. This abstract describes the temporal characteristics of early stage (<4 hours post LPS challenge) LPS induced oedema using MRI.

METHODS

LPS administration: Lung inflammation was induced in 17 female Sprague Dawley rats (200g-250g) with LPS i.t. (400µg/kg).

MRI imaging: Animals were then scanned continuously by MRI (Bruker 7T horizontal bore, 6 minute scan time) following LPS challenge, pilot scans and animal positioning. Parameters used: gradient echo (GE) FOV 6 x 6cm, slice thickness 1mm, TR/TE 10/1.1, 16 averages, receiver gain 5000, 15 slices, coronal section, non-triggered.

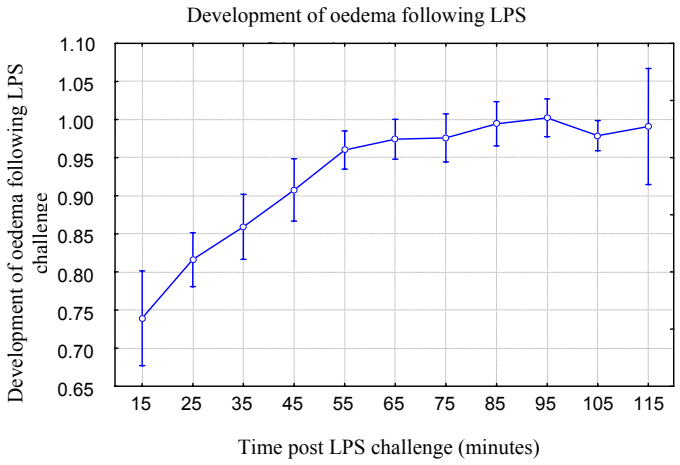
Image analysis: Images were acquired using Paravision software and analysed using in-house developed contour based region analysis software and volume quantification software.

RESULTS

The development of pulmonary oedema following i.t. challenge of LPS is displayed in graph 1 where oedema volume is normalised to baseline (pre-oedema development) lung volume and presented as a percentage of the total, final oedema volume. MR detection of pulmonary fluid (Figure 1) occurs within 15 minutes post LPS instillation and increases in volume (from 70% of total oedema to 95% of total oedema) gradually up to 180 minutes from dose. After 180 minutes post LPS challenge, the oedema development plateaus and the volume becomes stabilized. Often, it is impossible to scan earlier than 20 minutes post LPS dose due to positioning and pilot scans. This illustrates that the majority (up to 80%) of the final oedema volume will develop within the first 20 minutes post LPS dose.

The final oedema volume that develops was variable between animals depending on size of animal, lobes affected and technique of i.t. administration. The final oedema volume is 59.9% ± 10.7% of the total lung volume pre oedema development (n=17). The mean final oedema volume was 2.31 mL ± 0.63 mL (n=13) where an average 200-250g female Sprague Dawley rat lung had an MRI measured lung volume of 3.91 mL ± 0.52 mL (n=20).

Graph 1. Rats (n=17) were challenged with 400µg/kg LPS i.t. Oedema was measured by MRI over time. Oedema volume was calculated at each time-point using in-house image analysis software and normalized to baseline lung volume and expressed as fraction of the final oedema volume. Mean ± SE.



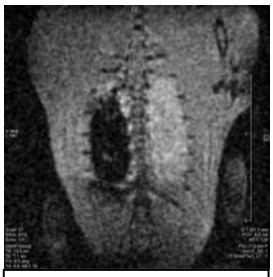


Figure 1. Typical coronal GE MR image of rat lung. Left lobe is oedema filled. Right lobes are air filled.

DISCUSSION AND CONCLUSION

This study demonstrates that MRI is a sensitive tool for the detection of pulmonary oedema. It allows the accurate repeat measurements of oedema and so enables the quantitative characterisation of oedema over time. The processes involved in ARDS development are not fully understood and there are few studies which characterise its early stages. It is known that early resolution and clearance of oedema in ARDS is related to improved patient recovery and survival. This study contributes towards our understanding of the early stages of pulmonary inflammation development. This MRI model also provides a quantitative 'real-time' tool to test therapeutic intervention.

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