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Exhaled Nitric Oxide and the Systemic Inflammatory Response Syndrome (SIRS) after Cardiac Surgery

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Abstract (English)

Background: Septic patients produce increased nitric oxide (NO). We postulated increased exhaled nitric oxide (exNO) in SIRS after cardiopulmonary bypass surgery (CPB).

Methods: Forty-two intubated patients were studied postoperatively and at two-hour intervals for eight hours or until extubated. Hemodynamic indices, including indexed systemic vascular resistance (SVRi) and cardiac index (CI) were measured. ExNO was analyzed by ozone chemiluminescence.

Results: Six patients (14%) manifested SIRS, defined as SVRI < 1800 dynes·sec/cm^5/m^2. ExNO indexed by expired volume of minute ventilation and body surface area (exNO·$\dot{V}_E$i) was less in SIRS patients at each interval. Overall, normal exNO·$\dot{V}_E$i was 4.3 ± 0.4 nL/min/m^2 with a CI of 2.56 ± 0.05 L/min/m^2 and an SVRI of 2488 ± 62 dynes·sec/cm^5/m^2, whereas in SIRS exNO·$\dot{V}_E$i was 0.7 ± 0.3 ($p < 0.001$) with a CI of 2.97 ± 0.09 ($p < 0.001$) and an SVRi of 1826 ± 86 ($p < 0.001$).

Conclusions: Pulmonary production of NO in post-CPB SIRS differs from sepsis and may not be reflective of systemic levels. Increased pulmonary blood flow may scavenge lung production of NO thereby decreasing exhaled levels.

Abstract (Français)

Introduction Les patients septique produisent d'avantage d'oxyde nitrique (NO). Nous avons postulé que le NO expiré (exNO) sera augmenté dans la syndrome de reponse inflammatiore systemique (SIRS) après la "bypass" cardio-pulmonaire.

Methods 42 patients intubés ont été suivi à chaque deux heures post-opératoires. Les indices hémodynamique incluant l'indice cardiaque (CI) et la résistance vasculaire systémique indexée (SVRi) ont été évalués. L'exNO a été analyzé par la chimiluminescence d'ozone.

Resultats Six patients (14%) ont manifesté le SIRS, defini par un SVRi < 1800 dynes·sec/cm^5/m^2. ExNO indexé par la volume expiré de ventilation minutaire et de la surface coporelle (exNO· $\dot{V}_E$i) était moindre dans le SIRS à chaque intervale. Surtout, l'exNO· $\dot{V}_E$i normal était 4.3 ± 0.4 nL/min/m^2 avec un CI de 2.56 ± 0.05 L/min/m^2 et un SVRI de 2488 ± 62 dynes·sec/cm^5/m^2, tandis que dans le SIRS, exNO· $\dot{V}_E$I était 0.7 ± 0.3 ($p < 0.001$) avec un CI of 2.97 ± 0.09 ($p < 0.001$) et un SVRi of 1826 ± 86 ($p < 0.001$).

Conlusion Il ya des différences importantes entre le SIRS après la chirugie cardiaque et la sepsis. La course sanguin pulmonaire augmente explique peut-être les niveaux diminué de l'ExNO dans le SIRS.

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Introduction

Biological Nitric Oxide

Gaseous nitric oxide (NO), a free radical molecule, is ubiquitous within the human body as a paracrine signal transducer. First described as a product of inflammatory mammalian metabolism by Tannenbaum and co-workers in 1981, NO was subsequently identified as endothelium-derived relaxing factor (EDRF) by Furchgott and Ignarro et. al. in 1986, and vascular endothelial production of NO was confirmed by ozone chemiluminescence in 1987[1,2].

Biological nitric oxide formation is catalyzed from the guanido group of L-Arginine by nitric oxide synthase (NOS), of which three main isoforms have been described: constitutive endothelial cell NOS (ecNOS), constitutive brain or neuronal NOS (bNOS), and inducible macrophage-type NOS (iNOS). Molecular oxygen is consumed in this process, yielding free radical NO and L-Citrulline. NO may then diffuse either freely or by S-nitrosylthiol intermediates through cellular membranes to bind with cytosolic guanylyl cyclase, thereby converting guanosine 5'-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). In vascular wall smooth muscle, this then triggers a decrease in intracellular calcium concentration by enhancing calcium extrusion and sequestration into intracellular stores, and increases transcellular potassium permeability

resulting in a hyperpolarization of the smooth muscle membrane. Protein kinase activation also occurs through cGMP, leading to dephosphorylization of myosin light chains, thereby preventing the interaction of actin with myosin. This results in vascular smooth muscle relaxation, a mechanism similar to the vasodilatation stimulated by exogenous nitrates (nitroglycerin, sodium nitroprusside, nitrosamines, and sodium nitrite) via substrate increased production of radical NO[1,2]. This process is summarized in **Figure 1**. In vascular endothelium, NO is generated by ecNOS in response to endothelial shear stresses or triggering mediators such as acetylcholine, bradykinin or histamine. Inducible NOS, found primarily in polymorphonucleocytes/macrophages but also in smooth and cardiac muscle, is stimulated/upregulated in response to a variety of proinflammatory mediators such as endotoxin/lipopolysaccharide, platelet activating factor (PAF), interleukin 1 (IL-1), and tumour necrosis factor (TNF-alpha).

In the aqueous phase *in vivo*, nitric oxide radicals are unstable, with a half-life of only a few seconds before reacting with oxygen to form nitrite. Nitrite in turn may react with a variety of biologically active species, including oxyhemoglobin (thereby forming methhemoglobin), myoglobin, cytochrome C, and of course guanylyl cyclase, resulting in stable plasma nitrate. Nitrate may then be excreted renally. Thus biologically significant production of NO can be measured, albeit indirectly, through a difficult,

costly procedure involving column reduction of deproteinized plasma nitrate to nitrite followed by reaction with Greiss reagent and subsequent spectrophotometric analysis[3].

In its gaseous phase, NO exists in a stable equilibrium with nitrogen dioxide by reacting with oxygen as depicted in **Figure 2a**. Gaseous biological NO can be measured directly through ozone chemiluminescence analysis, whereby O_3 reacts with NO to form NO_2. A byproduct of this reaction is a red/infrared photon, which can then be detected by a thermoelectrically cooled, red-sensitive photomultiplier tube as shown in **Figure 2b**. Exhaled NO from intubated patients bypasses upper airway contamination[4] and is representative of endogenous tracheo-broncho-alveolar production. This approach provides a rapid, non-invasive, and relatively inexpensive measurement of biologically produced nitric oxide.

Nitric Oxide and the Systemic Inflammatory Response Syndrome (SIRS)

Septic shock is a familiar clinical entity characterized by fever (or hypothermia), tachycardia, tachypnea, leukocytosis (or leukopenia), and profound, medically refractory hypotension secondary to inflammation of an infectious origin. Recently, there has been formal recognition that a septic shock-like state may manifest in the absence of an identifiable infection. This more inclusive entity is the Systemic Inflammatory

Response Syndrome (SIRS), and it likely represents the common end-point corporeal response to a variety of inflammatory insults, including but not limited to infection[5].

In both septic and non-septic inflammatory shock (SIRS), overproduction of NO has been directly implicated not only as the causative agent of severe vascular hyporeactivity, but also for its cytotoxic, antimetabolic, oxidant effects, thereby contributing to end-organ dysfunction and failure. Many of the molecules identified in the pathogenesis of the sepsis response listed in **Table 1** are direct activators of NO or are byproducts of NO metabolism[1, 2,6].

Elevated circulating biological NO has been clearly demonstrated in SIRS patients. In a large prospective cohort study of 223 children in the intensive care unit (ICU), those with physician-diagnosed sepsis had elevated serum nitrite/nitrate levels over those without sepsis (127 ± 91 μM versus 39 ± 24μM, $p < 0.001$)[7]. Tsukahara found elevated macrophage iNOS expression ($p<0.001$) and serum nitrate/nitrite levels ($p<0.05$) in 44 patients with sepsis/SIRS compared with controls[8]. Severe burn victims also had increased plasma nitrate/nitrite compared to nutritionally matched controls ($p<0.01$), with the septic burns exhibiting even higher plasma levels[9].

NO has been strongly associated with the exaggerated vascular dilatation that is a hallmark of septic shock and other circulatory

derangements. In a study of 31 children with sepsis syndrome compared with 16 children in the ICU without, mean serum nitrite/nitrate levels were elevated over three consecutive days (day 1, 118 ± 93μM; day 2, 112 ± 94 μM; day 3, 112 ± 93 μM; versus 43 ± 24 μM, $p < 0.05$). Furthermore, those sepsis syndrome children with hypotension had higher mean serum nitrite/nitrate levels than sepsis syndrome children without hypotension (145 ± 97 μM, n=18, versus 82 ± 76 μM, n=13, $p < 0.05$) [10]. Ochoa and colleagues reported high plasma levels of nitrates/nitrites in septic ICU patients compared with non-septics ($p < 0.02$) and associated this with SVR ($p = 0.029$) and endotoxemia ($p = 0.002$). Interestingly, Ochoa also noted low nitrate/nitrite levels in trauma patients, even in the face of sepsis ($p <= 0.001$), and suggested a mechanism of NO inhibition in the face of blood loss and hypovolemia. There was no correlation with serum levels of L-arginine or L-citrulline[11]. Patients with high-output hepatic failure likewise exhibit markedly elevated levels of exhaled NO (exNO) compared with healthy controls, 190 ± 11 nL/min/m^2 versus 97 ± 8 nL/min/m^2, $p < 0.001$. This increased exNO corresponded with elevated cardiac index (CI), 4.3 ± 0.3 L/min/m^2 versus 2.9 ± 0.2 L/min/m^2, $p< 0.001$; and decreased indexed systemic vascular resistance (SVRi), 1732 ± 125 dynes/s*cm^5/m^2 versus 2680 ± 235 dynes/s*cm^5/m^2, $p = 0.004$[12]. Associations between NO and circulatory hyperdynamics have also been amply demonstrated in multiple non-clinical animal models[13-15], based

primarily on a model of endotoxemia mediated shock which is known to occur in humans[16].

Cardiac Surgery and Cardiopulmonary Bypass Induced SIRS

Notwithstanding the recent progress of off-pump coronary arterial bypass (OPCAB), the vast majority of cardiac surgical procedures require cardiopulmonary bypass (CPB) of the systemic circulation through a mechanical surrogate, the pump-oxygenator device. The passage of blood through this 'non-self' extracorporeal system is well known to stimulate a nonspecific "whole body" inflammatory response[17]. This response involves the activation of a host of cytokines and proinflammatory molecules, including: complement (C3-5a, C5b-9), the kallikrein-bradykinin cascade, PAF, Prostaglandins (E_2 and I_2), Thromboxane A_2, Leukotrienes (LTB4, LTC4, and LTD4), Endothelin-1, Serotonin, and other products of neutrophilic granulocytes such as oxygen free radicals with co-factor lysosomal enzymes and proteases. Coupled with this blood component cascade are the released products of endothelial cells from tissue regions of local ischemia/hypoperfusion. Thus are released the inflammatory interleukins including types one, six, eight, (IL-1, 6, 8), and tumor necrosis factor alpha (TNF-α). As well, circulating bacterial endotoxin (aka LPS-lipopolysacharride) is released, perhaps as a result of bacterial intestinal translocation[17-26]. Taylor

eloquently expressed the consequence of this nonspecific activation of the host inflammatory response as a spectrum of response ranging from the relatively mild, perhaps subclinical, to the severe and potentially life-threatening[27].

In approximately 5-10% of post-CPB patients, SIRS manifests with severe hemodynamic alterations characterized by a high cardiac output, and a low systemic vascular resistance, often with pressor refractory hypotension[21, 27,28]. The gravity of this hypercirculatory 'post-pump' state is such that approximately 20% of these patients will suffer serious organ dysfunction or failure, such as Adult Respiratory Distress Syndrome (ARDS), of which up to 80% may die[29].

Hypotheses and Motivation

Based on the current understanding in the literature and our laboratory on the role of NO in the SIRS phenomenon, we postulated the following:

- Patients suffering from post-CPB SIRS as defined by hyperdynamic/low SVR hemodynamic criteria, have elevated endogenous NO production compared to those with more normal circulatory hemodynamics.
- Broncho-alveolar (pulmonary) exNO, as measured by ozone chemiluminescence, is reflective of circulating endogenous NO levels.
- Therefore we anticipated that pulmonary exNO production would be elevated in post-CPB SIRS.

In exploring this question, we purposed to contribute scientific knowledge and heighten professional awareness regarding the complex, often lethal pathophysiology underlying SIRS following cardiac surgery.

Methods and Materials

Patient Demographics

Study Population

Forty-two patients undergoing cardiovascular surgery under cardiopulmonary bypass were studied over a four-month period in the immediate postoperative phase for hemodynamic parameters and levels of exNO.

Exclusion criteria

Patients who had moderate to severe pulmonary hypertension, asthma or chronic obstructive pulmonary disease (COPD), previous or current pulmonary surgery, renal failure requiring dialysis, hepatic failure, or who were on immunosuppressive therapy (including corticosteroids) were not studied. Apart from the resections, these conditions have all been associated with altered NO levels[12, 30]. Patients who had their operations performed without pulmonary artery flotation catheters and therefore could not provide index hemodynamic data were also not studied.

