Macrophages were cultured with vehicle control (VC) or 2μg/ml lipopolysaccharide (LPS) plus 20μg/ml peptidoglycan G (PepG), to mimic sepsis, and 0.1/10/100μM 6OHM for 4h. Acid phosphatase activity was used as an indication of cell metabolic activity (viability). Caspase-1 activation was assessed using flow cytometry and supernatant levels of IL-1β were measured using enzyme immunoassay. Quantification of the NLRP3 inflammasome and sirtuin-1 was performed with flow cytometry, while pyroptosis was quantified using a luminescence assay. Nuclear factor κB (NFκB) translocation was assessed using imaging flow cytometry. Statistical analysis was performed using Kruskal-Wallis and Mann-Whitney U tests.

6OHM prevented the decrease in acid phosphatase activity ($p=0.0002$) and reduced caspase-1 activation under conditions mimicking sepsis ($p=0.0008$). Additionally, pyroptosis was higher in macrophages treated with LPS/PepG/6OHM than with LPS/PepG alone ($p=0.0001$) (Fig. 1). 6OHM also reduced NFκB translocation in macrophages incubated with LPS/PepG ($p=0.005$).

These results provide an insight into the mode of action of 6OHM in inflammation and suggest that 6OHM may have a therapeutic role in sepsis. Further work is required to describe the mechanisms behind the effects observed in this study.

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Myocardial inflammation after major non-cardiac thoracic surgery

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Following major non-cardiac surgery, large numbers of patients have biochemical evidence of perioperative myocardial injury (PMI) associated with increased perioperative and long-term morbidity and mortality.[1] Recent work suggests inflammation is a major driver of PMI.[2] Our research group have previously demonstrated right (but not left) ventricular dysfunction in patients undergoing lung resection and hypothesised that an inflammatory injury to the right ventricle (RV) was implicated in its aetiology.

With informed consent and ethical approval, 15 patients undergoing lobectomy underwent T1-weighted cardiac magnetic resonance imaging (CMR) pre and post contrast; pre-operatively, post-operative day two (POD2) and at 2-months. Imaging correlates of myocardial inflammation, native T1 time and extra-cellular volume (ECV) were measured on CMR in the LV and RV (at the ventricular insertion points) using Circle cvi42 (Calgary, Canada) post-processing software.

As previously reported, RV ejection fraction fell post-operatively from 62.3% (9.2) pre-op to 51.7% (9.6) on POD2 ($p=0.001$) whilst left ventricular ejection fraction was unchanged over time ($p=0.90$). Both native T1 time and ECV were significantly increased in the RV, but not in the LV (T1 changes depicted in Fig. 2); ECV rose from 25.9% (3.2) pre-operatively to 43% (4.4) on POD2 ($p=0.001$), with no change in LV ($p=0.50$).

