Basal and nitroglycerin-induced exhaled nitric oxide before and after cardiac surgery with cardiopulmonary bypass

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Background. Exhaled nitric oxide (NO) may reflect NO production and consumption but the pulmonary origin of NO in exhaled gas is not clear. There are also conflicting data on exhaled NO after cardiopulmonary bypass (CPB). Because intravenous nitrovasodilators increase exhaled NO by conversion to NO in the lung, we measured basal and nitroglycerin (GTN)-induced exhaled NO in patients having low-risk coronary artery bypass graft (CABG) operations using routine CPB. We reasoned that GTN-induced exhaled NO would be a primarily vascular mechanism, which would contrast with the airway epithelial origin of basal exhaled NO, and that they might be differentially influenced by CPB.

Methods. Breath-to-breath concentrations of gas phase NO were measured in 12 CABG patients before and 1, 3 and 6 h after CPB. After the baseline measurements, three increasing doses of 1, 2 and 3 μg kg⁻¹ intravenous GTN were given by a central venous catheter and exhaled NO and haemodynamic responses were recorded.

Results. Intravenous administration of 1, 2 and 3 μg kg⁻¹ doses of GTN produced a dose-dependent increase in exhaled NO and a reduction in systemic blood pressure. Baseline exhaled NO remained unchanged. Exhaled NO but not blood pressure responses were reduced 1 and 3 h after CPB.

Conclusions. The capacity of the lungs to increase exhaled NO in response to intravenous GTN is reduced after CPB, suggesting microvascular injury and/or atelectasis after routine open-heart surgery.

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Open-heart surgery causes postoperative pulmonary dysfunction ranging from a temporary and clinically insignificant reduction in arterial oxygenation to life-threatening injury manifested as acute respiratory distress syndrome.¹–³ Cardiopulmonary bypass (CPB) may cause this injury. The major mechanisms of severe lung dysfunction appear to be transient and incomplete lung ischaemia associated with pulmonary arterial blood flow diversion during CPB, followed by reperfusion of the pulmonary vascular bed together with a superimposed systemic inflammatory response.⁴–⁷

Nitric oxide (NO) is important in both the physiological control of lung function and in the pathophysiology of several lung diseases.⁸–¹⁰ In the lung, NO is an important regulator of intercellular communication, affecting pulmonary vascular and airway functions such as airway and microvascular reactivity and permeability.¹¹–¹⁴ Endogenous production of NO can be detected and monitored in the exhaled air of animals and man.¹⁵ In recent years, exhaled NO has become a valuable diagnostic and monitoring tool for airway inflammation in asthma and may become important for assessment of other inflammatory...
conditions. Although the cellular and molecular events underlying the pathological response to heart surgery are not entirely clear, NO is involved and could serve both to mediate and indicate lung injury in cardiac surgery with CPB.\textsuperscript{7, 16, 17}\n
NO concentrations are reduced in the expired air of patients after lung transplantation\textsuperscript{18} and in developed acute respiratory distress syndrome,\textsuperscript{19} but there are conflicting data on NO after routine CPB.\textsuperscript{19–22}\n
Several factors may be involved. One problem is the anatomical origin of NO in the expired air. Pulmonary vascular endothelial cells and airway epithelial cells generate NO continuously. Although Cremona and colleagues\textsuperscript{23} showed that vascular endothelial NO influenced NO concentrations in the expired air, expired NO is mainly of airway epithelial rather than of vascular endothelial origin.\textsuperscript{24} Hence altered pulmonary microvascular function may not affect expired NO.

Endogenous NO pathways can be augmented by administration of NO donors, such as nitroglycerin (GTN).\textsuperscript{25} Exhaled NO concentrations increase after vascular metabolism of intravenous NO donors,\textsuperscript{26, 27} and we have found this effect in humans using GTN.\textsuperscript{28} We suggest that GTN-induced exhaled NO could indicate the metabolic function of the pulmonary microvasculature.

We set out to clarify the characteristics of NO in the expired air after low-risk open-heart surgery with CPB. We compared airway epithelial mechanisms (basal exhaled NO) with vascular events (judged by exhaled NO responses to GTN). We hypothesized that CPB and open-heart surgery would cause pulmonary microvascular dysfunction and impaired gas exchange, and have different effects on airway and vascular NO mechanisms.

