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DEVOTED TO THE PRACTICES OF ADULT AND CONGENITAL HEART SURG HEART/LUNG TRANSPLANTATION, MECHANICAL ASSISTANCE CIRCULA

#### Low frequency ventilation during cardiopulmonary bypass for lung protection: A randomised controlled trial

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Keywords:	coronary artery disease, perfusion, cardiovascular research

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4 5	2	Low frequency ventilation during cardiopulmonary bypass for lung protection: A randomised controlled trial
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37 38	23	This trial is registered as ISRCTN No: 34428459
39 40	24	There is no conflict of interest for any of the authors
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8 9 10	38	Key question
11	39	Does low frequency ventilation (LFV) during cardiopulmonary bypass (CPB) improve
12	40	inflammatory markers and lung function compared to both lungs left collapsed in patients
13 14	41	undergoing CABG?
14 15 16	42	Key findings
17	43	There were no significant differences between groups in inflammatory markers measured in the
18	44	lung tissue and blood.
19 20		
20	45	Take-home message
22	46	LEV during CPB when compared to both lungs left collapsed does not reduce inflammation in
23	47	lung bionsies and blood
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25 26	48	
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2 3	67	
4 5 6	68	Glossary of Abbreviations
0 7 8	69	Low frequency ventilation (LFV)
0 9 10	70	Cardiopulmonary bypass (CPB)
10 11 12	71	Coronary artery bypass grafting (CABG)
12 13 14	72	Acute lung injury (ALI)
15 16	73	Adult respiratory distress syndrome (ARDS)
17 18 10	74	Positive end-expiratory pressure (PEEP)
19 20 21	75	cardioplegic arrest (CA)
22 23	76	Pulmonary function tests (PFTs)
24 25 26	77	Respiratory index [(PAO <sub>2</sub> -PaO <sub>2</sub> )
20 27 28	78	Forced vital capacity (FVC)
29 30	79	Forced vital capacity ratio (FVCR)
31 32	80	forced expiratory volume in one second (FEV <sub>1</sub> )
33 34	81	Forced expiratory volume after one second (FEV <sub>1</sub> )
35 36 37	82	Continuous positive airway pressure (CPAP)
38 39	83	Geometric means (GM).
40 41 42	84	Means and standard deviations (SDs)
42 43 44	85	Ventilation/perfusion distribution (V/Q)
45 46	86	Adenine nucleotides (ATP, ADP, AMP)
47 48 49	87	Conventional mechanical ventilation (CV)
50 51	88	Open Lung Concept (OLC)
52 53	89	Partial pressure of oxygen (pO <sub>2</sub> ) (paO <sub>2</sub> )
54 55 56 57 58 59	90	Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)

2 3 4	91	Abstract					
5	92						
7 8	93 <b>Objective:</b> Pulmonary dysfunction is a common complication in patients undergoing heart						
9 10	94	surgery. Current clinical practice does not include any specific strategy for lung protection. To					
11 12 13	95	compare the anti-inflammatory effects of low frequency ventilation (LFV), as measured by NF- $\kappa$ B					
14 15	96	p65 pathway activation, for the entire cardiopulmonary bypass (CPB) versus both lungs left					
16 17 18	97	collapsed in patients undergoing coronary artery bypass grafting (CABG)					
19 20	98	Methods: Two group parallel randomised controlled trial. Primary outcome was inflammation					
21 22 23	99	measured by NF-κB p65 activation in pre- and post-CPB lung biopsies. Secondary outcomes were					
23 24 25	100	additional inflammatory markers in both biopsy tissue and blood.					
25 26 27	101	<b>Results:</b> 37 patients were randomly allocated to LFV (18) and to both lungs left collapsed (19).					
28 29	102	The mean concentration of NF- $\kappa$ B p65 in the biopsies before chest closure (adjusted for pre-CPB					
30 31 32	103	concentration) was higher in the LFV group compared to both lungs left collapsed group but this					
33 34	104	was not significant (0.102, 95% CI -0.022 to 0.226, p=0.104). There were no significant					
35 36	105	differences between groups in the other inflammatory markers measured in tissue and blood.					
37 38 39	106	Conclusions: In patients undergoing elective CABG, the use of LFV during CPB when compared					
40 41	107	to both lungs left collapsed does not seem to reduce inflammation in lung biopsies and blood.					
42 43 44	108	Abstract woras count. 202					
45	105						
46 47 48	110	Keywords: Low frequency ventilation, cardiopulmonary bypass, lung protection, Lung biopsy,					
49 50	111	NF-kB					
51 52	112						
53 54 55 56 57 58 59	113						
60							