Operative Details

Perioperative management followed a standard protocol. Anesthesia consisted of a standard regimen of sufentanyl / midazolam / pancuronium and/or vecuronium. Two perfusion systems were used: CAPS Stockert-Shiley and HLM Stockert-Shiley. A bubble oxygenator (Bentley 10-Plus, Bentley Laboratories Division, Irvine, CA) was used for all cases. A synthetic colloid-crystalloid cardiopulmonary bypass priming solution based on pentastarch and lactated Ringer's solution was used. Anticoagulation was achieved with heparin bolus administered at a dose of 400 U/kg. Moderate systemic hypothermia (28° to 30° C by bladder probe) was used in all cases. Perioperative anemia to hematocrits of 0.18 L/L was accepted. Intraoperative blood removed by suction from the operative field was reinfused through the CPB circuit in all patients. At the end of bypass, anticoagulation was reversed with protamine sulfate at a rate of 1 mg of protamine to 100 U of heparin administered to achieve ACT values less than 140 seconds. Blood remaining in all components of the CPB circuit was returned entirely to the patients within 2 hours after weaning from CPB. All patients had mediastinal autotransfusion sump (ATS) catheters (Deknatel DSTC32S/ DRAC28S, FallRiver, MA) placed at the end of the operation. Drainage was to an underwater suction (20 cm H_20) unit (Atrium Single Collection Water Seal Chest Drain 2002, Hudson,

NH). ATS drainage was collected in-line with a citrate primed (Anticoagulant Citrate Dextrose, Baxter, Deerfield, IL) blood bag (Atrium in-line ATS blood bag 2550) permitting the reinfusion of lost autologous blood back to the patient. Collection was started as soon as 50% of the initial dose of protamine had been administered. All collected blood was filtered through an 80 μpore filter (Baxter 4c7752, Baxter Healthcare Corp., Glendale, CA) and autotransfused within four hours of collection. Additional chest tubes were placed at the surgeon's discretion at the end of operation. All operations were performed by one of four surgeons without significant change in surgical technique during the period of this study.

Postoperative Management

After surgery, all patients were admitted to the intensive care unit (ICU) for monitoring. No patients were re-explored postoperatively during the study period. Patients were extubated on the standard ICU fast track protocol based on established weaning criteria including adequate recovery of consciousness, hemodynamic stability on minimal pressor support, acceptable respiratory mechanics, and acceptable blood gases on minimal continuous positive airway pressure (CPAP). Using this

protocol, typically over 80% of patients are extubated within 12 hours of admission.

Study Protocol

Data Collection

Exhaled gas was collected immediately upon admission (time t=0) to the intensive care unit (ICU) and at two hour intervals thereafter until either extubated or eight hours postoperative. Hemodynamic indices (Cardiac Index (CI), Systemic Vascular Resistance (SVR), Central Venous Pressure (CVP), Mean Arterial Blood Pressure (MAP)) and the level of vasoactive pharmacological support (if any) were measured coincident with each exhaled gas sample collection. A pulmonary artery flotation catheter had been inserted intraoperatively with placement verified by chest radiography upon admission to the ICU. CI was measured using the thermodilution technique with the pulmonary artery flotation catheter. MAP was obtained via the radial or femoral arterial catheter inserted intraoperatively. CVP was measured using the proximal port of the pulmonary artery flotation catheter. Body temperature was obtained from a thermistor at the tip of the pulmonary artery flotation catheter and thus reflected core temperature. Indexed systemic vascular resistance (SVRi)

was calculated using standard techniques. These values were documented at 0, 2, 4, 6, and 8 hours after bypass or until the patient was extubated and NO was no longer collected. At each recording the coincident presence of nitrate drips, including nitroprusside, vasopressors (epinephrine, norepinephrine), and inotropes (dobutamine, amrinone, epinephrine) was noted. **Figure 3** shows an example of the data collection sheet used. This was subsequently modified to include MAP.

Definition of SIRS

The presence of SIRS was defined by the presence of a post bypass low-SVR state defined as SVRI < 1800 dynes·sec/cm^5/m^2 over two consecutive time intervals. This criterion was based on a hemodynamic cut-off of two standard deviations below the published normal mean value for SVRi[31].

ExNO Measurement

ExNO Sample Analysis

Samples were analyzed by chemiluminescence (Sievers 270, Boulder, CO, **Figure 4**) within 15 minutes of collection, an interval far less than the sixty-minute period during which these samples had been

determined to be stable. The principle of NO measurement is based on a gas-phase chemiluminescent reaction between NO and ozone. Photon emission from the electronically excited NO_2 to the ground state is in the red and near infrared spectral region and is detected by a thermoelectronically cooled red-sensitive photomultiplier tube, **Figure 2b**. The analyzer was configured simply according to the manufacturer's instructions with a glass purge assembly through which a constant flow of purified nitrogen carrier gas was directed to the analyzer inlet valve at a pressure of 6 torr subatmospheric. The analyzer signal, expressed in millivolts with an integration time of 2.0 seconds, was recorded graphically on an analog plotter (Servogar 120, Austria, **Figure 4**) and converted into parts per billion (ppb) of NO by comparing the sample signal with a calibration signal.

Analyzer Calibration

Initial analyzer calibration using NO standards established a linear response of the analyzer to varying quantities of NO up to 32 ppb. NO standards were created by diluting varying quantities of a known concentration of NO (8 ppm) with 50 ml purified nitrogen in glass syringes and then injecting 15 ml aliquots into the glass gas purge vessel. The NO detection threshold and sensitivity of the analyzer was 1 ppb. All readings below threshold were recorded as 0 ppb. Recalibration was performed

daily at 24 ppb. An example of a calibration assay is reproduced in **Figure 6**.

Baseline Measurements

Varieties of baseline studies were performed with normal, non-intubated human volunteer exNO, thereby including upper airway contribution. Ventilation was performed from a mouthpiece attached to an Ambu-bag with 100% O_2 inflow and a one-way valve via Tygon tubing and a T-connector. Pre-ventilation was performed for 5 minutes at a normal respiratory rate. Pre-hyperventilating (respiratory rate > 24) with 100% O_2 was noted to cause a moderate depression in expired NO levels as well as some subject discomfort and was not used. ExNO gas samples were drawn directly from the collection bag in 15 ml aliquots and injected into a glass reservoir connected to the analyzer inlet valve. The concentration of exNO in each sample was calculated from the arithmetic mean of three such aliquots. ExNO with normal 100% O_2 preventilation was approximately 8 - 18 ppb, or 96 – 230 nL/min, see **Figure 7**. The expired volume of minute ventilation ($\dot{V}_E$) had a significant impact on measured exNO production, as shown in **Figure 8**. The observed effect of ventilation on exNO has been suggested by other authors[32-34] and is likely more specific than the reporting of exNO as the raw peak NO

concentration[35]. These normal values for exNO are consistent with the findings of Dillon and Borland[4, 34].

Six intubated preoperative cardiac surgery patients were also studied, thereby bypassing the upper airway contribution to exNO. This had been done as a part of an earlier protocol that was later discarded over logistical concerns. ExNO in these patients, (not included this study), ranged from 1.3 – 7 ppb, with a mean of 3.8 ± 1.5 ppb. This is comparable to the published data[4, 36,37].

ExNO Study Protocol Sample Collection

Expired endotracheal airway gas was collected into a 5 liter Kevlar (Hans-Rudolph, Kansas City, MO) impermeable sampling bag after the patient had been pre-ventilated with 100% oxygen for two minutes. The sampling bag was connected via a one-way valve and a Wright volumetric flowmeter (Wright Inc, 100 L) to the center arm of a large three-way metal valve stopcock (W.E. Collins, Braintree, MA). 100% oxygen was supplied to the inlet arm of the three-way stopcock through manual pressure ventilation by an Ambu-Bag via 20 cm of polyvinyl (Tygon) tubing and a one-way valve. The inlet/outlet arm of the three-way stopcock was connected directly to the endotracheal tube with 20 cm of Tygon tubing. All tubing and valves as well as the sampling bag were flushed with the

patient's exhaled gas while on 100% oxygen prior to sample collection (**Figure 5**).

Two collection protocols were enacted according to the clinical situation. In unconscious patients, gas collection was performed by manually ventilating the patient over a series of 5-second breath holds during which total expired gas and total time was measured to calculate minute ventilation ($\dot{V}_E$). Reproducibility of the impact of the $\dot{V}_E$ parameter on exNO sampling was assessed in a subgroup of ten patients subjected to repeated measurement of twenty-second breath-holds. This was found to be accurate within 5%. All such repeat measurements were done within 15 minutes of the primary sampling. In spontaneously breathing conscious or semi-conscious intubated patients the collection bag was connected via a one-way valve and a Wright volumetric flowmeter (Wright Inc) to the outport of a #1400 Rudolph uniflow valve (Hans-Rudolph, Kansas City, MO). The patient's endotracheal tube was connected to the bidirectional port of the Rudolph valve with inflow provide by 100% oxygen from an Ambu-Bag reservoir. Again, total expired gas and time were measured to provide $\dot{V}_E$. Care was taken at all times to ensure against atmospheric contamination, although our comparison with normal volunteer ExNO suggested that the impact of this was minimal. Typical postoperative study subject output over each of the sampling intervals is shown in **Figure 9a,b**.

ExNO Standardization

As exNO was observed to vary with the $\dot{V}_E$ and correlated with body surface area (Spearman's rho = 0.27, $p < 0.001$), it was necessary to standardize exNO in these terms. Indexed in terms of $\dot{V}_E$, exNO in ppb $\cdot \dot{V}_E$ in L/min becomes exNO$\cdot \dot{V}_E$ in nL/min. When indexed for body surface area (BSA) this becomes exNO$\cdot \dot{V}_E$i (nL/min/m^2).

Statistical Analysis

Data were analyzed using SPSS 8.02 for Windows 98 (SPSS, Chicago, IL). All grouped data is expressed as mean ± SEM. Comparisons were made using the Student's t-test (two-tailed) for mean data or Fisher's exact test for proportional quantities. Assumption of equivalence of variance was based on Levine's test. Likelihood ratio chi-square statistic was used to compare subgroup proportions. One-way analysis of variance was used to determine changes over time. Nonparametric (two-tailed) Spearman's product moment coefficient was calculated for data co-relationships. Statistical significance was set in all tests to $p < 0.05$. All tables and charts were created using Excel 97 on Windows 98 (Microsoft, Seattle, WA).

Results

Baseline Parameters

Preoperative

Baseline preoperative parameters were similar between the SIRS and normal patients in terms of gender, age, weight and body surface area, renal function, circulating hemoglobin, cardiovascular morbidity, and smoking. Preoperative cardiovascular and non-steroidal anti-inflammatory pharmacology was likewise similar. One patient in the SIRS group, a catheter lab emergency, was on an intra-aortic balloon pump prior to surgery; a non-statistically significant incident (**Table 2a**). The majority of patients (33 of 42, 79%) underwent routine elective first-time cardiac surgery (**Table 2b**). There was no significant difference between groups in the types or distribution of procedures performed.

Intraoperative

The incidence of amrinone and transexamic acid use did not differ significantly between groups. Cardiopulmonary bypass times, cross-clamp times, and intra-operative blood loss were also similar. One patient in each group received two units of packed red blood cells intra-operatively (**Table 2b**).

Postoperative

There was a non-significant trend towards an increased incidence of nitrate drip usage (defined as present for two or more time intervals) in normal patients (**Table 2c**). Nonetheless, additional analysis was performed because of the theoretical concern that these drugs may serve as nitric oxide donors[53]. Two-sided t-testing of the group mean data failed to show a significant impact on exNO production. Patients on nitrate drips, including nitroprusside, exhaled 4.1 ± 0.5 versus 3.3 ± 0.5 nl/min/m^2 ($p = 0.29$) for those not on a drip (**Table 3a**). Likewise, paired t-testing of each patient while on/off the nitrate drips did not show a change in exNO production (**Table 3b**). Pressor and inotrope usage likewise had no impact on exNO.

While having similar intra-operative blood loss (**Table 2b**), patients with SIRS experienced twice as much bleeding on average as the normal group postoperative. However, with re-circulation of shed mediastinal blood, hemoglobin levels drawn between six and twelve hours postoperatively did not differ significantly (**Table 2c**). One patient in the SIRS group was transfused two units of packed red blood cells, a non-significant difference.

Attrition

The attrition secondary to extubation by the rapid weaning protocol was as follows: 4 within the first 2 hours postoperative, 10 by the 4th hour, 15 by the 6th hour, and 20 by the 8th hour. **Figure 10** illustrates the rate of attrition by group. These patients were no longer studied because of the significant contribution from the upper airways to exhaled NO[4]. These patients were therefore excluded from subsequent time points analysis. While there was a trend towards longer intubation times for SIRS patients, 66% (4/6) at 8 hours versus 50% (18/36) for the normal patients, there was no statistical difference.

Exhaled NO

Overall Postoperative Time Course of ExNO·$\dot{V}_E$i

The average concentration of postoperative exhaled NO across all time periods was 1.5 ± 0.1 ppb with a $\dot{V}_E$ of 4.8 ± 0.1 L/min, yielding an exNO·$\dot{V}_E$ of 7.1 ± 0.7 nL/min, indexed by BSA to 3.7 ± 0.3 nL/min/m^2.

Mean exNO·$\dot{V}_E$i decreased after two hours postoperative to reach a stable plateau by six hours (**Figure 11**, $p < 0.05$ by one-way ANOVA).

Correlative Associations

ExNO·$\dot{V}_E$i showed a significant inverse association with cardiac index during the initial postoperative phase (**Table 4, Figure 12**). After 4 hours, exNO·$\dot{V}_E$i became more strongly correlated with the duration of cardiopulmonary bypass (**Table 4, Figure 13**). No correlations were found between exNO·$\dot{V}_E$i and any preoperative (age, creatinine, hemoglobin), other intraoperative (cross-clamp time, operative blood loss), and other postoperative (creatinine, hemoglobin, total or interval bleeding, SVRi, MAP, PCWP, CVP, temperature) continuous variables. Of particular note, no significant association was found between exNO·$\dot{V}_E$i and SVRi.