**Methods**

**Patients**

The study was approved by the ethics committee of our institution and informed consent was obtained from all patients. We recruited 12 patients who were undergoing myocardial revascularization (coronary artery bypass grafting, CABB) using CPB. All patients had good ventricular function with ejection fraction $>45\%$ and normal lung function as indicated by respiratory function testing and routine chest x-rays. Two patients were later excluded from the study; one had unexplained high basal exhaled NO (peak concentrations $>50$ p.p.b.) and data were incomplete in the other patient.

**Anaesthetic and surgical management**

Anaesthesia was induced with fentanyl 250–500 $\mu$g, etomidate 10–20 mg and pancuronium 8–12 mg. After orotracheal intubation, the lungs were ventilated with 50% oxygen–nitrous oxide mixture containing isoflurane 0.5–1.0%. Central venous and pulmonary artery catheters were inserted via the right internal jugular vein.

After cannulation for CPB, nitrous oxide was replaced by i.v. administration of propofol 100–200 mg h$^{-1}$ to supplement anaesthesia. During CPB, anaesthesia was maintained with propofol and remifentanil 400–800 $\mu$g h$^{-1}$ infusion. Blood pressure was controlled with small doses of metaraminol and phentolamine, as required. Anticoagulation was obtained with 300 heparin IU kg$^{-1}$ and activated clotting time was monitored and maintained greater than 400 s. Myocardial preservation included mild hypothermia ($32^\circ$C) and intermittent aortic cross-clamping with ventricular fibrillation.

**Exhaled nitric oxide measurement**

Breath-to-breath measurements of NO concentrations in the lower airways were made with a real-time, computer-controlled, integrated system (2000 series; Logan Research).\textsuperscript{18} Gas for analysis of NO and carbon dioxide was continuously withdrawn directly through a thin Teflon sampling tube placed in the main lower airways at a flow rate of 150 ml min$^{-1}$. As the concentration of exhaled gases depends on both production rate and ventilation, ventilation was standardized for inspired gas (oxygen 100%), tidal volume (5 ml kg$^{-1}$), respiratory rate (10 b.p.m.) and inspiratory and expiratory ratio (1:3).\textsuperscript{29} To eliminate the influence of positive end-expiratory pressure on gas phase NO,\textsuperscript{30} PEEP was set to zero.

**Study design**

Baseline measurements were made before CPB to assess endogenous values for exhaled NO. After the baseline measurements, three increasing doses of GTN 1, 2 and 3 $\mu$g kg$^{-1}$ were given via the central venous catheter and the exhaled NO and haemodynamic response were recorded. Between doses of GTN, a short time was allowed for the haemodynamic and exhaled gas variables to return to baseline values. The procedure was repeated 1, 3 and 6 h after CPB. Arterial blood was collected simultaneously for haemoglobin, blood gas and electrolyte analysis and full blood count.

**Data analysis**

Dynamic NO and carbon dioxide concentrations in exhaled gases during mechanical ventilation were analysed using a Microsoft Excel 4.0 macro, which calculated the peak and average NO concentrations and area under the NO concentration–time curve (AUC). The peak concentrations are the maximum concentrations of NO achieved at end-expiration. AUC is the integration of the area under the NO concentration curve over 30 s of the measurement and the average value is the mean concentration of NO over the 30 s of the measurement. Haemodynamic changes were recorded
and analysed in comparison with the baseline values. Data are given as mean (SD). Statistical analysis was performed on a Sony Vaio laptop (PCG-F809K) using SigmaStat Statistical Software (version 2.0; SPSS, Chicago, IL, USA). Biochemical and haemodynamic data and the GTN-induced exhaled NO data before and after CPB were assessed by one-way repeated measures analysis of variance followed by multiple comparison with the pre-CPB control group using Dunnett’s method or the Student–Newman–Keuls method for all pairwise multiple comparisons. To test for a relationship between basal and GTN-induced exhaled NO and arterial oxygenation, changes in $P_{aO_2}/F_{IO_2}$ ratios were calculated 1 and 3 h after CPB and correlated with changes in exhaled NO data. Correlation was assessed by the Spearman rank order correlation and linear regression. Statistical significance was accepted if $P<0.05$.

Results

Patient data

Patient details are summarized in Table 1. Two patients developed moderate bleeding after surgery, which required blood transfusion but no reoperation. All patients were extubated within 24 h after surgery. One patient developed transient phrenic nerve paralysis requiring 4 days’ stay in the intensive care unit; all others were discharged to the surgical ward on the day after surgery. All patients survived to hospital discharge without major complications.

