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Title: Low dose inhaled LPS challenge – Reproducibility of the inflammatory response

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Body: Introduction: Inhalaled endotoxin (LPS) is used to study pulmonary inflammation. Conventional inhalation methods require substantial amounts of LPS (15–50µg) to induce a detectable inflammatory response. Authorities often permit LPS challenges only with GMP-grade LPS, which is of limited availability. Here we studied the reproducibility of the response to a low dose of LPS (2µg), which was inhaled by a flow/volume controlled procedure to increase lung deposition. Methods: Twelve healthy non-smoking volunteers were included. Baseline sputum was evaluated 2-4 weeks prior to the first challenge. On two occasions, separated by 4 weeks, subjects inhaled 2µg LPS (Clinical Center Reference Endotoxin CCRE, NIH), which was nebulized using an Aeroneb solo (Inspiration Medical). Sputum was induced 6h after LPS provocation. Results: The low dose LPS challenge was well tolerated. Both challenges induced a significant ($p<0.001$) increase in sputum neutrophils (median (IQR)% of sputum leukocytes at baseline: 24.4(31.2)%, 1.LPS: 75.3(13.3)%, 2.LPS: 59.0(19.3) %) and increased sputum IL8 and MPO. A significant ($p<0.01$) increase in sputum monocytes was only detected after the 2.LPS challenge (baseline: 4.3(1.5)%, 1.LPS: 7.7(7.0)%, 2.LPS: 11.0(8.1)%). Despite lower increases of neutrophils in the second challenge, the changes compared to baseline were correlated ($r=0.79$, ICC=0.64). Conclusion: Low dose LPS caused a reproducible inflammatory response. However, we found evidence for a more pronounced increase in monocytes in the second challenge. This needs to be considered in proof of concept studies for novel inflammatory compounds. CCRE was kindly provided by Dr. A. Suffredini, NIH, Bethesda.