Normal versus SIRS

Groups

Of the forty-two patients studied, six patients (14%) met the low SVRi definition for SIRS (**Table 5**). Between these two groups, ExNO·$\dot{V}_E$I, SVRi (by definition), CI, MAP, and bleeding were significantly different (**Table 5, Table 6**). This is summarized as follows:

Exhaled NO

Exhaled nitric oxide was decreased at all time intervals in SIRS patients (**Figure 14**). Averaged NO output over all the time intervals was

0.7 ± 0.3 nL/min/m^2 for the SIRS patients versus 4.3 ± 0.4 nL/min/m^2 for the normal patients ($p < 0.001$). The raw concentration of exhaled NO was 0.3 ± 0.1 ppb (majority below detection threshold) in SIRS patients, and 1.8 ± 0.2 ppb in the normal group.

Hemodynamic Parameters

SVRi was decreased at all measured time intervals for the SIRS patients (**Figure 15**). Averaged SVRi over all of the time intervals for the SIRS patients was 1826 ± 86 versus 2488 ± 62 dynes·sec/cm^5/m^2 for the normal patients ($p < .001$).

Cardiac index was increased at all time intervals in those with SIRS (**Figure 16**). Averaged CI was higher in the SIRS group, 3.0 ± 0.1 versus 2.6 ± 0.0 L/min in the normal patients ($p < 0.001$).

MAP was lower in SIRS patients for the majority of time points (**Table 5**), and was lower on average, 81.1 ± 2.2 versus 89.4 ± 0.9 mmHg ($p < 0.001$).

CVP and PCWP did not differ significantly between the two groups.

Other Parameters

Interval bleeding was greater in SIRS between most time points (**Figure 17**), and averaged 346 ± 36 versus 224 ± 17 ml ($p = 0.003$).

Temperature did not differ significantly between the two groups.

Discussion

Summary of Findings

We measured exNO from intubated patients following cardiopulmonary bypass surgery and found that levels decreased by four hours postoperative. Initially, exNO correlated inversely with CI. After the first few hours postoperative, the level of exNO tended to correlate with the duration of cardiopulmonary bypass. Patients with SIRS post CPB showed consistently higher CI, lower MAP, and greater bleeding with recirculation of blood. In contrast to our initial expectations, SIRS patients exhaled decreased amounts of NO at all time points.

NO levels post CPB

Published reports show conflicting results with regard to NO production during and after CPB. While cardiac surgery patients overall may exhale less NO compared to healthy individuals[52], the production of NO by these patients during and/or after surgery with CPB has been variously reported as being possibly increased[30, 38], unchanged[37, 39], or decreased[36]. In a study of 95 patients, circulating nitrite (nitrates not measured) was found to be elevated during and immediately following CPB, which was not sustained in the postoperative period ($p<0.005$) [40]. An earlier study by Hill et. al. showed progressively increasing levels of

exNO by ozone chemiluminescence during the course of CPB and found that randomized patients treated with methylprenisolone (MPSS) had decreased exNO both during and immediately following CPB, and associated this to decreased circulating TNF-α and IL-6 levels[30]. In contrast, SJ Brett and colleagues failed to detect any increased production of serum nitrate/nitrite or exhaled nitric oxide during or after CPB, despite clear increases in myeloperoxidase markers for inflammation. They found mean exhaled NO (non-indexed) was 7.3 ± 2.7 ppb on induction, 10 ± 2.9 ppb pre-bypass, 6.2 ± 1.3 ppb post-bypass before protamine, and 8.1 ± 2.1 ppb in the recovery room[37]. Similarly, serum nitrate/nitrites did not increase during or after CPB in a study designed to assess the impact of temperature and pulsitility of CPB flow on plasma nitrate/nitrite[41]. Michalopoulos likewise found low postoperative levels of exhaled NO, which on examination of the reported data, tended to decrease by 8 hours after cardiac surgery (from 3.7 to 2.6 ppb) [39]. More recently, in a finding interpreted as a positive marker for CPB induced pulmonary injury, exNO was found to be decreased 26% from 7 ± .8 to 4.4 ± 0.5 ppb ($p < 0.05$) in 30 children with acyanotic heart disease following CPB[36].

While NO measuring technique may explain some of these differences, it is likely that net NO production may be dependent on the interplay of several variables. Measuring plasma / urine nitrates or nitrites

in isolation may not give an accurate reflection of endogenous NO production. Certainly our own data suggest an important time course element to NO production, a finding reflected by others[39, 40] and perhaps sufficient to explain these apparently disparate findings. ExNO production may by subject to additional modulating factors.

ExNO and Pulmonary Blood Flow

Pulmonary blood flow may be one key factor regulating exhaled expression of NO. Carlin et al. showed that increasing flow rates was associated with decreasing exNO production in blood perfused isolated lung preparations. Administration of a NOS inhibitor (nitro-L-arginine) resulted in decreased NO production and simultaneously increased pulmonary artery pressures, supporting the role for NO in the regulation of basal vascular tone in the pulmonary circulation[42]. Furthermore, pulmonary excretion of exNO was specifically dependent on the flow rate of blood through the lungs in that exNO increased at low or static flow rates and decreased at higher flow rates. ExNO was higher in non-blood, fluid albumin perfused lungs and did not vary with flow rate suggesting a scavenging effect related to hemoglobin[43]. Stitt and colleagues showed that pulmonary blood carries away nearly three-quarters of lung generated NO in male Sprague-Dewey rats[44].

We found that exhaled NO was inversely related to cardiac index, particularly in the initial hours postoperatively. Cardiac index necessarily mirrors overall pulmonary blood flow. Interestingly, while cardiac index remained relatively stable throughout the study period, exNO decreased significantly after four hours. This may be due to improved regional blood flow as pulmonary vascular regulation recovers from the insult of CPB. Byrick and Noble found that CPB with bubble oxygenators resulted in an immediate postoperative increase in pulmonary vascular resistance of greater than 100% with a coincident increase in cardiac output compared to preoperative levels[45]. This increase in PVR following CPB was likewise observed by Heinonen[46]. Elevated PVR may translate into regional pulmonary disparities in blood flow (shunting) at a given CI with a consequently inefficient blood scavenging of NO and therefore greater elimination via exhaled alveolar gas. Further support for inefficient NO washout may be evident in Morita's study, where CPB induced an increase in PVR and a decrease in serum NO levels in piglets[47]. This would explain the higher stable levels we saw in the early post-operative period that were sensitive to changes in cardiac index. Once PVR decreased and washout occurred, exNO subsequently decreased and became more reflective of CPB time.

ExNO and Bypass time – iNOS induction

Later production of exhaled NO was directly associated with bypass time and may reflect changes wrought by CPB induced inflammatory injury on the lung. This may represent a growing contribution of inducible calcium/calmodulin independent NOS production as an inflammatory sequela to the insult of CPB perfusion. Lu et al showed that ischemia-reperfusion alone could upregulate iNOS mRNA expression and iNOS enzyme activity and downregulate cNOS enzyme activity over 180 min reperfusion in isolated, blood perfused rat lung[48]. A time course of four hours or greater would certainly be concordant with the known lag time of biological enzyme synthesis.

ExNO and ecNOS - Autoregulation

Alternatively, the initially higher NO levels measured overall may reflect an increase in pulmonary Ca2+/calmodulin dependent (e-c)NOS activity. The work of Fuji, Goldberg and Hussain in the LPS septic pig model suggested that this activity could occur in the absence of enhanced protein expression of ecNOS, possibly as a result of increased cofactor and substrate availability[49]. Beginning with the initiation of CPB, this is concordant with the essential time course of protein-enzyme synthesis, a process of mRNA induction and transcription requiring several hours to complete under normal circumstances. Such an upregulation of enzyme activity would be teleologically advantageous to improve blood flow in

hypoperfused alveolar-adjacent regions of pulmonary tissue in vasoconstricted lungs. As blood flow improved, and milieu homeostasis was re-established, whatever mechanisms involved in activating ecNOS would be feedback inhibited to down regulate NO production to lower levels. In fact, NO itself is known to be inhibitory to NOS activity[1]. Thomae KR et al. found that NO produced by cytokine activated rat pulmonary artery smooth muscle was cytotoxic to cocultured rat pulmonary artery endothelium[50]. Furthermore, as regional blood flow improved, hemoglobin turnover would be augmented, enhancing the intravascular scavenging effect, which might adsorb any additional NO that might otherwise have diffused into the intra-alveolar compartment for atmospheric excretion.

Hemodynamic SIRS and NO post CPB

The recognition of SIRS by hemodynamic criteria has been well documented. Cremer et al. identified 10 α-constrictor dependent post CPB patients with SVR < 800 dynes*sec/cm^5 with increased cardiac indices (hyperdynamic) and compared them with 10 control post CPB patients and found significantly elevated IL-6 levels as well as elevated elastase, TNF-α, soluble TNF receptor, IL-8, E-selectin, soluble intercellular adhesion molecule, and endotoxin[21]. Kristof and Magder

similarly categorized low SVR as a probable manifestation of SIRS in 35 of 79 non-sequential patients (44%), defined as two consecutive time intervals post-CPB with indexed SVR < 1800 dyne*sec/cm^{5}m^2. While not strictly α-constrictor dependent, these patients did exhibit a decreased mean arterial pressure (MAP) over time ($p < 0.05$) [31].

We discovered that patients suffering from SIRS hemodynamics had decreased exhaled NO following cardiopulmonary bypass compared to normal patients. A search of the world English language Medline literature from 1966 to mid 2000 failed to show any other studies measuring exhaled NO in SIRS post CPB. Other markers have been looked at however. Myles compared 15 cases of "low SVR syndrome" defined as SVR < 750 dynes*s/cm^5 on at least two occasions more than two hours apart with 29 controls with normal SVR > 900 dynes*s/cm^5 at all times. While cases required significantly more epinephrine / norepinephrine support ($p < 0.001$), had longer ventilation times ($p < 0.05$), and prolonged ICU courses ($p < 0.05$), there was no difference in the measured plasma or urine nitrate (but not nitrite) with controls. As in our study, there was no association in plasma nitrate levels and perioperative nitroglycerin infusion[28]. The only other study extant described three patients with a 'vasoplegic syndrome'; SVR < 900 dyne*sec/cm^5*m^2 and α-constrictor dependent, having a sustained

increase in plasma nitrites postoperatively. Nitrate levels were not measured[40].

The detection of decreased NO levels post bypass is interesting in light of the expectations for increased levels from the septic literature. Clearly, CPB induced inflammation differs pathophysiologically from inflammatory sepsis despite sharing clinically similar endpoints. Perhaps this shouldn't be surprising, given the nature of cardiac surgery, sharing as it does the biophysiologic interplay of a traumatic / hemorrhagic insult, tissue ischemia while on bypass, and CPB pump-oxygenator induced inflammation.

Our finding that exhaled NO is particularly decreased in post CPB SIRS is perhaps explained by the increased pulmonary blood washout of NO into the systemic circulation as a consequence of elevated CI seen in these patients. Furthermore, these patients experienced significantly greater post-operative bleeding with recirculation of shed blood. It may be that the prolonged circulatory pathway with the filtering of larger formed blood elements diminishes the NO content and production capacity of the blood before it is reintroduced back into the circulation, thus enhancing the blood scavenge effect. Alternatively, patients with very severe inflammation may simply produce less exhaled NO. In patients with adult respiratory distress syndrome, exhaled NO is decreased from a normal

5.5 ± 0.8 to 1.13 ± 0.36 ppb, levels similar to what we observed (1.5 ± 0.1 ppb)[51]. Trauma patients with sepsis, a closer analogy to post CPB SIRS than sepsis alone, exhibit decreased serum nitrate levels compared to healthy controls[11]. This is not inconsistent with septic animal models of SIRS secondary to endotoxemia, where the increase in NO markers is a delayed phenomenon, not coincident with the onset of hyperdynamic circulation[13, 44,49,50].

Conclusion

Cardiopulmonary bypass engenders a complex, poorly understood inflammatory response in the cardiac surgery patient. The expression of exNO consequent to this phenomenon likely represents the interplay of changing endogenous lung production, pulmonary blood flow elimination and hemoglobin scavenging. There may also be contributions from systemic NO production, and a time response dependent element related to upregulation of iNOS transcription. SIRS in this setting is associated with decreased exhaled NO, for which increased pulmonary blood flow scavenging may be largely responsible. A study of the potential relationship between exNO and pulmonary vascular hemodynamics may provide insight on the precise role of endogenous lung production of nitric oxide and the pathophysiology of post CPB pulmonary hypertension.