Blood results

These results are summarized in Table 2. An inflammatory response to CPB was seen, with increased white blood cell and neutrophil counts, reaching a maximum 1 h after bypass and decreasing by the 6 h post-bypass measurement. In contrast, lymphocyte count appeared to be lower after CPB, and the number of circulating monocytes decreased markedly. There was a decrease in haemoglobin concentration and platelet counts during the perioperative period. Blood pH, $P_{CO_2}$, $HCO_3^-$ and electrolytes ($K^+$, $Ca^{2+}$) were consistent over the perioperative course, showing no significant change throughout the study period. The $P_{aO_2}/F_{IO_2}$ ratio decreased significantly after CPB, with return to a near-normal value 6 h after CPB.

Cardiovascular measurements

Mean systemic artery pressure was slightly reduced 1 and 3 h after CPB when compared with pre-CPB values. Pulmonary artery pressure showed no significant changes during the observation period. Cardiac index increased slightly after CPB and the systemic and pulmonary vascular resistance indexes decreased. Haemodynamic data are summarized in Table 3.

Exhaled nitric oxide

NO was detected in the exhaled air of all patients before CPB as a characteristic oscillating signal which appeared to increase with expiration, as judged by the carbon dioxide. Figure 1 shows representative NO and carbon dioxide signals before and after injection of GTN 1, 2 and 3 μg kg$^{-1}$ before CPB. Mean (SD) basal NO concentrations were 4.8

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Table 1 Patient details

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.0 (6.1)</td>
<td>54–75</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (8.8)</td>
<td>154–184</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>80 (9.2)</td>
<td>70–100</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>100 (30)</td>
<td>60–154</td>
</tr>
<tr>
<td>AXC time (min)</td>
<td>46 (20.8)</td>
<td>27–87</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>14 (4.4)</td>
<td>7–19</td>
</tr>
<tr>
<td>ITU stay (days)</td>
<td>1.3 (0.9)</td>
<td>1–4</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6.2 (0.9)</td>
<td>5–8</td>
</tr>
</tbody>
</table>

AXC=aortic cross-clamping; ITU=intensive therapy unit.

Table 2 Perioperative biochemistry data before and 1, 3 and 6 h after CPB. Data represent mean (SD) of 10 patients. *$P<0.05$ compared with appropriate values before CPB

<table>
<thead>
<tr>
<th></th>
<th>Before CPB</th>
<th>After CPB</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>4.7 (0.4)</td>
<td>5.1 (1.1)</td>
</tr>
<tr>
<td>$P_{O_2}/F_{IO_2}$ (kPa)</td>
<td>46 (10)</td>
<td>32 (12)*</td>
</tr>
<tr>
<td>$HCO_3^-$ (mM)</td>
<td>23 (2.6)</td>
<td>21.6 (2.4)</td>
</tr>
<tr>
<td>Base excess (mM)</td>
<td>−1.4 (1.3)</td>
<td>−3.5 (2.2)*</td>
</tr>
<tr>
<td>Potassium (mM)</td>
<td>4.1 (0.3)</td>
<td>4.2 (0.4)</td>
</tr>
<tr>
<td>Calcium (mM)</td>
<td>1.1 (0.1)</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td>Haemoglobin (g litre$^{-1}$)</td>
<td>12.6 (1.7)</td>
<td>9.4 (1.2)*</td>
</tr>
<tr>
<td>Platelets (10$^9$ litre$^{-1}$)</td>
<td>231 (55)</td>
<td>150 (32)*</td>
</tr>
<tr>
<td>WBC (10$^3$ litre$^{-1}$)</td>
<td>9.4 (4.4)</td>
<td>14.0 (2.9)*</td>
</tr>
<tr>
<td>Neutrophil granulocytes (10$^9$ litre$^{-1}$)</td>
<td>5.0 (1)</td>
<td>11.0 (1.7)*</td>
</tr>
<tr>
<td>Lymphocytes (10$^9$ litre$^{-1}$)</td>
<td>3.4 (3.8)</td>
<td>2.4 (2)</td>
</tr>
<tr>
<td>Monocytes (10$^9$ litre$^{-1}$)</td>
<td>0.7 (0.3)</td>
<td>0.3 (0.3)*</td>
</tr>
</tbody>
</table>

WBC=white blood cells.
Intravenous doses of GTN 1, 2 and 3 mg kg\(^{-1}\) caused a rapid, transient and dose-dependent increase in the exhaled concentration of NO (Figs 1 and 2) regardless of whether it was expressed as AUC or mean or peak exhaled NO. The time between injection and the increase in exhaled NO was about 10–12 s. Along with the transient increase in exhaled NO, systolic arterial blood pressure decreased transiently by 17, 22 and 27% and diastolic arterial pressure fell by 17, 21 and 21%. Similar changes were observed in pulmonary artery pressure after GTN. Blood pressure usually returned quickly to baseline values, spontaneously or after a small dose of methoxamine. Changes in heart rate and central venous pressure with GTN were negligible.