- Introduction Pulmonary dysfunction is a common complication for patients after cardiac surgery using cardiopulmonary bypass (CPB) [1]. Severity ranges from mild atelectasis to life threatening acute lung injury (ALI) or respiratory failure requiring prolonged postoperative ventilation [2] or adult respiratory distress syndrome (ARDS) [3-5]. Harmful effects of CPB on pulmonary function persist despite advances in anaesthetic techniques [6]. Pulmonary dysfunction after cardiac surgery also affects clinical outcomes with increasing morbidity, mortality and delaying discharge from hospital, leading to increase in the health care resources used and their associated cost [3, 7-13] Presumed causative factors for atelectasis and ALI, include inflammation, prolonged lung collapse, pulmonary ischemia and related reperfusion injury, blood contact with the surface of the heart-lung machine, endotoxemia, surgical trauma, blood loss and transfusion [14, 15]. Inflammatory activation and cytokine release have been correlated with outcome after cardiac surgery [16]. Pulmonary function 24 hrs after CPB is associated with raised plasma levels of inflammatory cytokines and reduced levels of anti-inflammatory cytokines [17]. The inflammatory response from the lung during CPB and mechanical ventilation originates at the alveolar membrane as a result of collapse, ischemia, reperfusion injury and mechanical stress [18-20]. Suppression of activation of inflammatory mediators during CPB is associated with a reduction in pulmonary dysfunction [21]. Current clinical practice does not include any specific strategy for lung protection during CPB. When CPB is started, often both lungs are left collapsed for the entire CPB duration. We recently provided evidence in an experimental pig model that low frequency ventilation (LFV) during CPB reduces post-CPB lung injury [22]. Here, we report an evaluation of the effect of ventilating the lungs at low frequency during CPB comparing to collapsing the lungs in patients having coronary artery bypass graft surgery (CABG) with respect to inflammation measured by NF- $\kappa$ B p65 pathway activation and post-operative pulmonary dysfunction. We used a primary outcome measure that would give an early indication of inflammatory changes in the lungs and would allow detection of a large effect in a relatively small trial. **Materials and Methods** This study was a single-centre, two-group parallel randomised controlled trial. Patients were randomly assigned in a 1:1 ratio, using a secure concealed internet-based randomisation system (Sealed Envelope<sup>TM</sup>, https://www.sealedenvelope.com/). Cohort minimisation was used to achieve balance between groups with respect to baseline lung function ( $\geq 60\%$  predicted FEV<sub>1</sub>). Patients returned to hospital for a follow up visit 6-8 weeks following the operation. Study period between 07 January 2013 to 27 June 2014. Trial registration ISRCTN-34428459,
  - Study period between 0/ January 2013 to 2/ June 2014. Trial registration ISRC1N-34428459,
     protocol approved by the NRES London- Camden and Islington (REC-12/LO/0458). Protocol
     published at <u>http://www.isrctn.com/ISRCTN34428459</u>.
  - 57 153 Trial Population
  - <sup>58</sup> 154 Patients having elective or urgent CABG with CPB and cardioplegic arrest (CA) at the
  - <sup>59</sup> 155 Hammersmith Hospital. (Table 1)

<ul> <li>Inclusion criteria</li> <li>Age ≥40 and &lt;85 years</li> <li>Left ventricular ejection fraction &gt;30%</li> <li><i>Exclusion criteria</i></li> <li>Previous pulmonary embolism requiring long term warfarin for ≥3 months</li> <li>Previous cardiac surgery</li> <li>Current congestive heart failure (NYHA class IV)</li> <li>Current congestive heart failure (NYHA class IV)</li> <li>Chronic renal failure</li> <li>Emergency or salvage operation</li> <li>On corticosteroid or immunosuppressive treatment</li> <li>Severe chronic obstructive pulmonary disease, lung pathology, previous radiotherapy,</li> <li>Bedor satisfies and the satisfies and the</li></ul>
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<ul> <li><i>Exclusion criteria</i></li> <li>Previous pulmonary embolism requiring long term warfarin for ≥3 months</li> <li>Previous cardiac surgery</li> <li>Current congestive heart failure (NYHA class IV)</li> <li>Chronic renal failure</li> <li>Chronic renal failure</li> <li>Corrent congestive heart failure (NYHA class IV)</li> <li>Chronic renal failure</li> <li>Chronic renal failure</li> <li>Corrent congestive heart failure (NYHA class IV)</li> <li>Chronic renal failure</li> <li>Severe chronic obstructive pulmonary disease, lung pathology, previous radiotherapy,</li> <li>Body mass index &gt;35</li> <li><i>Ventilation Protocol</i></li> <li>Before starting CPB, for all participants, the lungs were ventilated with a tidal volume of 6-8</li> <li>ml.kg<sup>-1</sup>, I:E ratio of 1:2, positive end-expiratory pressure (PEEP) of 5cm H<sub>2</sub>O and FiO<sub>2</sub> of 0.5 (range 0.45-0.55 O<sub>2</sub>). The ventilatory rate was set to keep the PaCO<sub>2</sub> between 4.5 and 5.5 kPa.</li> <li>In the comparator group (both lungs left collapsed), at the onset of CPB the lungs were disconnected from the ventilator and allowed to collapse completely for the duration of CPB.</li> <li>In the treatment group (low frequency ventilation, LFV), the respiratory rate was maintained at GPB patients in both groups had a lung recruitment manoeuvre using an FiO<sub>2</sub> of 0.5 and holding the lungs inflated for 15see at 30cm H<sub>2</sub>O, before the lungs were reconnected to the ventilator. The recruitment manoeuvre was repeated if necessary, though this yeart was not recorded on the data.</li> <li>No other variation in ventilation was permitted or necessary. The same ventilator protocol was used after CPB as before CPB with a PaO<sub>2</sub>/FiO<sub>2</sub> &gt;50 required on first post-bypass gas (i.e. PaO<sub>2</sub>&gt;25kPa). If PaO<sub>2</sub>/FiO<sub>2</sub> &lt;50 then the recruitment manoeuvre was repeated.</li> <li><i>Anaesthetic protocol</i></li> <li>Following premedication with temazepam (dose 20-30mg), anaesthesia was i</li></ul>
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45 188 propotol and remitentanil, using pancuronium 0.1 mg/kg for muscle relaxation. This was
46 189 maintained by infusion of propofol and remifentanil (5mg remifentanil to 1g propofol), with
<sup>47</sup> 190 isoflurane if required to keep the entropy value of the processed EEG below 55. At chest closure,
<sup>48</sup> 191 $7\mu g/kg$ fentanyl was given in combination with plain propofol, which was switched to a
$\frac{47}{10}$ 192 proposed proposed in the start of the transfer to the cardiac intensive care unit. It is important to
50 132 proportion remainmentation for the transfer to the earenee intensive care unit. It is important to
51 193 mention that mixing remifertanil in propofol was at the time of our study common practice and
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*Perfusion protocol* A standard CPB was used, primed with 1400 ml of Hartmann's solution and 10000 IU of heparin. Systemic temperature was between 32°C and 35°C. Cardioplegic arrest was achieved with intermittent antegrade cold blood cardioplegia. Lung biopsy protocol To measure inflammatory markers in the lung, two lung biopsies (1cm x 1cm) were taken using the LigaSure Impact<sup>™</sup> instrument (LF4318, Covidien, Minneapolis, USA). The first (pre-CPB) biopsy was taken from the left upper lobe immediately after sternotomy and the second from the left lower lobe prior to weaning from CPB after lung recruitment manoeuvre (see above). The criteria for extubation were: Normothermia (a core temperature range of  $36.0^{\circ}$ C to  $37.0^{\circ}$ C); haemodynamical stability and blood loss <50mls/h; comfortable breathing with good bilateral air entry (RR 10-20/min, tidal volumes 8-10mls/kg, minimal tracheal suction) and arterial blood gases with parameters  $PaO_2 > 10$ kpa on FiO<sub>2</sub> <0.5, PCO<sub>2</sub><7 kPa, BE -5 to +5. Blood samples were taken: i) after anaesthetic induction and pre-sternotomy, ii) 10 minutes after the end of CPB, and iii) 2, 6 and 24 hours after the end of CPB. No blood sample were taken during CBP as our end points was to look into the effect before and after CPB. Outcomes The primary outcome was inflammation measured by NF-kB p65 activation in pre- and post-CPB lung biopsies. This outcome measure was chosen because exposure of a cell to a cytokine or an infectious agent leads to binding to a cell surface receptor and activation of a kinase cascade resulting in the nuclear translocation of the master pro-inflammatory transcription factor NF- $\kappa$ B. NF- $\kappa$ B is known to drive the expression of most inflammatory genes [24, 25]. Secondary outcomes included additional inflammatory markers in both biopsy tissue and blood. Namely, p38 MAPK phosphorylation, expression of  $TNF\alpha$ , IL1 $\beta$ , IL18, IL6, IP10, IL8, IL10, chemokine receptor CXCR3 and Caspase 3 measurements of apoptosis in biopsies. ROS levels, phosphorylation of p38 and NF-kB p65 in blood. Laboratory analysis Blood samples were taken: i) after anaesthetic induction and pre-sternotomy, ii) 10 minutes after the end of CPB, and iii) 2, 6 and 24 hours after the end of CPB. Leukocytes were fixed and lysed with BD Phosflow Lyse /Fix buffer, (BD Biosciences, Oxford, UK). Samples were stained using a redox-sensitive fluorescent probe 3'-(p-aminophenyl) and stained with antibodies raised against phosphorylated p38 (Thr180/Tyr182) (Cell Signaling #6908, Danvers, MA, USA) and NF-κB p65 (Ser529) (Cell Signaling #4887). Samples were analysed by flow cytometry compared to unstained controls. Biopsies: The pre-CPB biopsy provided a within-subject control for the second, post-CPB biopsy. NF-kB p65 nuclear localization and activation was assessed by immunofluorescent staining followed by confocal microscopy and by testing nuclear lysates by DNA-binding ELISA (TransAm Assay, Carlsbad, USA). Measurements of *p38 MAPK* phosphorylation in biopsies were carried out using Western blotting and were analysed and expressed as ratio of phosphorylated p38 and total p38. Expression of 