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Figures

Figure 1

Mechanism of NO mediated vasorelaxation

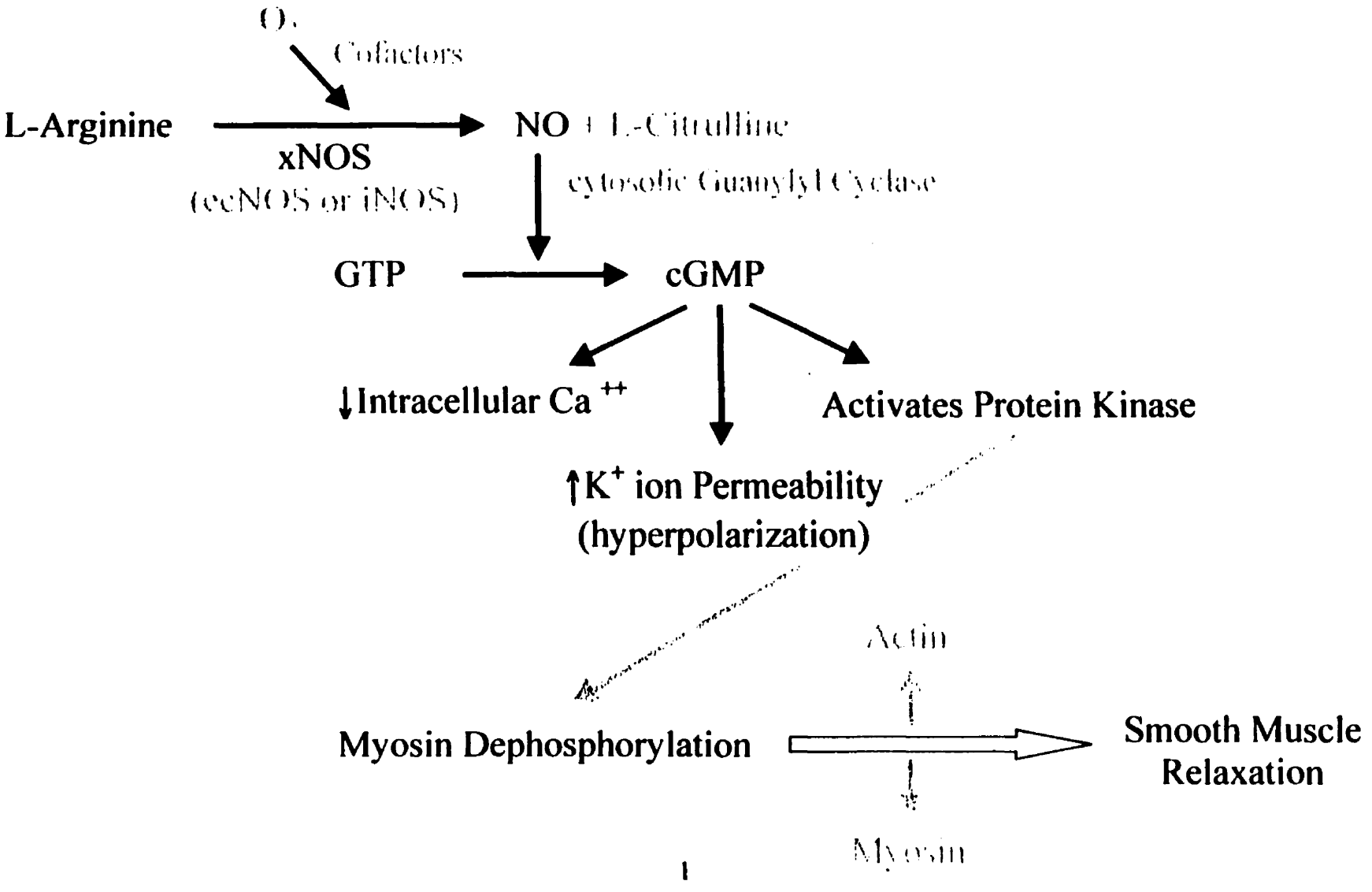
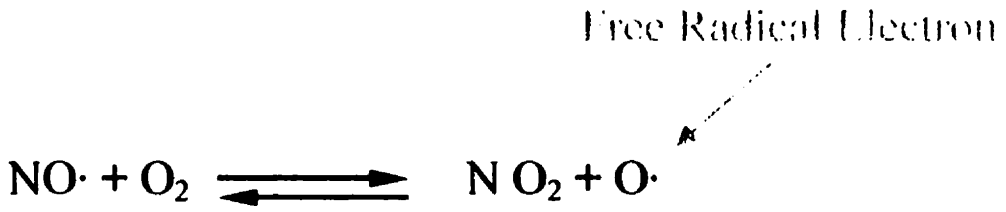

O2
Cofactors
L-Arginine
xNOS
(ecNOS or iNOS)
NO + L-Citrulline
cytosolic Guanylyl Cyclase
GTP
cGMP
↓Intracellular Ca ++
Activates Protein Kinase
↑K+ ion Permeability
(hyperpolarization)
Actin
Myosin Dephosphorylation
Smooth Muscle
Relaxation
Myosin

Figure 2a

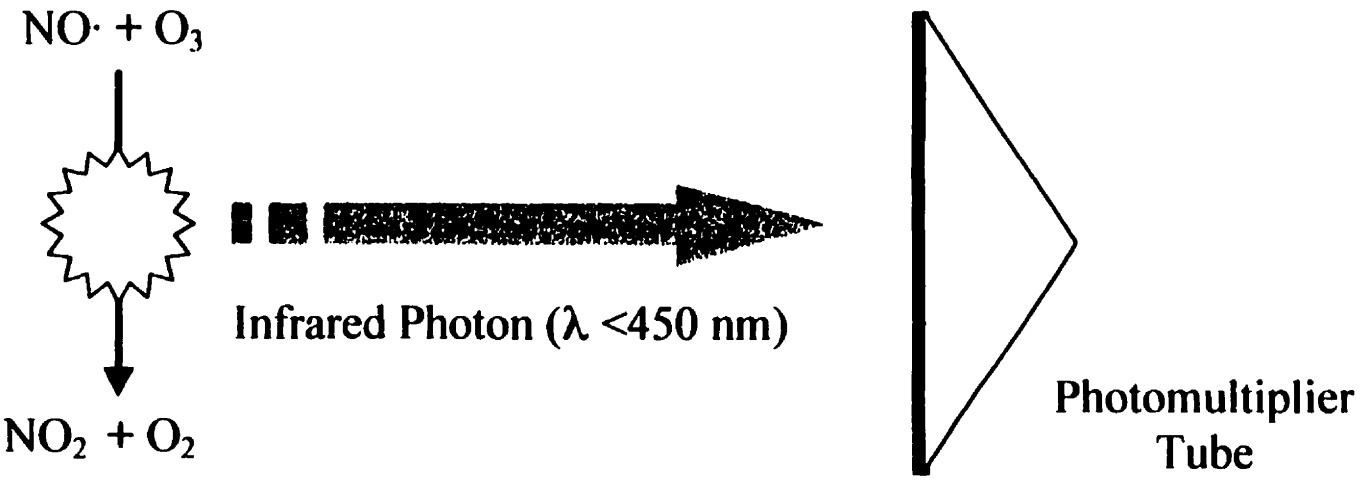
Gaseous NO free radical equilibrium

Figure 2b

Mechanism of ozone chemiluminescent detection of NO via released infrared photon byproduct of gaseous NO reaction with generated ozone


Free Radical Electron
NO· + O2
N O2 + O·

2a


NO· + O3
Infrared Photon (λ <450 nm)
NO2 + O2
Photomultiplier Tube

2b

Figure 3

Sample data collection form

Name

RVH Number

Operation

Surgeon

O.R. Start

X-Clamp On

X-Clamp total

PMHx

Meds

O.R. Notes

Date

Age

Weight

BSA

O.R. End

X-Clamp Off

Bypass Time

Cardioplegia

Albumin

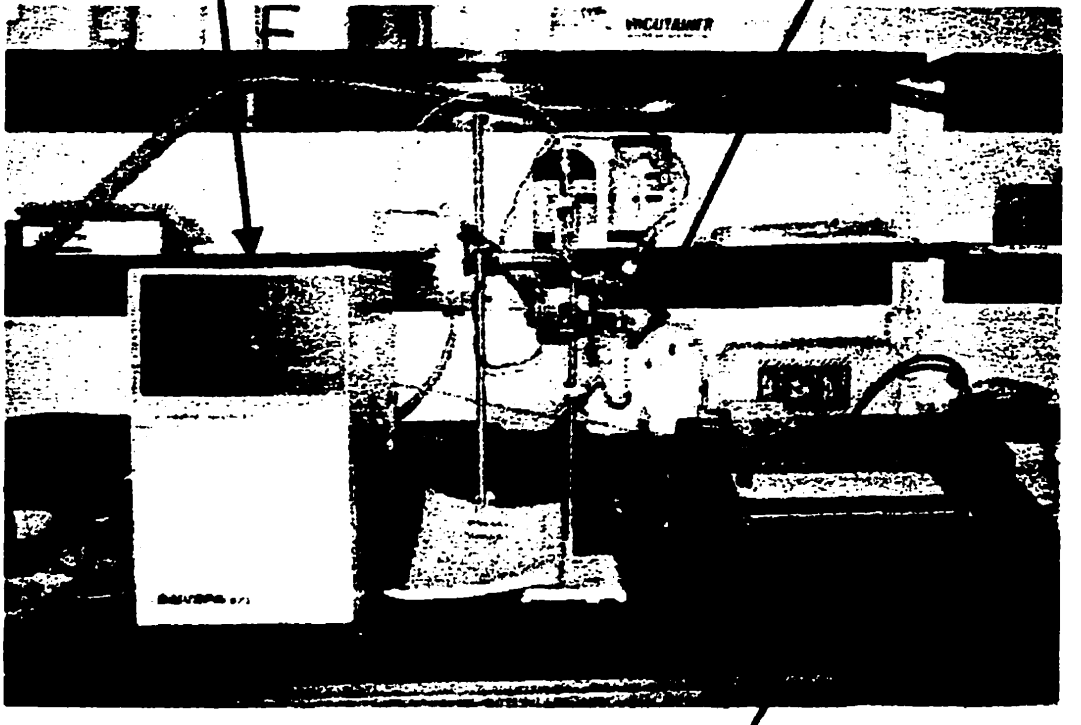
	T = 0	T=2 hours	T= 4 hours	T= hours	
Cardiac Index Heart Rate					
CVP PCWP SVR					
Drugs					
NO ex (ppb) Vm (L/min)					
NOex *Vm NOex*Vm/Wt Renal [Ur] Renal [Cr]					
Temp SIMV FIO2 pH pO2 pCO2 Notes					

Figure 4

ExNO sample analysis equipment setup: gas-purge input, ozone chemiluminescence analyzer, and analog plotter output

Sievers 270 - Ozone Chemiluminescence Analyzer

Gas Purge Assembly with N_2 carrier



Servogar 120 - Analog Plotter

Figure 5

Expired NO collection system for intubated patients

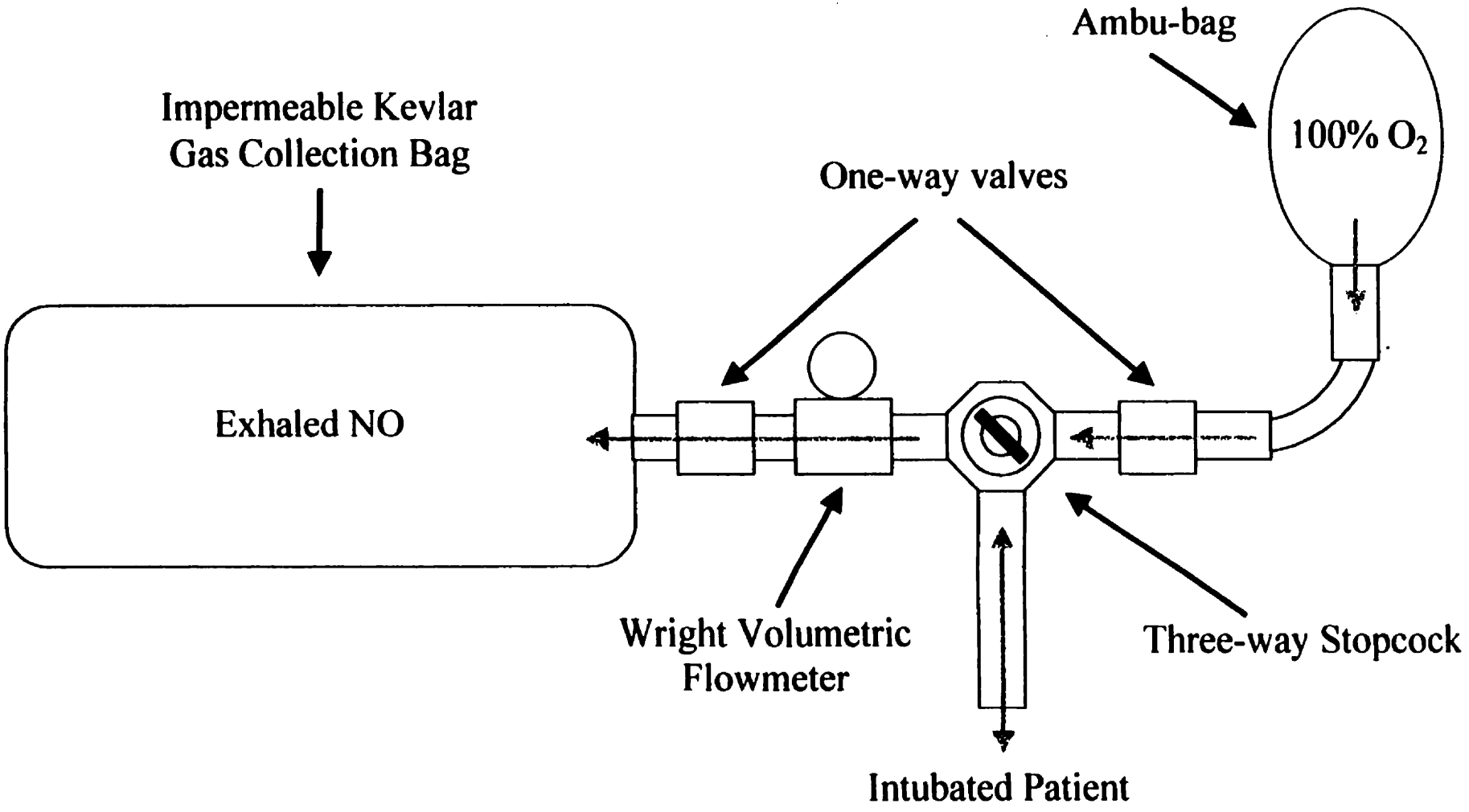

Ambu-bag
Impermeable Kevlar
Gas Collection Bag
100% O_2
One-way valves
Exhaled NO
Wright Volumetric
Flowmeter
Three-way Stopcock
Intubated Patient

Figure 6

Ozone chemiluminescence NO calibration curve with 10, 20, 30, 40, and 50 μL of 10 ppm NO standard gas diluted in 50 ml N_2 and delivered in 15 ml aliquots to gas-purge delivery assembly