Endogenous exhaled NO concentrations did not change 1 and 3 h after CPB in these patients (Fig. 3). Measurements were made in the intubated patients 6 h after the operation, but at this time most patients were already making spontaneous breathing efforts. Although the data do not appear to be different from those at 1 and 3 h after CPB, they cannot be compared directly with those obtained during controlled mechanical ventilation.

The GTN-induced response in exhaled NO after CPB showed characteristic changes. The increases in exhaled NO caused by GTN were less than before CPB for peak, mean exhaled and AUC (Fig. 4). Because of spontaneous breathing 6 h after CPB, GTN administration and measurement of the exhaled NO response was often abandoned. As an internal control for the exhaled NO data, we also measured carbon dioxide output to ensure that the changes in exhaled NO were not caused by changes in exhalation profiles. The baseline peak exhaled carbon dioxide was similar before and 1 and 3 h after CPB [4.5 (0.2), 4.6 (0.2) and 4.6 (0.3)% respectively]. Similarly, end-tidal carbon dioxide remained the same for each GTN dose before and after CPB (data not shown).

In contrast to the reduced NO response to GTN after CPB, circulatory responses to GTN were comparable to those measured before CPB (Fig. 5).

### Discussion

We studied the effect of open-heart surgery with CPB on NO concentration in the expired air. Previous studies

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**Table 3** Perioperative haemodynamic data before and 1, 3 and 6 h after CPB. Data represent mean (st) of 10 patients. *P*<0.05 compared with appropriate values before CPB

<table>
<thead>
<tr>
<th></th>
<th>Before CPB</th>
<th>After CPB</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
<td>3 h</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats min(^{-1}))</td>
<td>64 (12)</td>
<td>78 (12)*</td>
<td>82 (8)*</td>
<td>76 (8)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>81 (13)</td>
<td>68 (9)*</td>
<td>68 (9)*</td>
<td>73 (10)</td>
<td>0.01</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>20 (4.3)</td>
<td>19 (2.8)</td>
<td>20 (3.5)</td>
<td>21 (5.3)</td>
<td>0.521</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>8 (3.6)</td>
<td>10 (3.3)</td>
<td>10 (3.4)</td>
<td>10 (4.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiac index (litres min(^{-1}) m(^{-2}))</td>
<td>2.2 (0.5)</td>
<td>2.6 (0.4)</td>
<td>2.9 (0.8)*</td>
<td>2.8 (0.6)*</td>
<td>0.01</td>
</tr>
<tr>
<td>SVRI (dyn s(^{-1}) cm(^{-5}) m(^{-2}))</td>
<td>2721 (377)</td>
<td>1809 (388)*</td>
<td>1763 (588)*</td>
<td>1832 (440)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVRI (dyn s(^{-1}) cm(^{-5}) m(^{-2}))</td>
<td>366 (151)</td>
<td>199 (102)*</td>
<td>271 (112)*</td>
<td>279 (101)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

MAP=mean arterial pressure; MPAP=mean pulmonary artery pressure; CVP=central venous pressure; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index.
reported no change, an increase or a decrease in NO concentrations using a variety of methods. \cite{19, 22, 28, 31}

We hypothesized that some of the contradiction might arise because basal exhaled NO might not directly reflect pulmonary vessel activity, which is thought to be the primary component of lung injury associated with open-heart surgery and CPB. To assess this possibility, we studied bioconversion of i.v. nitrovasodilators. \cite{26, 28} During this process, GTN is metabolized to NO, which is released and increases the NO concentration in the expired air.

We found that basal concentrations of expired NO did not change in the immediate perioperative period, and that exhaled NO induced by i.v. GTN was decreased after surgery. We consider that basal and GTN-induced exhaled NO are distinct features and that the physiological mechanisms contributing to exhaled NO are affected differently by CPB and heart surgery.