2		
3 4 5	240 241	TNF $\alpha$ , IL-1 $\beta$ , IL-18, IL-6, IP-10, IL-8, IL-10 and chemokine receptor CXCR3 were done using ELISA and qPCR.
6 7 8 9	242 243 244	For RNA extraction biopsies were homogenised in RLT buffer (Qiagen, Hilden, Germany), containing beta mercaptoethanol (Sigma-Aldrich, St Louis, USA). RNA was quantified using nanodrop and reverse transcribed to (ThermoFisher Scientific, Waltham, USA).
10 11 12	245 246	Gene expression was measured using Taqman qPCR and normalised to $18S$ rRNA using the $\Delta\Delta$ ct method.
13 14 15 16	247 248	For protein extraction biopsies were homogenised in either radioimmunoprecipitation assay (RIPA) (Sigma Aldrich) buffer or Lysis buffer AM1 (Active Motif).
17 18 19 20	249 250 251	Protein concentration was determined using the bicinchoninic acid assay (ThermoFisher Scientific). ELISA was used to measure expression of TNF $\alpha$ , IL-1 $\beta$ ,IL-18, IL-6, IP-10, CXCL-8, and IL-10 in the cytoplasmic fraction. Caspase 3 activity was measured by colormetric assay kit (Abaam, Cambridge, LW), p28 phagehore lation by ELISA and Western Plat [26]
21 22 23 24 25	252 253 254	Other secondary outcomes included pulmonary function tests (PFTs), pulmonary gas exchange and adverse events
25 26 27 28 29 30	255 256 257 258	Pulmonary gas exchange was assessed by the respiratory index [(PAO <sub>2</sub> -PaO <sub>2</sub> ) / (PaO <sub>2</sub> )] measured i) post-induction and pre-sternotomy, ii) 10 minutes following CPB weaning, iii) 2 hours post CPB, iv) 4 hours post CPB, v) first gas post extubation, vi) 12 hours post CPB, and vii) before removal of the arterial line.
31 32 33 34 35 36	259 260 261 262 263	Pulmonary function tests (PFTs) were carried out pre-operatively and at 6-8 weeks post-surgery. PFTs included forced vital capacity (FVC), forced vital capacity ratio (FVCR), forced expiratory volume in one second (FEV <sub>1</sub> ), forced expiratory volume after one second (FEV <sub>1</sub> ) and FEV to FEV <sub>1</sub> ratio. Pulmonary function was assessed by a combination of the following tests: spirometry, gas diffusion and thoracic gas volume.
37 38 39	264 265	During hospital stay and at the follow up visit patients underwent a pulmonary function test and any documented occurrence of adverse events were recorded.
40 41 42	266 267	
43	207	Statistical Analysis
44 45	200	Without taking the baseline biopsy into account, it was calculated that a sample size of 32 patients
46	205	would be able to detect a standardised difference of 1.0 with 80% power and 5% significance (2-
47	270	tailed) If the baseline biopsy improves the relative efficiency of the comparison (with an
48 40	272	estimated correlation of 0.5 between measures of the primary outcome for the pre/upper lobe and
49 50	273	post/lower lobe), the trial either had more power (88%) or was able to detect a smaller target
51	274	difference (0.9SD) These standardised differences (1.0 or 0.9) represent large differences
52	275	between groups: we justified the plausibility of this large target difference on the grounds that the
53 54	276	primary outcome was chosen to assess the biomarker and site (i.e. the lungs) which we
54 55 56	277	hypothesised would be most directly influenced by the intervention.
57 58 59 60	278 279	This target sample size was able to detect a standardised difference of 0.75 in biomarkers measured in the serum with 80% power and 5% significance (2-tailed), assuming a correlation of