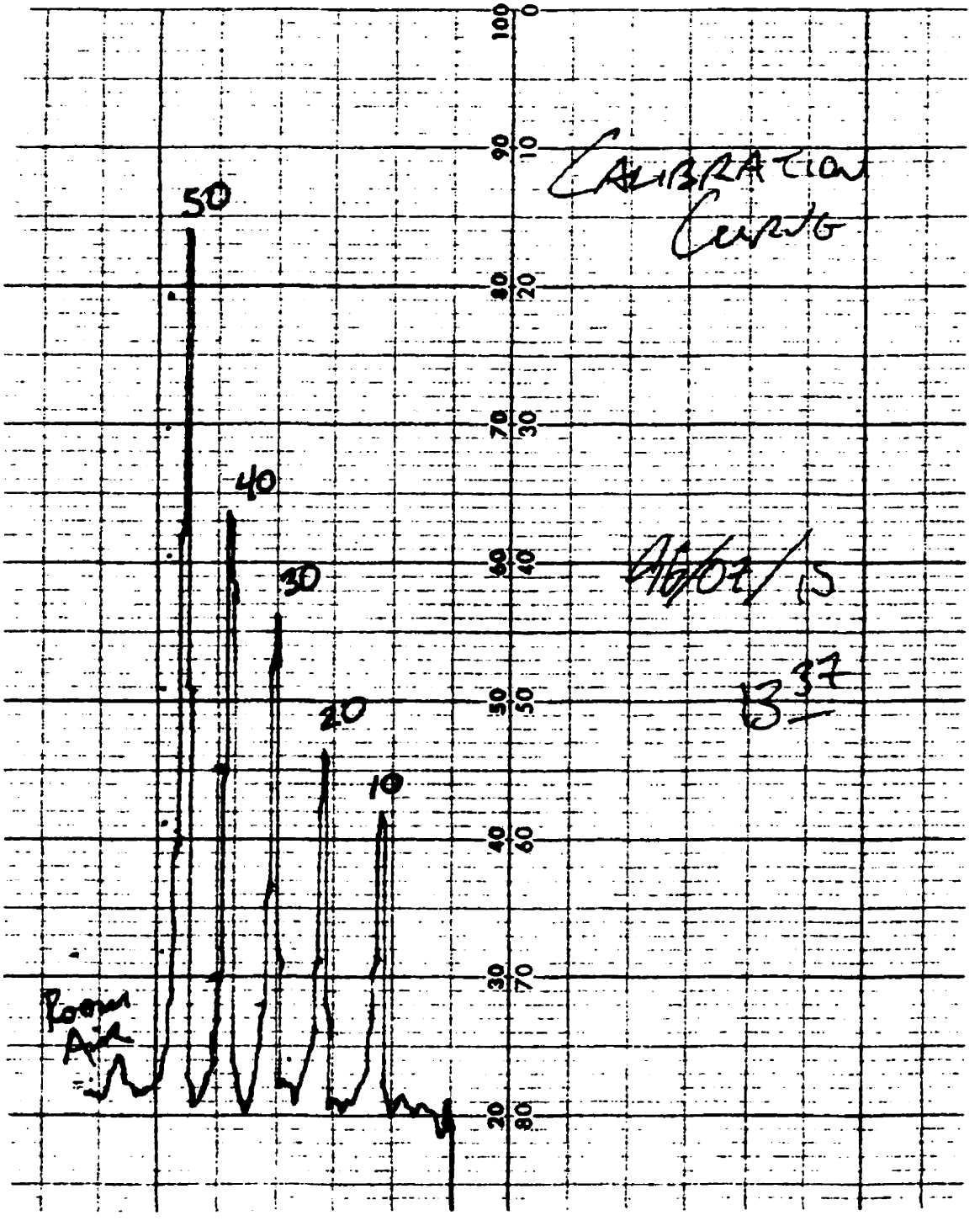

CALIBRATION
CURVE
50
40
30
20
10
Room Air

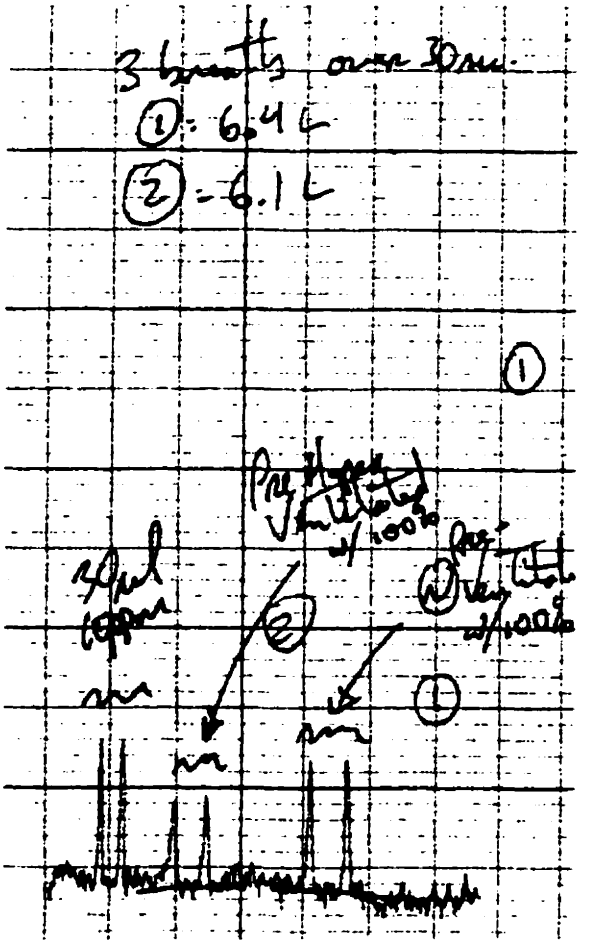
Figure 7

Example of ExNO of a normal (non-intubated, nares occluded) volunteer pre-ventilated with and on 100% O_2 with deep slow exhalations

Calibration with 30 μL of 10ppm NO standard gas to derive unit standard amount

Trial 1: 15 ml of exhaled gas causes an average deviation of 8 standard units for a total amount of 18 ppb exNO. Adjusted for expired volume of minute ventilation ($\dot{V}_E$) to 230 nL/min of exNO

Trial 2 (pre-hyperventilated): 15 ml of exhaled gas causes an average deviation of 6 standard units for a total amount of 13 ppb exNO. Adjusted for expired volume of minute ventilation ($\dot{V}_E$) to 158 nL/min of exNO



Calibration:
$10x10^{-6}$ NO * $30x10^{-6}$L = 9 units
∴ 1 unit = .033 ppb·L NO

Trial 1 (pre-ventilated with 100% O_2):
$15x10^{-3}$ L (sample size) * exNO = 8 units = 0.267ppb·L NO
∴ exNO = 18 ppb
$\dot{V}_E$ = 12.8 L/min (3 breaths, 6.4 L over 30 seconds)
exNO· $\dot{V}_E$ = 230 nL/min

Trial 2 (pre-hyperventilated with 100% O_2):
$15x10^{-3}$ L (sample size) * exNO = 6 units = 0.198ppb·L NO
∴ exNO = 13 ppb
$\dot{V}_E$ = 12.2 L/min (3 breaths, 6.1 L over 30 seconds)
exNO· $\dot{V}_E$ = 158 nL/min

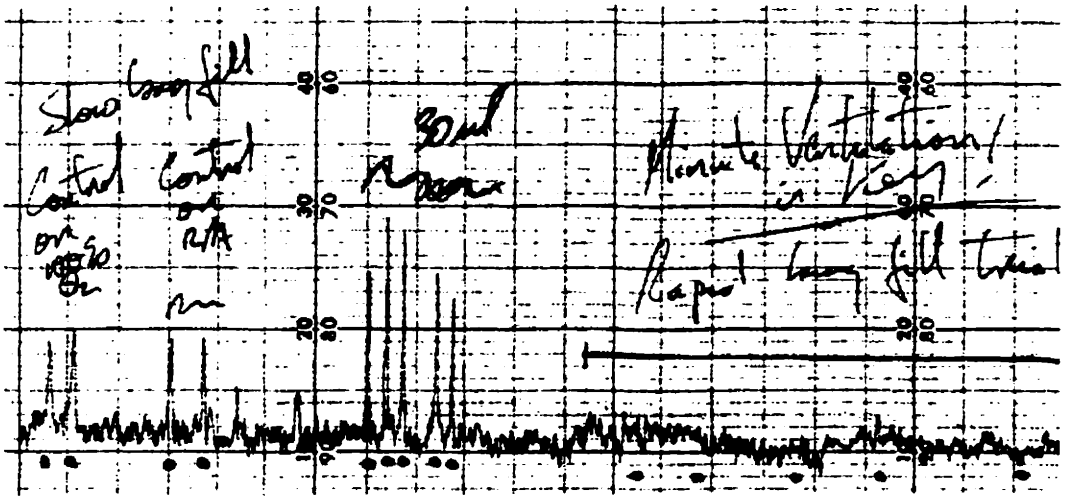
Figure 8

Example of ExNO of a normal (non-intubated, nares occluded) volunteer on 100% O_2 with a low expired volume of minute ventilation versus a high expired volume of minute ventilation

Calibration with 30 μL of 10ppm NO standard gas to derive unit standard amount

Slow bag fill trial: 15 ml sample of exhaled gas causes an average deviation of 8.5 standard units for a total amount of 11 ppb exNO. Adjusted for expired volume of minute ventilation ($\dot{V}_E$) to 134 nL/min of exNO. No significant difference when repeated after 15 minutes on room air

Rapid bag fill trial: 15 ml sample of exhaled gas causes an undetectable deviation of 0 standard units for a total amount of 0 ppb exNO. Adjusted for expired volume of minute ventilation ($\dot{V}_E$) to essentially 0 nL/min of exNO



Calibration:
$10x10^{-6}$ NO * $30x10^{-6}$L = 15 units
$\therefore$ 1 unit = .020 ppb·L NO

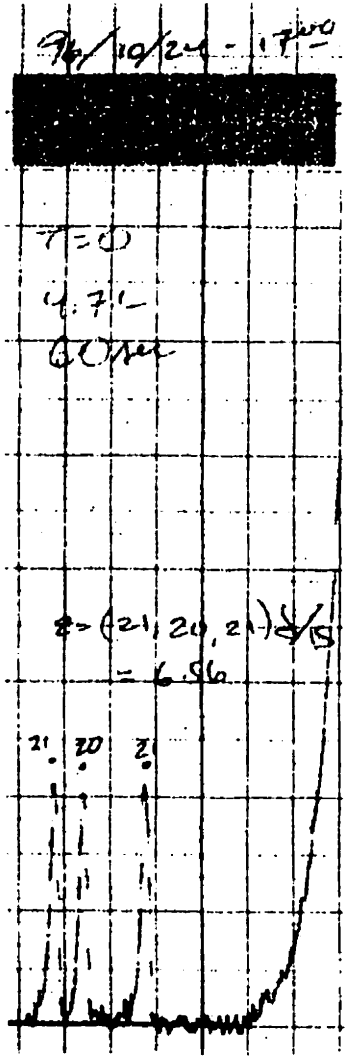
Slow Breathing Bag Fill Trial:
$15x10^{-3}$ L (sample size) * exNO = 8.5 units = 0.17ppb·L NO
$\therefore$ exNO = 11.3 ppb
$\dot{V}_E$ = 11.8 L/min (3 breaths over 30 seconds for 5.9 L)
exNO·$\dot{V}_E$ = 134 nL/min

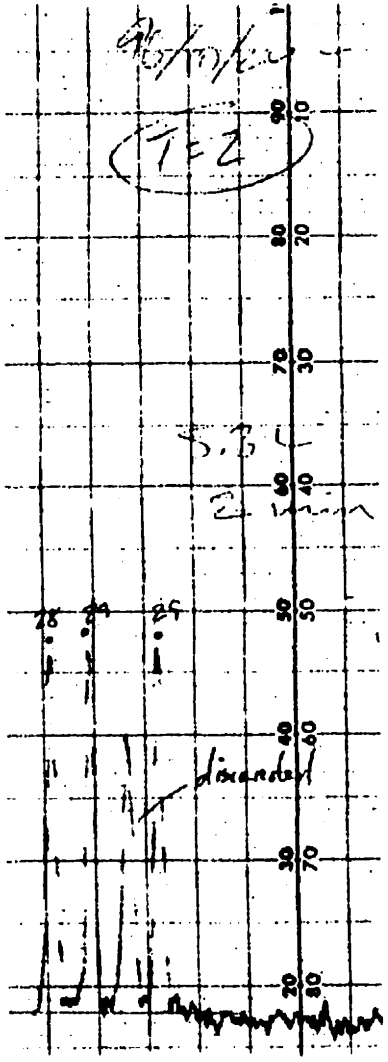
Rapid Breathing Bag Fill Trial:
$15x10^{-3}$ L (sample size) * exNO = 0 units = 0.0 ppb·L NO
$\therefore$ exNO = 0 ppb
$\dot{V}_E$ ≈ 72 L/min (3 - 4 breaths over 5 seconds for ~ 6 L)
exNO·$\dot{V}_E$ ≈ 0 nL/min