The anatomical site and the type of cells responsible for the production of NO remain a matter of debate. \cite{32} There is now little doubt that exhaled NO is generated within the lungs. Animal experiments show that NO does not come from systemic sources. \cite{23} We have also shown that cessation of pulmonary arterial blood flow in patients at the onset of CPB, or complete absence of pulmonary blood supply during lung transplantation, does not eliminate exhaled NO. \cite{18}

The pattern of exhaled NO overlaps with carbon dioxide, suggesting a lower airway origin of NO. \cite{33} Although vascular mechanisms could contribute to exhaled NO, recent considerations suggest that bronchiolar epithelial cells might be the principal source of NO in the gas phase. First is the distribution of nitric oxide synthase (NOS) isoenzymes. Type II NOS, found in the bronchial epithelium, can produce large amounts of NO. \cite{34} On the other hand, the small quantity of NO produced by type III or endothelial NOS is more likely to be scavenged by haemoglobin. Proinflammatory cytokines can induce a high-output NO pathway by type II NOS expression in airway epithelial cells. \cite{35} This mechanism is suggested to contribute to higher exhaled NO in asthmatic subjects, the first condition for which exhaled NO has been approved as a clinical diagnostic test. \cite{36} In addition to their effect on type II NOS induction, proinflammatory cytokines can affect type III NOS expression. However, the result of this effect seems to be downregulation by destabilization of NOS mRNA. \cite{37, 38} Finally, elegant studies by Sartori and colleagues, \cite{24} using inhaled or infused NOS inhibitor, suggest that exhaled NO is mostly of airway epithelial rather than of vascular endothelial origin. \cite{24} They concluded that basal exhaled NO does not indicate vascular production or endothelial function in healthy humans.

Although measurement of exhaled NO under basal conditions does not distinguish between airway and vascular
origin of exhaled NO, the preceding considerations suggest that basal exhaled NO in our study probably reflects airway epithelial activity, which is not affected by routine CPB and CABG. It remains possible that an inflammatory process affecting the epithelium could have produced an increase in NO production that was exactly balanced by increased degradation and metabolism.

Oxidative stress during ischaemia–reperfusion generally reduces NO generation and release by several mechanisms. We also know that NO is subjected to a number of consumption reactions in the fluid phase. One of the most important of these reactions, with potential relevance to acute lung injury, is consumption of NO by superoxide to form peroxynitrite. This reaction will produce a more potent oxidant, and also reduces NO bioavailability as a signalling molecule. We found that loss of NO bioactivity was one of the most sensitive biochemical targets of oxidant stress. In a model of leucocyte activation, NO-induced cGMP accumulation was reduced earlier and at lower leucocyte concentrations than other cellular responses, such as endothelial ectoenzyme function, changes in permeability, and cytotoxicity. Similar effects are found in rats. NO release at the surface of the lung is reduced during ischaemia and reperfusion. This could be partially prevented by giving superoxide dismutase, suggesting that superoxide-mediated consumption of NO was responsible for diminished NO.

These mechanisms may have reduced exhaled NO, as reported previously. Although these studies concluded that the decrease might indicate vascular injury with diminished endothelial contribution of NO, this is unlikely as Sartori and colleagues found that inhibition of endothelial NO did not affect exhaled NO. The study of Beghetti and colleagues is difficult to compare with our study because of differences in the methods, such as manual gas-sampling compared with our continuous analysis. They studied children who had surgery with CPB for repair of congenital heart defects, in whom the responses could be different from those in adults undergoing CABG. Others have reported reduced NO concentrations in the expired air after CPB, but these patients had longer CPB and manifest lung injury shown by changes in compliance and pulmonary vascular resistance. In obvious lung injury, both Brett and Evans and we found reduced basal exhaled NO concentrations, suggesting airway epithelial injury, as opposed to the studies of more routine CPB in this study and that of Brett and colleagues.

Although measurements of exhaled NO indicate NO concentrations in the gas phase, how these data may indicate in vivo NO metabolism is far from straightforward. The fluid phase reactions of NO may differ according to the anatomical location within the lung and may be affected in different ways by many physiological conditions and pathological processes. For instance, human lung ischemia–reperfusion causes a complicated picture of NOS expression, NO generation and consumption, and NO concentrations will depend on the local cytokines, the extent of airway inflammation, neutrophil activation, production of reactive oxygen species, and the condition of endothelial and airway epithelial cells. In addition, measured concentrations in the gas phase are affected by tidal volume, respiratory rate, PEEP and inspiratory time. Comparison of exhaled NO data both between and within different studies is difficult and limits research on exhaled NO in ventilated patients.