0.5 between pre and post-intervention measures and a correlation of 0.7 between the four repeated post-intervention measures. The study was not powered to detect differences between the groups in pulmonary function or adverse events. Specific adverse events were too infrequent to be able to detect differences between groups. Frequencies of these adverse outcomes are tabulated, in line with guidelines for reporting adverse events in trials. The trial was an "early phase" and it aimed at identifying an intervention worth taking forward to late phase 3 trials quickly and relatively inexpensively, hence the choice of a primary outcome and an effect size that would allow a small sample size. Primary analyses were by intention-to-treat. The final analyses were performed after the database had been locked and the statistical analysis plan approved. The statistical software STATA (version 13.2) was used to analyse the data as well as to generate tables, figures, and listings. Most of the data measured continuously scaled outcomes which are summarised as means and SD, at each time point if measured more than once, in each treatment group. If distributions were non-normal, appropriate transformations were used. Analyses were carried out on the transformed data and the findings were transformed back to the original scale where possible, e.g. if a logarithmic transformation was used then the results are presented as geometric means (GM). For inflammatory markers in biopsy samples, where only one post-intervention measure was collected, models were fitted using linear regression to adjust for the baseline level. Each model estimated the main effect of group allocation (LFV vs. conventional management) and the baseline covariate For inflammatory markers in monocytes and polymorphonuclear cells from peripheral blood samples and pulmonary gas exchange expressed as A-a gradient, mixed regression models were fitted. These models estimated coefficients for group allocation and the interaction term for group allocation by time. If the interaction was significant (p < 0.05), then a group comparison is reported at each time point. All results are presented as differences between, or ratios of, the means for the two groups with 95% CIs. Results **Study Population** Forty-nine patients were eligible and were invited to take part in the trial between January 2013 and June 2014; 38 gave written informed consent, 8 declined for personal reasons and 3 preferred the standard procedure. One patient became ineligible (had off-pump CABG) and was withdrawn (see consort diagram, Fig 1); available data for the remaining 37 patients were analysed (18 in the LFV group and 19 in both lungs left collapsed CPB group). Baseline characteristics, pre-operative co-morbidities, operation details and baseline respiratory measurements were balanced (Table 1). Means and standard deviations (SDs) for all the markers are tabulated in (TableA1 and TableA2). Adverse events during hospital stay and at follow up are tabulated in (Table 2), Figure 2 illustrates the treatment effect and (Figure 3) illustrates the raw data on a log scale (for y axis). Primary outcome The mean concentration of NF-κB p65 in the biopsies before chest closure (adjusted for pre-CPB concentration) was higher in the LFV group compared to both lungs left collapsed CPB group but 

this was not significant (Table A1, Table A2a), (Figure 2a, Figure 3a); (0.102, 95% CI -0.022 to 0.226 p=0.104). Secondary outcomes Biopsy markers analysis results are summarised in (Table A2) and (Figure 2a). The mean concentration of p38 MAPK in the biopsies before chest closure (adjusted for pre-CPB concentration) was lower for the LFV group compared to both lungs left collapsed CPB group but this was not significant. Expression of *IL18* and *IL10* were also lower in the LFV group compared to both lungs left collapsed CPB group but not by statistically significant amounts. Gene expression of TNFA, IL1B, IL6, IP10, IL8 and CXCR3 as well as caspase activity were higher in the LFV group compared to the standard CPB group. These differences were statistically significant for *IL1B* and *IL6*. There were no significant differences in cytokine levels between each group. Blood markers analysis results are summarised in (Table A1b, Table A2) and (Figure 2b). Leukocytes were separated into monocytes, granulocytes and lymphocytes by forward and side scatter. The permeabilised monocytes and granulocytes, when measuring p38 MAPK and NF-KB p65, showed significant overlap by this method and were therefore treated as a single group. There were no statistically significant differences in NF- kB, MAPK, ROS, or A-a gradients between groups. NF-kB p65 and p38 MAPK levels in combined monocytes and granulocytes were lower in the LFV group compared to both lungs collapsed CPB group, but these differences were not statistically significant. NF-kB p65 levels in lymphocytes were higher in the LFV group compared to both lungs left collapsed CPB group but not significantly so. ROS levels were not significantly lower in all cell types in the LFV group compared to both lungs left collapsed group. When time was fitted in the model, we found that p38 MAPK in lymphocytes levels were significantly lower in the LFV group at 2, 6 and 24 hours compared to 10 min. The interaction of intervention x time was not significant at any time point for any of the blood markers. The A-a gradient was higher in the LFV group compared to both lungs left collapsed CPB group, but this was not significant Table A3. When time was fitted in the model, we found that there was a significant reduction in A-a gradient in time compared to 10 min in the LFV group. However, the interaction of intervention x time was not significant at any time point. No difference was found in lung functions between the two groups (Table A3b) Frequency of adverse events are summarised in (Table 2). Mask CPAP was necessary for one patient in the LFV group and 2 in both lungs left collapsed CPB group. Arrhythmia occurred in 50% of patients in the LFV group and 37% of patients in both lungs left collapsed CPB group. The biggest difference in groups for occurrence of adverse events was in relation to the need for haemodynamic support, 89% of patients in the LFV group vs 47% in both lungs left collapsed CPB group. Hospital and post discharge infective complications were similar between groups. Discussion This trial investigated the possibility of reducing the inflammatory response associated with CABG by a technique of ventilating of the lungs at low frequency during CPB. The change in