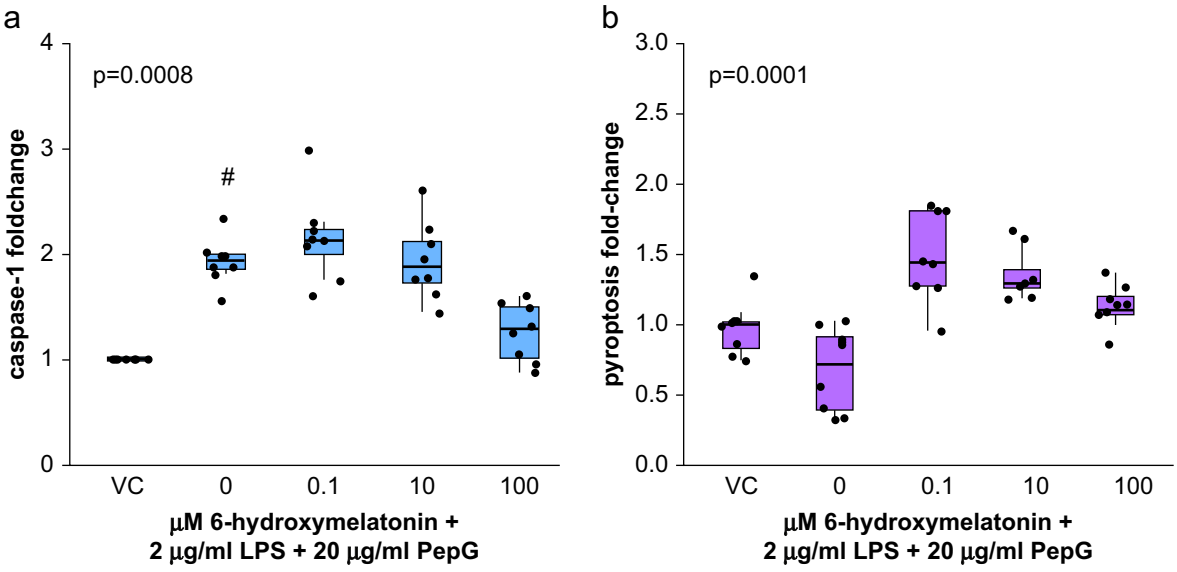

Fig 1. (a) Caspase-1 activation and (b) pyroptosis in THP-1 macrophages incubated with LPS/PepG and 6OHM (n=8). Data are shown as data points with box and whisker plots showing median, interquartile range and full range. P value shown is Kruskal-Wallis.

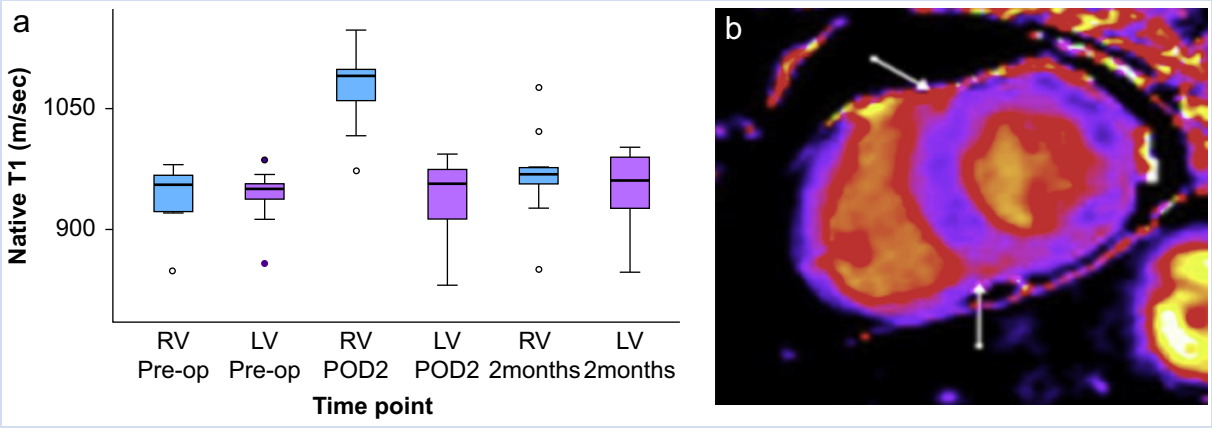

Fig 2. **Comparison of native T1 values in the RV and LV and a native T1 map.** Image **a** demonstrates a change in native T1 value over time at the RVIPs (blue) (p =0.001 Friedman's) and the LV (purple) (p =0.60 Friedman's). Values are median and IQR. Image **b** is a native T1 map from POD2 in a 57-year-old woman undergoing lung resection. The arrows in white highlight an area of increased native T1 at the RVIPs.

This is the first study to demonstrate imaging correlates of myocardial inflammation in patients undergoing major non-cardiac surgery supporting the hypothesis that inflammation drives PMI. Changes were restricted to the RV; it is plausible that pulmonary vascular effects of lung resection drive RV dysfunction through increased afterload in this patient group. Further work is required to explore the role of RV dysfunction and inflammation in PMI in patients undergoing other forms of major non-cardiac surgery.

References

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