Reduced GTN metabolism to NO after heart surgery might be explained by several mechanisms. Although the enzymes responsible for conversion of GTN to NO have not been fully identified, the reaction appears to involve reduction–oxidation processes, particularly reduced cellular sulphhydrils. Oxidant stress associated with ischaemia–reperfusion could affect this enzyme system, and decreased GTN-converting enzyme activity could explain alterations in exhaled NO after GTN. Alternatively, NO produced by the activity of GTN-converting enzyme could be consumed by the fluid phase reactions we have discussed. Because the GTN-induced increase in exhaled NO is reduced even in
patients whose endogenous exhaled NO remains normal, altered GTN metabolism is a vascular effect rather than the result of airway or gas phase actions.

Reduced GTN induced responses caused by oxidant stress have been reported before, and could be the mechanism of both primary and secondary nitrate tolerance. Exhaled NO accurately reflects the development of nitrate tolerance in animal models. We have extended these observations to humans. Measurement of GTN-induced exhaled NO could be used to follow primary and secondary nitrate tolerance in the clinical setting and to assess treatment to modulate these events.

The vascular mechanisms that increase NO evolution in response to GTN could be affected by increased pulmonary blood flow and increased shear stress on the surface of endothelial cells. In rabbits, changes in blood flow around normal levels produced little change in expired NO, but in humans these phenomena are not yet clear. Endothelial injury could reduce NO production in response to increased shear stress, which might explain the reduction in exhaled NO after GTN. Although the reduced pulmonary vascular resistance after bypass and the similar effects of GTN on pulmonary artery pressure before and after CPB suggest that shear stress has only a minor influence on the differences in exhaled NO, further studies are required to investigate endothelial responses after CPB.

Although lung function is often impaired after CPB, only a few patients (1–2%) fulfil the criteria of acute respiratory distress syndrome. The risk factors for this syndrome appear to be independent of CPB. None of our patients developed severe lung injury, but some systemic inflammatory response was evident, with changes in blood pressure, cardiac output, and systemic vascular resistance. Inflammatory blood cells changed, with neutrophilia and reductions in lymphocytes and monocytes. These changes could have contributed to our observations. Activated neutrophils could cause oxidative stress, affecting GTN metabolism and increasing consumption of NO, as discussed above. Secondly, changes in lymphocytes and monocytes might alter cytokines. Although it is widely believed that CPB causes the release of proinflammatory cytokines, this issue remains controversial. A proinflammatory cytokine response seems to be paralleled by a phased anti-inflammatory response, and the net balance of inflammatory mediators is unclear. Bioassays in vitro suggest no net inflammatory imbalance in patients undergoing routine CPB, which might explain why, as in the report of Brett and colleagues, we found no increase in basal exhaled NO.

We had no clinical evidence of altered pulmonary vascular reactivity, from the decrease in pulmonary artery pressure after GTN, but gas exchange was impaired, as gauged from the alveolar–arterial oxygen gradient. Interestingly, this was associated with the decreased pulmonary metabolism of organic nitrates and release of NO.

Atelectasis could explain both gas exchange dysfunction and altered GTN-induced exhaled NO. This often occurs after open-heart surgery, and depends on anaesthetic

![Fig 5](image_url)Changes (Δ) in haemodynamic values compared with baseline concentrations (100%) after doses of GTN 1, 2 and 3 μg kg⁻¹ before and 1 and 3 h after CPB. Data represent mean and SEM of 10 patients. MAP=mean arterial pressure; MPAP=mean pulmonary arterial pressure; CVP=central venous pressure; HR=heart rate.
factors, surgical aspects and alveolar injury.1–3 Greater shunt and ventilation–perfusion mismatch could affect the distribution of GTN in the pulmonary vasculature. Exhaled NO could decrease despite no change in endothelial conversion of GTN to NO in non-ventilated alveoli, with a similar effect on pulmonary artery pressure. Further studies are needed to clarify the relationship between shunt and NO pathways after heart surgery, but two observations would argue against this explanation. First, basal exhaled NO remained unchanged in our study and we would expect that atelectasis would reduce basal exhaled NO by decreasing effective airway/alveolar epithelial function. Secondly, the increased shunt should also compromise carbon dioxide excretion, and this was not observed in our patients. Thus, we speculate that the observed compromise in GTN-induced exhaled NO is related to microvascular changes.

In conclusion, our data suggest that, after routine open-heart surgery, inflammatory responses and ischaemia–reperfusion injury are insufficient to impair the endogenous NO mechanisms that produce exhaled NO. The pulmonary and systemic haemodynamic response to a dose of GTN is also preserved, but the evolution of NO into expired air after GTN is reduced. This response could be further evaluated as a bedside test of metabolic function of the lung.

Acknowledgements

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