- inflammatory response was measured in both tissue biopsy and blood using NF- $\kappa$ B p65 in lung biopsies and other inflammatory markers in both tissue and blood. Our selection for NF-kB as a primary end point was because its activation can be induced upon physical or oxidative stresses resulting from cardiac surgery using CPB [27]. NF-κB seems to be a reasonable end point reflecting the adverse effect of the inflammation on the lungs. We could argue that it might not be very specific to lung tissue but rather systemic inflammatory status as it can be also produced by, physiological changes including ischemia and hyperosmotic shock, or by numerous inflammatory cytokines and chemokines [27]. Our choice to measure NF- $\kappa$ B in the lung tissue with a control sample as the primary end-point can be justified as CPB enhanced lung and systemic inflammation. Samples have been collected for future transcriptomic and proteomic analysis and this may help provide insight into possible pathways driving CPB. Results showed levels of all markers apart from p38 MAPK, IL18 and IL10 measured in the lung biopsy tissue were higher in the LFV group compared to both lungs left collapsed CPB group. However only the increases in *IL6* and *IL1B* gene expression were statistically significant and these differences were counter to our working hypothesis that LFV would reduce inflammation following surgery. We observed a marked increase in the expression of a number of NF-kB-induced inflammatory markers at both the protein and mRNA level in lung tissue following CPB. The failure to observe any change in NF- $\kappa$ B p65 activation in tissue may reflect the rapid early nature of NF-κB activation compared to the time under CPB (in the LFV group median of 71min, IQR 63.5-93.5 and in both lungs left collapsed group median of 80min, IQR 60-92). Gene stimulation can lead to waves of NF-kB activation over time [28] and we may have missed a second round of NF- $\kappa$ B activation at the time points analysed chosen. However, we detected a marked effect on p38 MAPK activity in both lung tissue and in peripheral blood following CPB and the effect in blood reached significance over the time series and may have been greater if subsets of cells were analysed. It is possible that CPB is a greater activator of inflammation in response to oxidative stress than NF-kB and further studies would be required in disease models to test this hypothesis. Overall, there was no significant difference in the inflammatory markers measured in the blood between LFV and both lungs left collapsed CPB group. A clinical study reported the use of continuous positive airway pressure (CPAP) during CPB in 14 elective cardiac surgery patients. Seven patients received CPAP at 10cm H<sub>2</sub>O during CPB, and in the other seven patients, the lungs were open to the atmosphere (control). CPAP at 10cm H<sub>2</sub>O resulted in significantly more perfusion of lung areas with a normal ventilation/perfusion distribution (V/Q) and significantly less shunt and low V/Q perfusion 4h after CPB in comparison with the control group. The authors concluded that CPAP at 10cm H<sub>2</sub>O during CPB is a simple manoeuvre that improves postoperative gas exchange and resulted in significantly more perfusion of lung areas with a normal ventilation/perfusion distribution (V/Q) and significantly less shunt [29]. The effect of both low frequency ventilation (LFV) and continuous positive airway pressure (CPAP) during CPB to reduce post-CPB lung injury have been evaluated in an established experimental pig model [22]. This study strongly suggested that the use of LFV is associated with significantly better pulmonary gas exchange, higher adenine nucleotide, lower lactate dehydrogenase levels and reduced histological damage in lung biopsies as well as lower DNA levels in bronchoalveolar lavage compared to the control group. The rationale for this
  - 408 experimental study was to maintain some degree of ventilation during CPB to prevent persisting 58 409 lung collapse and complete loss of gas exchange by passive diffusion at the blood–gas barrier. A
  - <sup>58</sup> 409 lung collapse and complete loss of gas exchange by passive diffusion at the blood–gas barrier. A
     <sup>59</sup> 410 similar concept was used by Reis Miranda and colleagues who studied 62 patients post cardiac

surgery, randomly assigned to three groups: (1) conventional mechanical ventilation (CV), (2) Open Lung Concept (OLC) started after arrival on the ICU and (3) OLC started directly after intubation. They observed an increase in functional residual capacity, reduced risk of hypoxemia and lower levels of IL-10 and IL-8 release, hence concluded that OLC ventilation leads to an attenuated inflammatory response, presumably by reducing additional lung injury after cardiac surgery [30]. 

A recent study was undertaken to examine the effect of maintaining ventilation during bypass compared with discontinued ventilation upon several parameters that may be indicative of lung injury. Twenty-three elective patients for CABG were randomised to either ventilation (VB) (n=12) or non-ventilation on bypass (NVB) (n=11). The post-bypass extravascular lung fluid was significantly smaller in the VB group compared to the NVB group and extubation time was significantly shorter [31], hence this study has shown the benefits of maintaining ventilation during CPB on post-CPB oxygenation and included shorter mechanical ventilation [31]. On the other hand, a small study of fifty-nine patients prospectively randomised to continuous ventilation and no ventilation, during CABG on CPB, showed there was no statistically significant difference in most of inflammatory makers (IL-6, IL8, IL-10 & lactate) [32]. A recent metanalysis for patients undergoing cardiac surgery and received ventilation during CPB, included seventeen trials with 1162 patients, showed that ventilation during CPB significantly increased post-CPB PaO2/FiO2 ratio, but there was no sufficient evidence to show that ventilation during CPB could influence long-term prognosis of these patients [33]. 