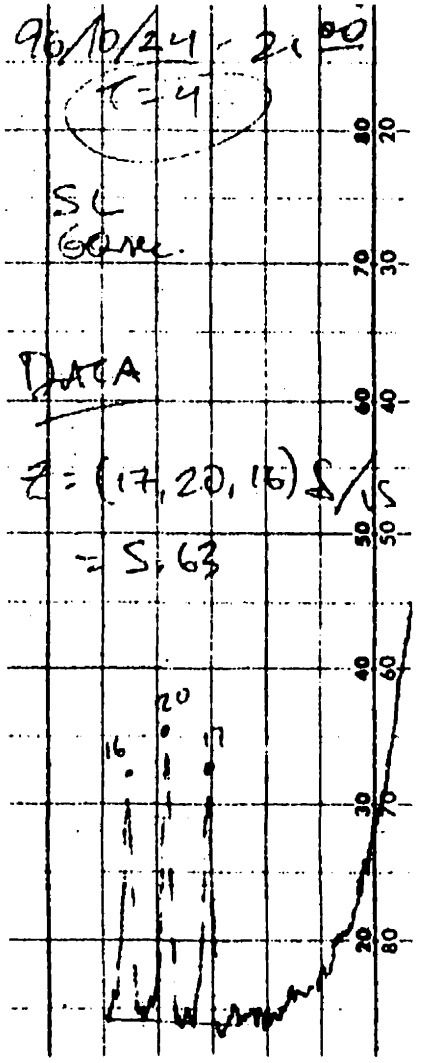
Figure 9a,b

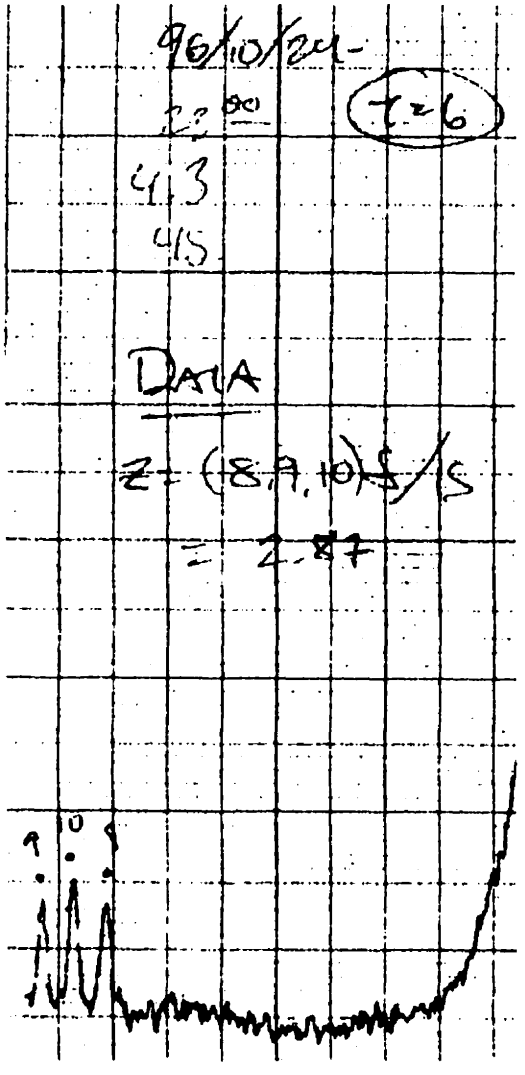
Representative sample data* from a patient for each time interval: t = 0 hrs., t = 2 hrs., t = 4 hrs., t = 6 hrs., and t = 8 hrs. Note that δ, the NO calibration unit standard, is .0478 ppb·L for this sample run

* The presented data has been modified to preserve patient confidentiality.


96/10/24 - 17h00
[redacted]
T=0
4.7 L
60sec
Z=(21,20,21)$/s
=6.56
21
20
21


96/10/24 - 17h00
T=2
5.3 L
2 min
25
24
25
diminution


96/10/24 - 21h00
T=4
5 L
60sec.
DATA
Z=(17,20,16)$/s
=5,63
16
20
17


96/10/24-
T=6
4.3
4.5
DATA
Z=(8.9.10)5/15
=2.87
9
10
8

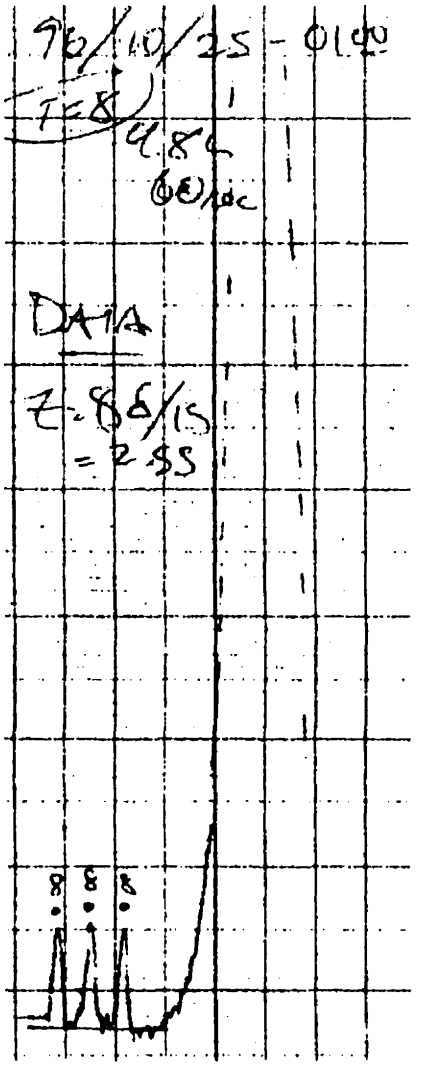

96/10/25-0140
T=8
4.8
DATA
Z=86/15
=2.55
8
8
8

Figure 10

Remaining intubated patients in normal versus SIRS groups at each time point postoperative.

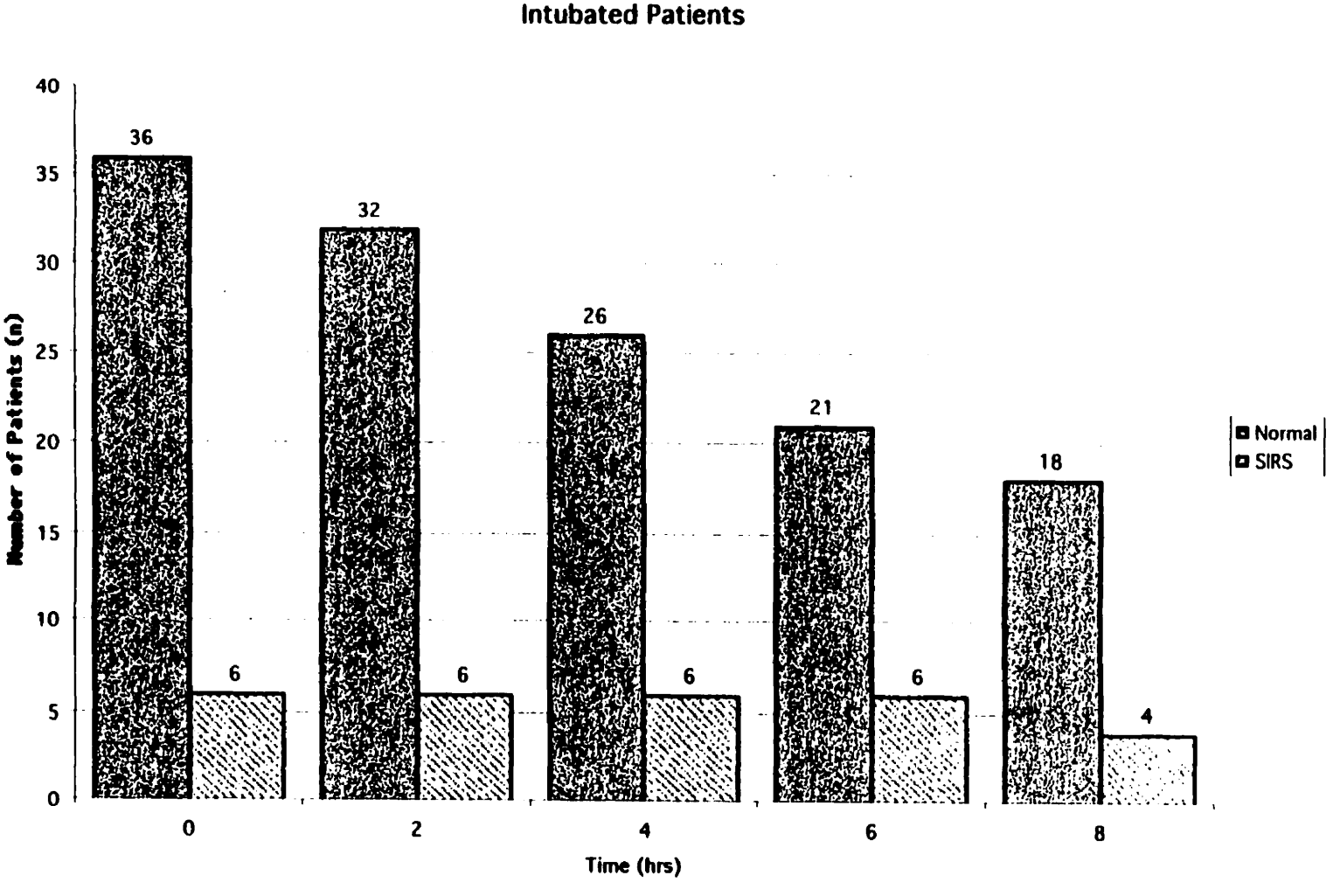

Intubated Patients
Number of Patients (n)
40
35
30
25
20
15
10
5
0
36
6
32
6
26
6
21
6
18
4
0
2
4
6
8
Time (hrs)
Normal
SIRS

Figure 11

Mean (± Standard Error of Mean) postoperative exhaled Nitric Oxide (exNO, in ppb) indexed by expired volume of minute ventilation ($\dot{V}_E$, in L/min) and body surface area (m^2) for each time point (t = 0 hours, 2 hours, 4 hours, 6 hours, 8 hours).

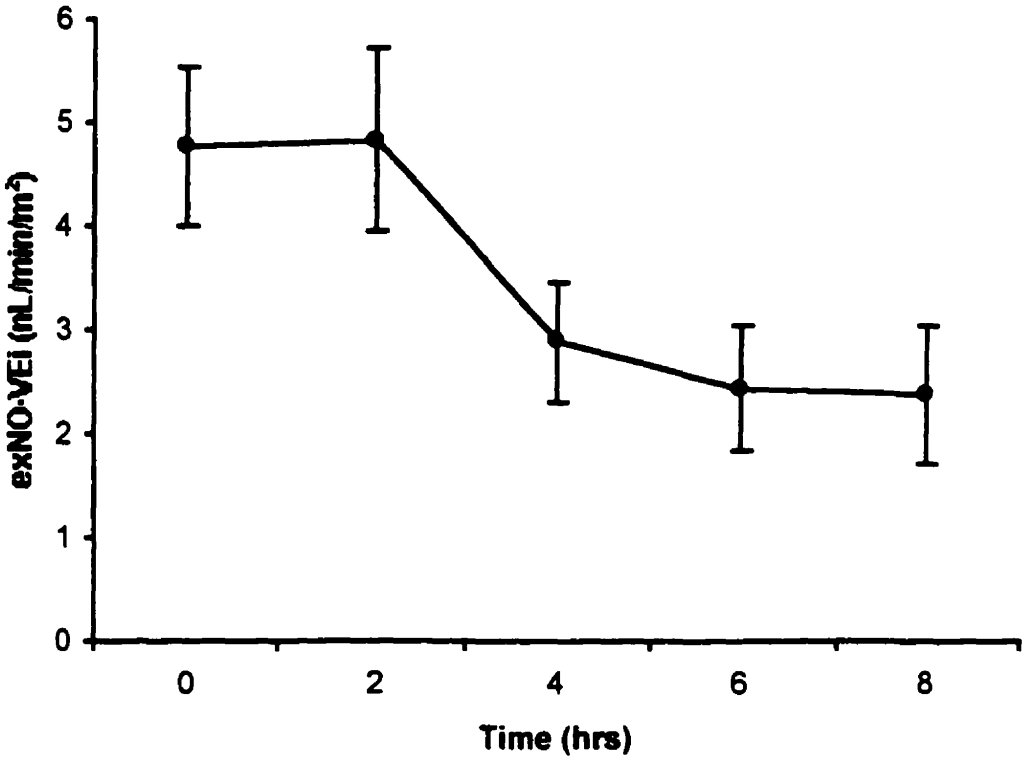

6
5
4
3
2
1
0
exNO·VEi (nL/min/m²)
0
2
4
6
8
Time (hrs)

Figure 12

Dataplot of indexed lung production of nitric oxide (exNO· $\dot{V}_E$i, in nL/min/m^2) versus cardiac index (CI, in L/min/ m^2) at less than 4 hours post-operative

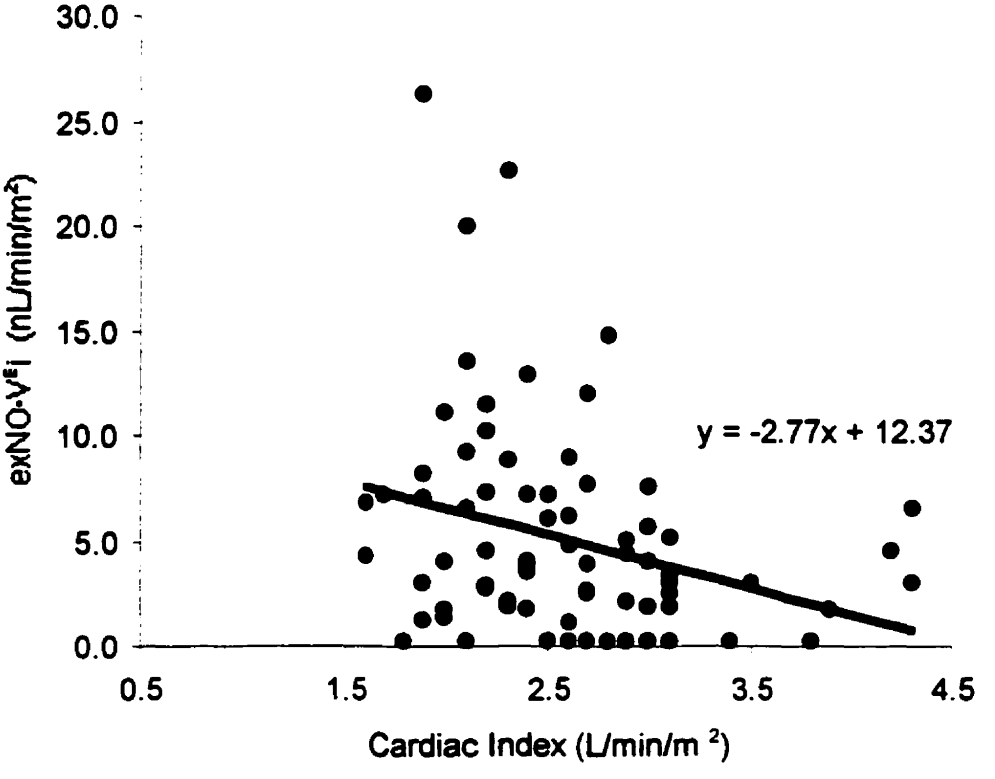

30.0
25.0
20.0
15.0
10.0
5.0
0.0
exNO-V'i (nL/min/m²)
y = -2.77x + 12.37
0.5
1.5
2.5
3.5
4.5
Cardiac Index (L/min/m ²)