- 431 The discordant conclusion from all previous studies on the effect of low frequency ventilation
  432 during CPB on lung function, was what prompted us to design and conduct this study. This is the
  433 first RCT to investigate the effects of low frequency ventilation in patients undergoing CABG
  434 with CPB by measuring inflammation directly in lung biopsies and blood samples.
- 35 435 Strengths and limitations

436 Our trial to the best of our knowledge is the first to report the effects of LFV on pulmonary
 437 inflammation in the blood and directly in lung biopsy in patients undergoing CABG with CPB.

438 Random allocation was concealed, retention was good, data collection was blinded, and analyses
439 were carried out and reported in accordance with a prespecified analysis plan. Therefore, the trial
440 was at low risk of bias [34]. Although the sample size was small, there was no suggestion of any
42 441 benefit from the adoption of LFV.

The surgical team could not be blinded, and we cannot rule out the possibility that this led to variations in surgical technique by group. The use of PEEP in the intraoperative mechanical ventilation has been associated with a reduction of atelectasis in postoperative period as reported by studies using high PEEP level (10 cm H2O) [35-37]. Overall the role of PEEP in surgery has been extensively studied with positive impression [33, 38-40]. In cardiac surgery particularly as the chest cavity is open, the lungs are arbitrarily exposed to atmospheric pressure, rather than normal negative intrathoracic pressure. Hence the transpulmonary pressure (airway pressure minus intrathoracic pressure) becomes abnormally low at end-expiration leading to collapse of the lungs, if we do not apply PEEP of at least 3-5 cm H2O. Nevertheless, in our treatment group we applied the LFV without PEEP. This is probably a major limitation that we could have avoided by adding PEEP to our LFV group. 

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3	453	Conclusion
4		
6	454	Contrary to our working hypothesis low frequency ventilation (LFV) during CPB has not been
7	455	demonstrated to reduce pulmonary or systemic inflammation compared to both lungs left
8	456	collapsed and may in fact increase the levels of specific inflammatory cytokines.
9 10 11	457	
12 12	458	Acknowledgment
13 14 15	459	We wish to thank the patients who participated and the staff in the cardiothoracic unit, who made
16 17 18	460	this study possible.
19	461	Funding and support
20 21	462	The study was jointly supported by the British Heart Foundation (BHF) and the National Institute
22 23 24	463	for Health Research (NIHR) Bristol Biomedical Research Centre.
25 26	464	Neither the BHF nor the NIHR had any role in the design, conduct, analysis or reporting of the
27 28 29	465	trial.
30 21	466	Figure Legends
32	467	Figure 1 Consort diagram
33	407	rigule 1. Consolt diagram
34	469	
35	405	Figure 2a, b. Forest plot illustrating the treatment effect for each inflammatory marker
36	470	a in the lung tissue bionsies
3/	472	b' in the blood samples
30 39	473	Figure 3 Raw data on log scale (for y and x axis) [solid line=LFV dash line=both lungs left
40	474	collapsed] for p65, p38, ROS and HEME in blood
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59 60	57 58	572		
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## Figure 2 (a-b)

a: forest plot illustrating the treatment effect for each inflammatory marker measured in the lung tissue biopsies



b: forest plot illustrating the treatment effect for each inflammatory marker measured in the blood samples



LFV=Low frequency ventilation

Control= both Lungs left collapsed

## Figure 3









<u> </u>		
Variable*	LFV (N=18)	Lungs left collapsed (N=19)
Age (years) – mean (SD)	65.39 (12.09)	62.86 (10.08)
Height (m) - mean (SD)	1.70 (0.09)	1.69 (0.06)
Weight (kg) - mean (SD)	85.72 (15.49)	80.84 (15.29)
<b>BMI</b> (kg/m2) - mean (SD)	29.69 (4.14)	28.15 (4.82)
NYHA class – no. of patients (%)		
0	0	0
1	4 (22%)	9 (47%)
2	12 (67%)	9 (47%)
3	2 (11%)	1 (5%)
4	0	0
Left Ventricular Function – no. of patients (%)		
Poor (<30%)	0	0
Moderate (30-50%)	4 (22%)	4 (21%)
Good (>50%)	14 (78%)	15 (79%)
Smoker/ex-smoker – no. of patients (%)	14 (78%)	12 (63%)
Asthma – no. of patients (%)	4 (22%)	0
COPD – no. of patients (%)	0	1 (5%)
Operation details		
Bypass, minutes - median (IQR)	87.5 (68-97)	69 (54-79)
Cross-clamp, minutes - median (IQR)	44.5 (37-50)	35 (30-43)
Intubation, hours - median (IQR)	8.7 (7.1-10.3)	7 (6.4-10)
Time to discharge, days - median (IQR)	• 6 (6-7)	6 (5-7)

Table 1 - Patient population characteristics and operative details

\*The median and interquantile range are reported for the variables whose distribution is skewed.

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### Table 2 - Adverse events

Adverse event	LFV N=	n (%) =18	Lungs left collapsed (%) N=19	
	In hospital	At follow up	In hospital	At follow up
Respiratory				
Re-intubation/Ventilation	0	0	0	0
Mask CPAP	1 (5.6%)	0	2 (10.5%)	0
Tracheostomy	0	0	0	0
Prolonged ventilation (24 h)	0	0	0	0
ARDS	0	0	0	0
Pneumothorax / Effusion	0	0	0	0
Cardiovascular				
MI	0	0	0	0
Cardiac arrest	0	0	0	0
Arrhythmias	9 (50%)	0	7 (36.8%)	0
Haemodynamic support	16 (89%)	0	9 (47.4%)	0
Neurological		I	I	I
Permanent Stroke	0	0	0	0
TIA	0	0	0	0
Renal		I	I	I
Hemofiltration / dialysis	0	0	0	0
Other			-	-
GI complications	0	0	0	0
Thromboembolic complications	0	0	0	0
Bleeding complications	0	0	0	0
Wound complications	0	0	0	1 (5.3%)
Infective complications	4 (22.2%)	3 (17%)	4 (21.1%)	3 (15.8%)
Reoperation	0	0	0	0

### Table A1 (a-b)

a) Comparison between LFV and both lungs left collapsed on lung tissue inflammatory markers

Inflammatory	LFV	(N=18)	Lungs left collapsed (N=18)				
Marker	Before CPB	Before chest	Before CPB	Before chest			
NF-кВ р65	-1.92 (0.27)	-1.86 (0.32)	-1.87 (0.18)	-1.91 (0.22)			
p38 MAPK	-1.12 (1.09)	-1.19 (1.05)	-1.26 (1.05)	-1.08 (0.75)			
TNFa	-7.36 (1.12)	-6.91(0.73)	-7.34(1.12)	-7.33(0.86)			
IL-1β	-5.72(1.05)	-3.15(1.13)	-5.64(1.16)	-4.10(1.17)			
IL-18	-8.63(0.81)	-8.67(0.56)	-8.67(0.71)	-8.42(1.09)			
IL-6	-0.99(1.31)	-6.12(1.10)	-2.56(1.75)	-6.03(0.87)			
IP-10	-7.86(1.27)	-7.54(1.24)	-7.84(1.01)	-7.66(1.33)			
IL-8	-5.45(1.77)	-1.30(1.39)	-5.64(0.78)	-2.30(1.72)			
IL-10	-6.03(1.05)	-5.03(2.30)	-6.32(1.09)	-5.26(1.63)			
CXCR3	-4.22(1.77)	-4.28(1.07)	-4.59(1.95)	-4.98(1.20)			
Caspase 3	-2.46(0.38)	-2.60(0.47)	-2.56(0.60)	-2.50(0.64)			

b) Comparison between LFV and both lungs left collapsed on blood inflammatory

markers with time fitted in the model

Inflammatory	LFV					Lungs left collapsed					
Marker Mean(SD)*	Post- inducti on	10 min post CP	2 h	6 h	24 h	Post- inducti on	10 min post CP	2 h	6 h	24 h	
		B					B				
Leukocytes											
NF-кВ р65			-		-					-	
		0.40	0.03	0.08	0.30		0.10	0.11	0.21	0.05	
	0.16	(0.6	(0.8	(0.9	(1.2	0.44	(0.6	(1.2)	(1.5	(0.9	
	(0.54)	3)	0)	9)	6)	(0.44)	/)	2)	6)	4)	
p38 MAPK			4.57		4.90	4.75	4.41	4.72	4.63	5.00	
	4.84	4.22	(1.2	4.79	(1.1	(0.83)	(1.0	(1)	(0.7	(1.1	
	(0.80)	(1)	6)	(1)	9)		7)		7)	1)	
ROS**	4.43	4.46	4.41	3.80	4.35		4.69	4.51	3.79	4.75	
	(1.48)	(1.3	(0.7	(1.6	(1.1	4.71	(0.4	(0.4	(1.2	(0.5	
		3)	6)	0)	3)	(0.51)	5)	6)	4)	4)	
Monocytes/Granulocy tes***				2							
NF-κB p65					-						
<b>p</b>		0.32	0.37	0.21	0.07		0.60	0.28	0.43	0.60	
	0.03	(0.4	(0.8	(0.6	(0.9	0.38	(0.7	(1.2	(0.7	(1.0	
	(0.60)	1)	5)	3)	4)	(0.88)	3)	2)	6)	2)	
p38 MAPK	6.63	6.38 (0.4	6.50	6.42 (0.5	6.46 (0.7	6.42	6.25 (0.6	6.44	6.21 (0.5	6.40 (0.7	
	(0.55)	8)	9)	9)	2)	(0.60)	4)	2)	4)	6)	
Monocytes											
ROS**		5.52	5.47	5.38	5.78		5.87	5.58	5.55	5.82	
	5.54	(1.5	(1.4	(0.9	(0.8	5.73	(0.4	(0.4	(0.5	(0.4	
	(1.11)	8)	5)	1)	9)	(0.24)	5)	9)	1)	6)	
Granulocytes											
ROS**		6.27	6.21	6.17	6.42		6.48	6.44	6.36	6.54	
	6.25	(1.3	(1.2	(0.9	(0.9	6.52	(0.3	(0.3	(0.2	(0.3	
	(1.07)	8)	[7]	3)	4)	(0.36)	3)	1)	1)	8)	

Heme (µM)	3.05	3.79	3.65	3.08	2.81	2.95	3.58	3.35	2.93	2.60
	(0.38)	(0.5	(0.6	(0.3	(0.4	(0.51)	(0.5	(0.5	(0.4	(0.4
		7)	4)	4)	3)		0)	6)	8)	9)

\*Data are transformed because their distribution is not normal, the mean of the transformed data is tabulated.

\*\*Negative data for ROS was set to missing. Most time points and cell type had only one value set to missing. ROS in Leukocyte at baseline and 2 hours had three missing values, ROS in Leukocyte at 6 hours had 6 missing values.