Figure 13

Consolidated dataplot associating indexed lung production of exhaled nitric oxide ($exNO \cdot \dot{V}_E i$, in $nL/min/m^2$) at 4, 6 and 8 hours postoperative with intraoperative cardiopulmonary bypass duration (in minutes)

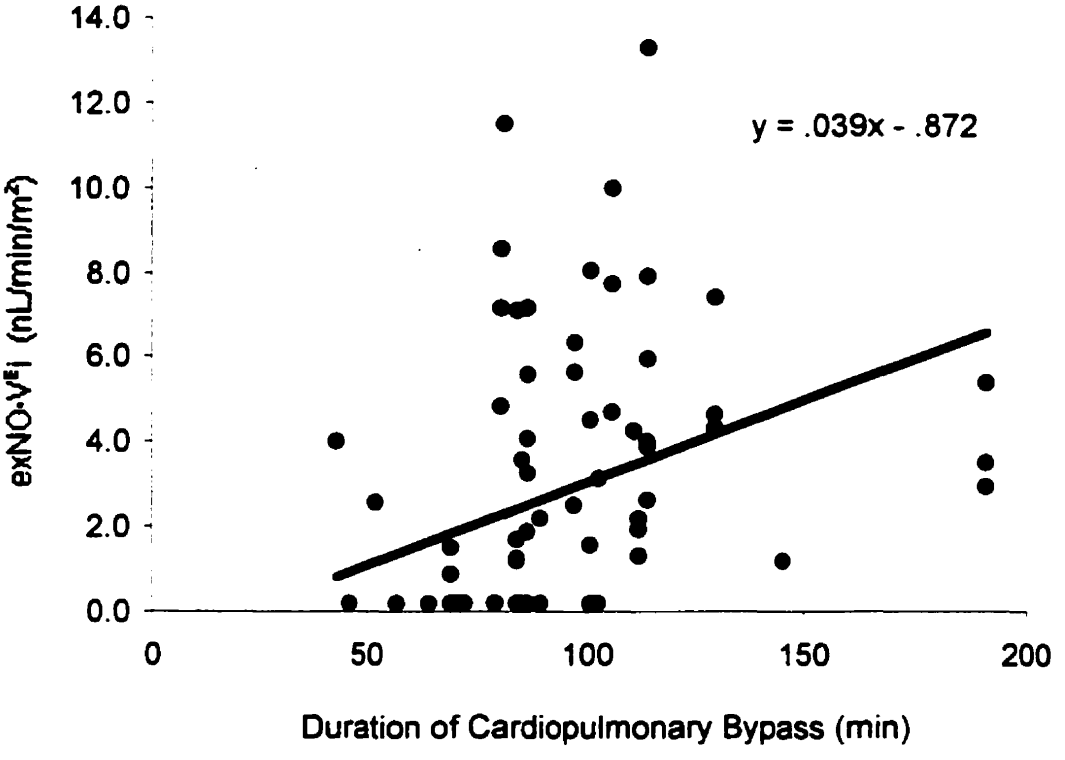

14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
50
100
150
200
y = .039x - .872
exNO·V̇E| (nL/min/m²)
Duration of Cardiopulmonary Bypass (min)

Figure 14

Indexed exhaled nitric oxide (exNO· $\dot{V}_E$i, in nL/min/m^2) between the normal and Systemic Inflammatory Response Syndrome (SIRS) hemodynamics groups at each time point postoperative (t = 0 hours, 2 hours, 4 hours, 6 hours, 8 hours).

Statistical (t-test) significance:

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

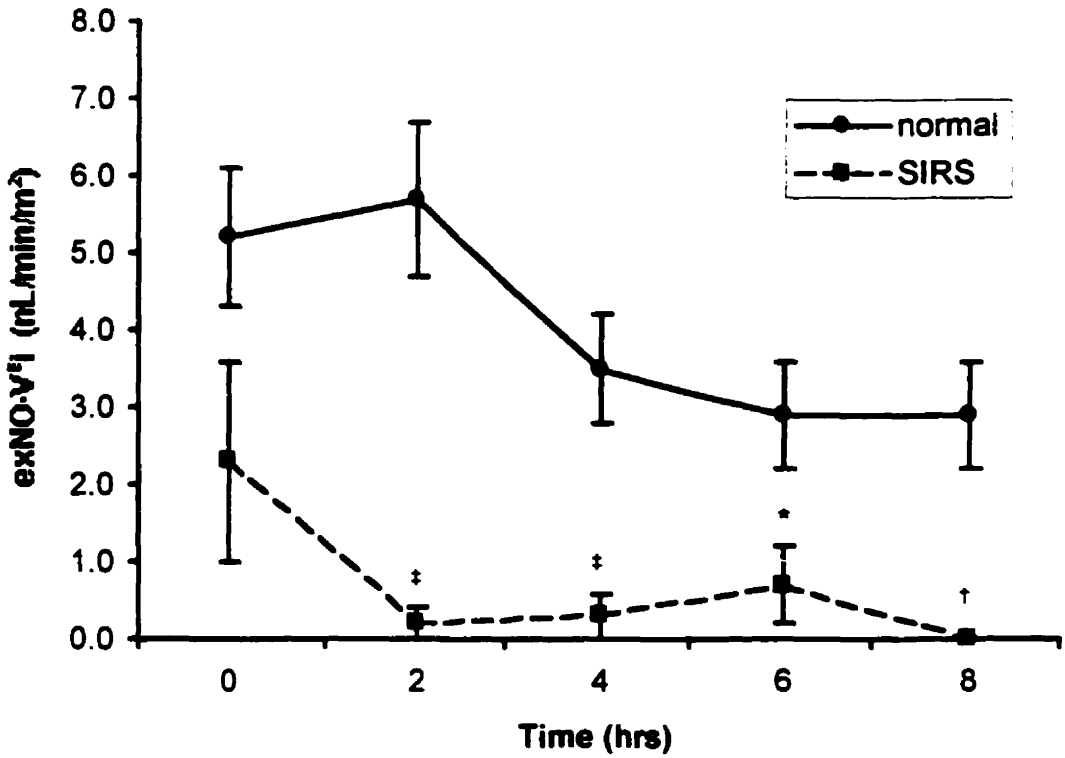

8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
exNO·V̇i (nL/min/m²)
normal
SIRS
‡
‡
*
†
0
2
4
6
8
Time (hrs)

Figure 15

Indexed systemic vascular resistance (SVRi) between the normal and Systemic Inflammatory Response Syndrome (SIRS) hemodynamics groups at each time point (t = 0 hours, 2 hours, 4 hours, 6 hours, 8 hours) postoperative

Statistical (t-test) significance:

* $p < 0.05$, † $p < 0.001$.

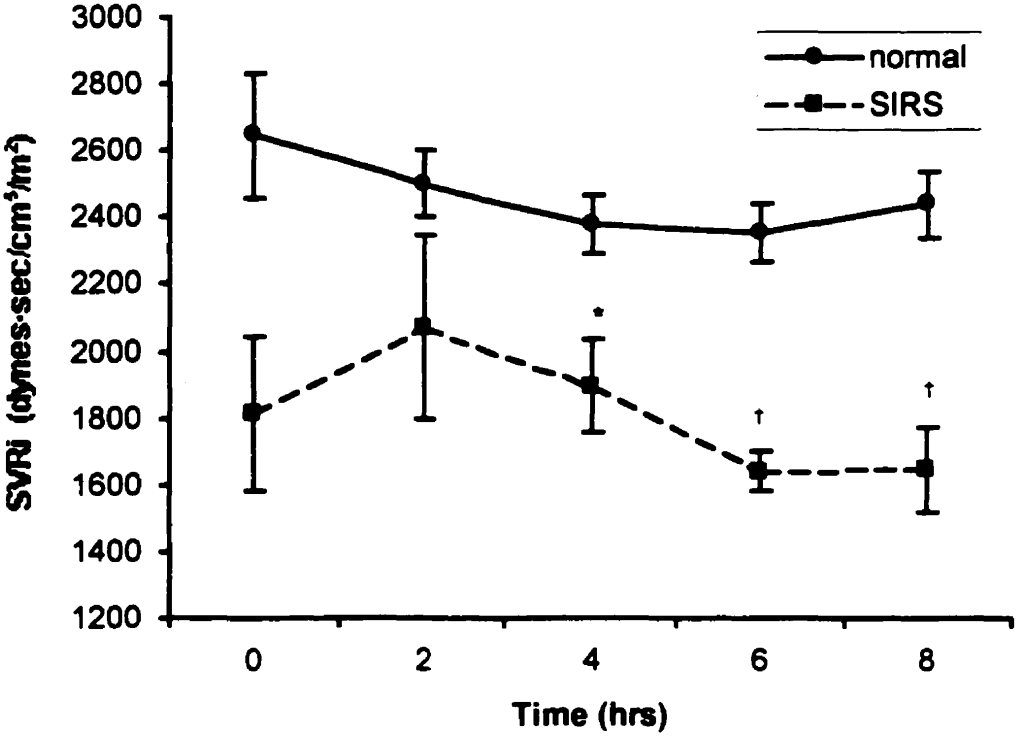

3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
SVRi (dynes·sec/cm⁵/m²)
normal
SIRS
*
†
†
0
2
4
6
8
Time (hrs)

Figure 16

Cardiac index compared between the normal and Systemic Inflammatory Response Syndrome (SIRS) hemodynamics groups at each time point (t = 0 hours, 2 hours, 4 hours, 6 hours, 8 hours) postoperative

Statistical (t-test) significance:

* $p < 0.05$.

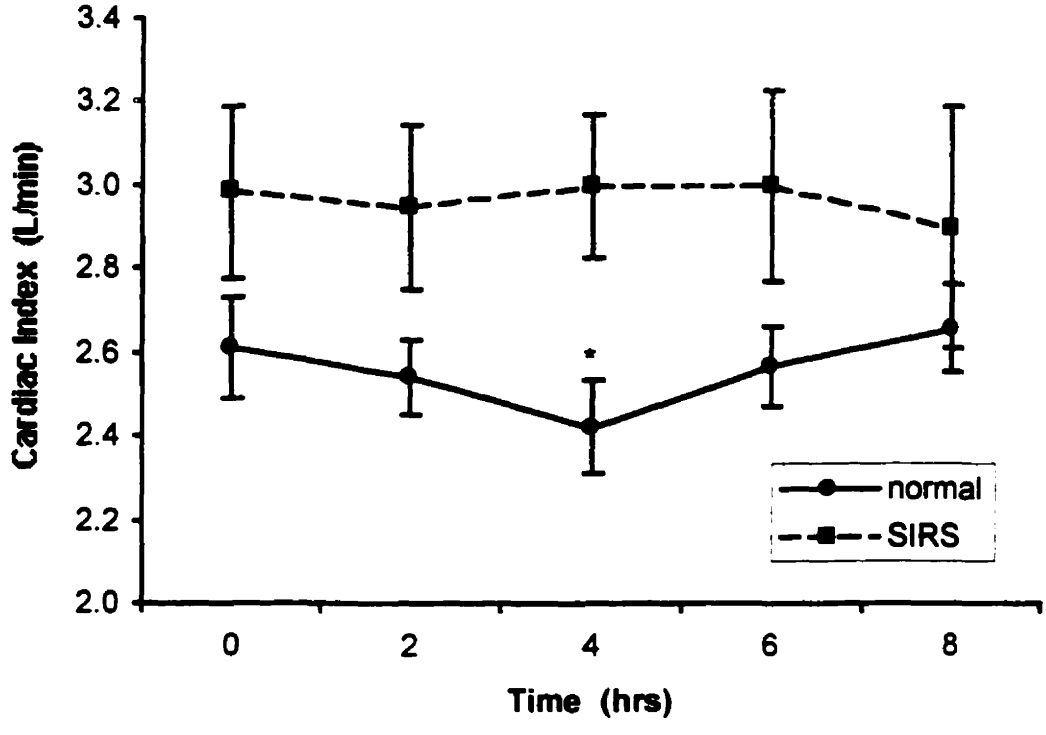
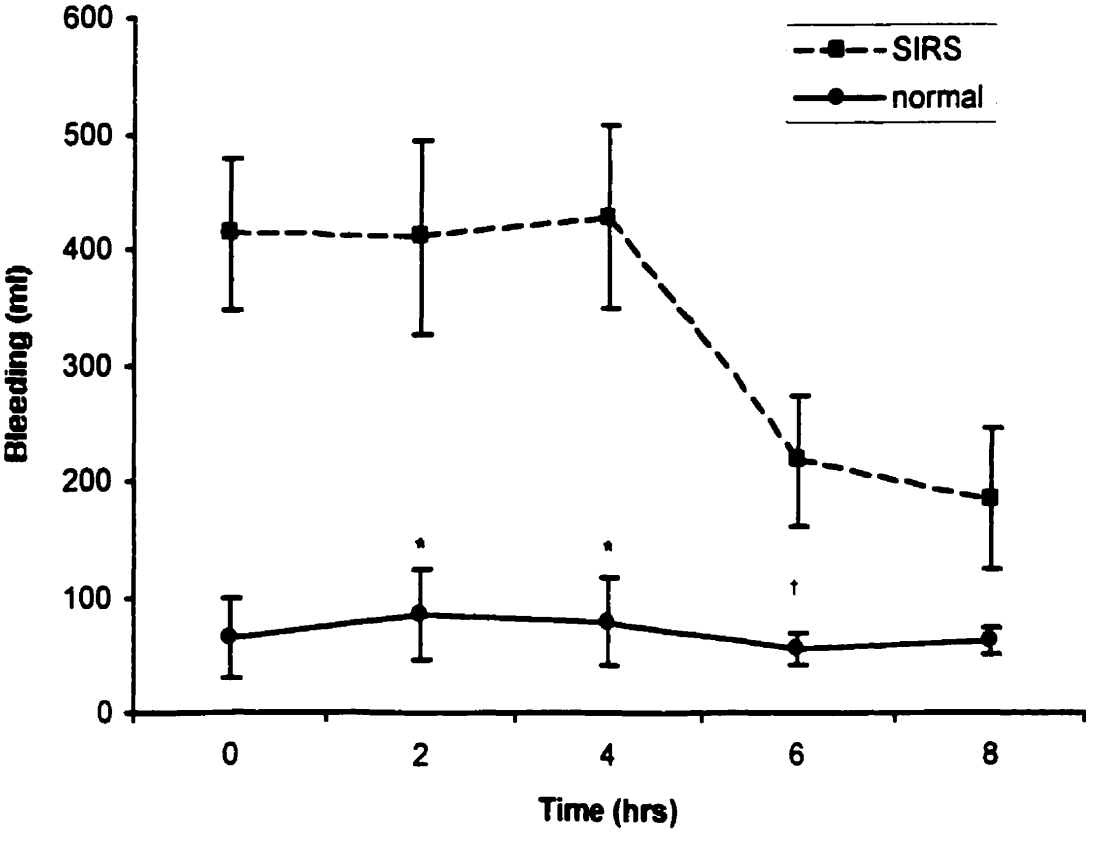

3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
Cardiac Index (L/min)
0
2
4
6
8
Time (hrs)
normal
SIRS
*

Figure 17

Bleeding at each time point postoperative (t = 0 hours, 2 hours, 4 hours, 6 hours, 8 hours) between the normal and Systemic Inflammatory Response Syndrome (SIRS) patients.