\*\*\*Monocytes overlapped with granulocytes for NF-κB p65 and p38 MAPK

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#### Table A2

Summary of the main effects for primary and secondary endpoints in inflammatory markers (LFV vs Lungs left collapsed)

	Event	LFV vs Lui	p value		
		Treatment effect	95% CI		
	NF-кВ р65	0.102	-0.022 0.226	0.104	
In Biopsy	р38 МАРК	-0.173	-0.723 0.376	0.525	
	ΤΝFα	0.425	-0.128 0.977	0.127	
	IL-1β	0.985	0.228 1.742	0.012	
	IL-18	-0.310	-0.845 0.224	0.244	
	IL-6	1.59	0.528 2.654	0.005	
	IP-10	0.251	-0.567 1.06	0.533	

	IL-8	0.995	-0.098 2.088	0.073
	IL-10	-0.053	-1.244 1.138	0.929
	CXCR3	0.551	-0.058 1.159	0.075
	Caspase 3	0.186	-0.204 0.576	0.334
	NF-κB p65 leukocytes	0.023	-0.420 0.467	0.918
In Blood	NF-κB p65 monocytes_granulocyte	-0.125	-0.433 0.182	0.424
	p38 MAPK leukocytes	-0.146	-0.524 0.232	0.448
	p38 MAPK monocytes_granulocyte	-0.029	-0.284 0.226	0.823
	ROS monocytes	-0.100	-0.353 0.152	0.436
	ROS granulocyte	-0.010	-0.196 0.176	0.913
	ROS leukocytes	-0.213	-0.585 0.159	0.262
	Heme	0.142	-0.050 0.334	0.148
	5	3		
		2		
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Results of the statistical inference summary showing the main effect for primary and secondary end points in standard care vs. LFV. Cytokines increased following surgery. A positive value indicates that standard care was better than LFV whilst a negative value indicates an improved response to LFV.

## Table A3 (a,b)

### a) Pulmonary gas exchange parameters (LFV vs Lungs left collapsed)

Pulmonary	LFV							Lungs l	eft colla	psed				
gas exchange Median (IQR)	Post - indu ctio n	10 min post CP B	2 h	4h	Post extubat ion	12 h	24 h	Post- induct ion	10 min post CP B	2 h	4h	Post extub ation	12 h	24 h
PaO <sub>2</sub> (mmhg)	215. 25 (144 .7- 344. 3)	168 (14 5.5- 264 )	133. 9 (103 .5- 203)	119. 25 (105 - 130. 5)	110.25 (84.7- 117.8)	102. 35 (94. 5- 122. 3)	99 (86. 3- 114. 8)	229.55 (164.3 - 293.3)	211. 5 (117 - 328. 5)	129 (117- 184.5 )	132 (106 -5- 157. 5)	114.8 (94.5- 148.5 )	122.3 (105.8 - 146.3)	97 (90.8- 111.8)
A-a Gradient	148. 19 (33. 18 - 204. 96)	176 .74 (12 1.3 9 - 233 .55)	114. 89 (108 .5 - 150. 53)	116. 26 (91. 63 - 126. 95)	113.63 (77.56 - 133.00)	97.5 6 (80. 36 - 116. 88)	104. 04 (81. 97 - 132. 83)	111.59 (85.05 - 168.65 )	178. 21 (40. 63 - 336. 49)	113.7 8 (95.1 - 146.8 3)	90.6 3 (62. 75 - 144. 45)	105.9 5 (58.4 3 - 122.4 0)	62.68 (35.86 - 99.70)	67.98 (46.47 - 114.63)

## b) Lung function parameters (LFV vs Lungs left collapsed)

Lung Function test	LI	<b>TV</b>	Lungs left collapsed		
Mean(SD)*	Pre-op	Follow up	Pre-op	Follow up	
FEV1 (% predicted) litres - mean (SD)	90.94 (21.58)	82.06 (19.86)	97.22 (18.83)	91 (20.20)	
FVC (% predicted) litres - mean (SD)	93.24 (20.73)	83.00 (18.37)	97.11 (18.51)	91.25 (16.55)	
MEF75(% predicted) litres/sec - mean (SD)	84.13 (42.32)	85.31 (39.01)	87.87 (30.83)	87.00 (30.37)	
MEF25(% predicted) litres/sec - mean (SD)	68.27 (36.25)	60.56 (25.77)	70.47 (25.82)	67.33 (23.94)	
TLC(% predicted) litres - mean (SD)	97.40 (14.53)	88.94 (11.76)	103.27	90.08 (13.57)	
RV (% predicted) litres - mean (SD)	112.73	98.75 (24.47)	116.33	95.17 (21.44)	
TL <sub>CO</sub> (% predicted) (mmol/Kpa/min) - mean (SD)	89.79 (18.13)	84.75 (18.05)	84.14 (12.98)	76.92 (18.13)	
K <sub>CO</sub> (% predicted) (mmol/Kpa/min) - mean (SD)	103.71 (17.29)	108.56 (17.53)	96.00 (12.17)	97.75 (15.36)	
FEV1(measured) litres - mean (SD)	2.51 (0.91)	2.36 (0.81)	2.75 (0.81)	2.58 (0.89)	
FVC(measured) litres - mean (SD)	3.27 (1.07)	3.04 (0.99)	3.47 (0.95)	3.30 (0.99)	
MEF75 (measured) litres/sec - mean (SD)	5.40 (3.32)	5.87 (2.93)	5.93 (2.41)	6.09 (2.45)	
MEF25 (measured) litres/sec - mean (SD)	1.40 (2.02)	1.17 (1.57)	0.97 (0.51)	0.97 (0.55)	
TLC(measured) litres - mean (SD)	5.87 (1.19)	5.59 (1.07)	6.15 (1.07)	5.58 (1.16)	
RV (measured) litres - mean (SD)	2.57 (0.61)	2.29 (0.7)	2.61 (0.87)	2.17 (0.51)	
TL <sub>CO</sub> (average) (mmol/Kpa/min) - mean (SD)	7.63 (1.93)	7.29 (1.8)	7.53 (2.56)	6.69 (2.40)	
K <sub>CO</sub> (average) (mmol/Kpa/min) - mean (SD)	1.39 (0.26)	1.46 (0.25)	1.29 (0.19)	1.31 (0.27)	
Percentage O <sub>2</sub> saturation - mean (SD)	96.33 (1.05)	96.88 (1.58)	97.07 (1)	98 (0.85)	

\*If data are transformed because of the distribution is non-normal, then the mean of the transformed data will be tabulated.