Statistical (t-test) significance:

* $p < 0.05$, † $p < 0.01$.


600
500
400
300
200
100
0
Bleeding (ml)
SIRS
normal
*
*
†
0
2
4
6
8
Time (hrs)

Tables

Table 1

Molecules involved in the mammalian inflammatory response

Bradykinin

CD-14

Complement

Elastase

Endotoxin

G-CSF

Histamine,

Interleukins 1,2,6,8,15

Leukotrienes

Monocyte chemoattractant proteins

Nitric Oxide

Oxygen radicals (superoxide, hydrogen peroxide, peroxynitrite)

PAF

Plasminogen activator inhibitor-1

Prostacyclin

Prostaglandins

Protein kinaseß

Serotonin

Soluble adhesion molecules

Thromboxane

TNF-alpha

Tyrosine kinase

Vasoactive neuropeptides

Table 2a

Preoperative patient characteristics of normal versus the SIRS hemodynamics patients

n = number of patients in group

mean ± standard error of mean

(y / n) = present / absent

BSA = body surface area

ACE = angiotensin converting enzyme

NSAID = non-steroidal anti-inflammatory

IABP = intra-aortic balloon pump

	Normal n = 36	**SIRS** n = 6	**p**
Gender (f / m)	12 / 24	1 / 5	0.65
Age (years)	62 ± 2	65 ± 4	0.65
Weight (kg)	76.9 ± 2.6	75.3 ± 2.7	0.82
BSA (m^2)	1.90 ± 0.03	1.92 ± 0.05	0.83
Serum creatinine	101 ± 5	121 ± 35	0.63
Hemoglobin (g/L)	137 ± 2	122 ± 13	0.09
Hypertension (y / n)	21 / 15	2 / 4	0.38
Diabetes (y / n)	8 / 28	1 / 5	1.0
Hypercholesterolemia (y / n)	17 / 19	2 / 4	0.67
Smoker (y / n)	7 / 29	1 / 5	1.0
Nitrates (y / n)	22 / 14	2 / 4	0.38
Beta Blocker (y / n)	24 / 12	4 / 2	1.0
Calcium Channel Blocker (y / n)	16 / 20	2 / 4	0.67
ACE Inhibitor (y / n)	13 / 23	1 / 5	0.65
NSAID (y / n)	21 / 15	4 / 2	1.0
IABP (y / n)	0 / 36	1 / 5	0.14

Table 2b

Intraoperative patient characteristics of normal versus the SIRS hemodynamics patients

n = number of patients in group

mean ± standard error of the mean

(y / n) = present / absent

CABG = Coronary Artery Bypass Grafting

Valve = aortic or mitral valve replacement

Other = nonstandard cardiovascular operation:

excision of atrial myxoma (1)

CABG + left ventricular aneurysm repair (2)

Bentall procedure (1)

CABG + aortic valve + aortic arch replacement (1)

RBC = red blood cell

	Normal n = 36	SIRS n = 6	p
Operation			0.17
CABG only	22	4	
Emergency CABG	0	1	
Redo CABG	3	0	
Valve +/- CABG	6	1	
Other	5	0	
Bypass time (min.)	91.9 ± 5.5	77.7 ± 5.7	0.32
Aortic cross-clamp time (min.)	74.3 ± 4.6	59.8 ± 3.8	0.22
Amrinone (y / n)	5 / 31	0 / 6	1.0
Transexamic acid	3 / 33	0 / 6	1.0
Operative Blood Loss (ml)	645 ± 76	630 ± 112	0.94
RBC transfusion (y / n)	1 / 31	1 / 5	0.27

Table 2c

Postoperative patient characteristics of the normal versus the SIRS hemodynamics groups

n = number of patients in group

mean ± standard error of the mean

(y / n) = present / absent

pRBC = packed red blood cell

* = presence of drip for two or more time periods

† = no significant impact on exNO· $\dot{V}_{E}$i by pooled or paired analysis (see text)

	Normal n = 36	SIRS n =6	p
Nitrate drip (y / n)*	16 / 20	0 / 6	0.07†
Nipride drip (y / n)*	13 / 23	0 / 6	0.15†
Pressor drip (y / n)*	2 / 34	2 / 4	0.09†
Inotrope (y / n)*	7 / 29	2 / 4	0.59
Serum creatinine	87 ± 5	90 ± 21	0.83
Hemoglobin (ml)	89 ± 2	85 ± 6	0.83
Total Bleeding (ml)	773 ± 68	1556 ± 93	< 0.001
Hemoglobin after 6 hrs.(ml)	97 ± 2	90 ± 8	0.23
pRBC Transfusion (y / n)	0 / 36	1 / 5	0.14

Table 3a

Comparison of exNO· $\dot{V}_E$i on/off vasoactive drip using grouped mean data over all time points (two-sided student's t-test)

Mean ± standard error of the mean

exNO· $\dot{V}_E$i = exhaled nitric oxide indexed by minute ventilation and body surface area in nL/min/ m^2

Nitrate = nitroglycerin and/or nitroprusside drips

Pressor = epinephrine and/or norepinephrine drips

Inotrope = dobutamine and/or amrinone and/or epinephrine drips

	Mean exNO· $\dot{V}_E$i (nL/min/m^2)		
Post-operative Drip	**on drip**	**not on drip**	**p**
Nitrate (including nitroprusside)	4.1 ± 0.5	3.3 ± 0.5	0.29
Nitroprusside alone	4.0 ± 0.4	3.5 ± 0.5	0.45
Pressor	4.0 ± 1.3	3.7 ± 0.4	0.77
Inotrope	3.7 ± 0.8	3.7 ± 0.4	0.96

Table 3b

Comparison of each individual patient's exNO· $\dot{V}_E$i while on/off vasoactive drip (paired t-test analysis)

Mean ± standard error of the mean

exNO· $\dot{V}_E$i = exhaled nitric oxide indexed by minute ventilation and body surface area in nL/min/ m^2

Nitrate = nitroglycerin and/or nitroprusside drips

Pressor = epinephrine and/or norepinephrine drips

Inotrope = dobutamine and/or amrinone and/or epinephrine drips

	Mean exNO·$\dot{V}_{E}$i (nL/min/m^2)		
Post-operative Drip	**on drip**	**not on drip**	**p**
Nitrate (including nitroprusside)	4.7 ± 1.2	4.0 ± 1.0	0.30
Nitroprusside alone	5.1 ± 1.4	4.0 ± 0.9	0.28
Pressor	3.5 ± 1.3	3.7 ± 1.0	0.83
Inotrope	3.5 ± 0.9	4.2 ± 1.1	0.28

Table 4

Correlation coefficient (Spearman's rho) between exNO· $\dot{V}_E$i and Cardiac Index, Bypass Time with level of significance.

ns = not significant

Time hours	Cardiac Index Spearman's r	Bypass Time Spearman's r
0	-0.30 ($p < 0.05$)	0.28 (ns)
2	-0.46 ($p < 0.005$)	0.25 (ns)
4	-0.32 (ns)	0.53 ($p < 0.005$)
6	-0.04 (ns)	0.66 ($p < 0.001$)
8	-0.18 (ns)	0.53 ($p < 0.01$)

Table 5

Hemodynamic parameters for normal versus SIRS hemodynamics patients by postoperative time interval

Parameters:

exNO· $\dot{V}_{E}i$ = exhaled nitric oxide indexed by minute ventilation and body surface area in nL/min/ m^2

SVRi = indexed systemic vascular resistance in dynes·sec/cm^5/m^2

CI = cardiac index in L/min/ m^2

MAP = mean arterial pressure in mmHg

PCWP = pulmonary capillary wedge pressure in mmHg

CVP = central venous pressure in mmHg

Temperature = axillary temperature in °C

Bleeding = blood loss in ml over the two hour interval between time points t=0 indicates chest tube output from chest closure to arrival in the ICU)

Statistical significance:

$^{\bullet}$ $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$, § $p < 0.10$

Group	Time	#	ExNO·$\dot{V}_E$i	SVRi	CI	MAP	PCWP	CVP	Temperature	Bleeding
	hours	n	nL/min/m^2	dyne·sec/cm^5/m^2	L/min/m^2	mmHg	mmHg	mmHg	°C	ml
Normal	**0**	32	5.2 ± 0.9	2647 ± 189[§]	2.61 ± 0.12	84.6 ± 2.1	9.8 ± 0.9	8.9 ± 0.7	35.0 ± 0.1	349 ± 34
	2	32	5.7 ± 1.0[*]	2500 ± 100[§]	2.54 ± 0.09[§]	94.0 ± 1.5[‡]	12.4 ± 0.1	9.7 ± 0.8	36.2 ± 0.1	254 ± 39[‡]
	4	26	3.5 ± 0.7[*]	2377 ± 87[‡]	2.42 ± 0.11[‡]	88.4 ± 2.0[‡]	12.0 ± 0.9	9.6 ± 0.7	37.3 ± 0.1	232 ± 38[‡]
	6	21	2.9 ± 0.7[‡]	2357 ± 89[*]	2.57 ± 0.10[§]	90.5 ± 2.2[§]	12.1 ± 1.1	10.3 ± 0.1	37.5 ± 0.1	99 ± 14[†]
	8	18	2.9 ± 0.7[*]	2442 ± 99[*]	2.66 ± 0.10	90.8 ± 2.1[†]	11.7 ± 1.4	9.7 ± 0.6	37.3 ± 0.1	80 ± 11
SIRS	**0**	6	2.3 ± 1.3	1814 ± 231	2.98 ± 0.20	84.2 ± 5.3	9.4 ± 1.4	7.3 ± 1.1	35.5 ± 0.2	413 ± 65
	2	6	0.2 ± 0.2	2072 ± 277	2.95 ± 0.20	84.2 ± 5.9	9.4 ± 1.3	6.3 ± 1.3	36.4 ± 0.1	411 ± 84
	4	6	0.3 ± 0.3	1896 ± 142	3.00 ± 0.20	71.8 ± 6.2	13.0 ± 2.7	10.7 ± 2.0	37.3 ± 0.3	428 ± 79
	6	6	0.7 ± 0.5	1640 ± 60	3.00 ± 0.27	81.7 ± 2.1	10.2 ± 1.3	7.8 ± 0.1	37.3 ± 0.3	218 ± 56
	8	4	0.0 ± 0.0	1647 ± 128	2.90 ± 0.19	76.3 ± 3.9	13.3 ± 3.5	10.7 ± 3.2	37.8 ± 0.3	185 ± 62

Table 6

Comparison of mean hemodynamic data between normal and SIRS patients grouped over all time points

n = number of patients in group

mean ± standard error of mean

exNO· $\dot{V}_E$i = exhaled nitric oxide indexed by minute ventilation and body surface area in nL/min/ m^2

SVRi = indexed systemic vascular resistance in dynes·sec/cm^5/m^2

CI = cardiac index in L/min/ m^2

MAP = mean arterial pressure in mmHg

PCWP = pulmonary capillary wedge pressure in mmHg

CVP = central venous pressure in mmHg

Temperature = axillary temperature in °C

Interval Bleeding = blood loss between time points in ml

	Normal (n = 36)	SIRS (n = 6)	p
ExNO· $\dot{V}_E$**i** (nL/min/m^2)	4.3 ± 0.4	0.7 ± 0.3	< 0.001
SVRi (dynes·sec/cm^5/m^2)	2488 ± 62	1826 ± 86	< 0.001
CI (L/min/m^2)	2.56 ± 0.05	2.97 ± 0.09	< 0.001
MAP (mmHg)	89.4 ± 0.9	81.1 ± 2.2	< 0.001
PCWP (mmHg)	11.5 ± 0.5	10.9 ± 0.9	0.60
CVP (mmHg)	9.1 ± 0.4	8.4 ± 0.8	0.19
Temperature (°C)	36.4 ± 0.1	36.9 ± 0.2	0.10
Interval Bleeding (ml)	224 ± 17	346 ± 36	< 0.005