Effects of Sublingual Nitroglycerin on Resting Pulmonary Gas Exchange and Hemodynamics in Man

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SUMMARY Simultaneous hemodynamic, ventilation and blood gas measurements were performed in 19 males during cardiac catheterization for evaluation of chest pain syndrome before and 3 to 5 min after 0.4 mg sublingual nitroglycerin. Pulmonary arterial pressures and total pulmonary vascular resistance fell (P < 0.001 for both), and mean systemic arterial pressure decreased (P < 0.05). However, peripheral vascular resistance, cardiac output, and mixed venous PO₂ did not change.

Total and tidal ventilation, PCO₂, pH, and base excess remained unchanged. However, the arterial PO₂ decreased from a mean of 80 ± 3 (SEM) to 72 ± 2 mm Hg (P < 0.001) and mean venous admixture increased from 8.8 ± 1% to 12.6 ± 1.5% (P < 0.001). The alveolar-arterial PO₂ difference increased (P < 0.001) and the dead space tidal volume ratio rose (P < 0.05).

We conclude that the decrease in arterial PO₂ following sublingual nitroglycerin is caused by redistribution of pulmonary blood flow with imbalance in ventilation-perfusion relationships or shunting.

The purpose of the present study was to investigate the possible effects of an even more widely used vasodilator, sublingual nitroglycerin, on the resting pulmonary gas exchange and simultaneous hemodynamics in man.

Patients and Methods

Nineteen male patients aged 26 to 70, admitted for evaluation of chest pain syndromes, were the subjects of this study. Five patients were normal, 11 had coronary artery disease (including four with abnormal left ventriculograms), two had primary myocardial disease, and one had rheumatic mitral regurgitation.

The studies were performed in the postabsorptive state in the cardiac catheterization laboratory during the course of right and left heart catheterization and coronary arteriography. Prior informed consent was obtained appropriately. Patients were in the supine position and were breathing room air during the entire procedure. All hemodynamic and blood gas data were obtained before the
performance of either ventriculography or coronary arteriography.

After insertion of the right heart catheter into the pulmonary artery and a brachial arterial line under local anesthesia, and following a subsequent equilibration period of at least 10 min marked by stability of vital signs, the control hemodynamic and blood gas measurements (vide infra) were obtained. Glyceryl trinitrate (nitroglycerin), 0.4 mg, tablet was then administered sublingually. Absorption of the drug was facilitated by prior moistening of the buccal mucosa by a sip of water. Following the administration of sublingual nitroglycerin, when the oscilloscopic monitor with the computerized display showed a consistent increase in heart rate by more than 5 beats/min, or a decrease in mean pulmonary artery pressure by at least 20%, or a fall in mean intra-arterial pressure by 10% or more, the hemodynamic, ventilation and blood gas measurements were repeated. The heart rate and/or pulmonary or systemic arterial pressure responses were observed between 2½ and 5 min after administration of the drug. Withdrawal of blood samples (vide infra), recording of pressures and collection of expired gas were completed within 10 min from the onset of drug action.

The hemodynamic measurements included heart rate, mean arterial pressure (MAP), pulmonary artery pressure (mean and diastolic), and cardiac index. The peripheral systemic and total pulmonary vascular resistances were calculated using standard formulae.

The pulmonary artery diastolic pressure was used as a reflection of left ventricular filling pressure and was within ±3 mm Hg when compared in 14 patients with the mean pulmonary capillary wedge pressure. Hence in the present study the pulmonary artery diastolic pressure will be used to represent left ventricular filling pressure.

The indices of blood flow and ventilation perfusion were determined in the following manner. With the subject breathing through a one-way valve, after a period of accommodation to the apparatus, two mixed expired gas collections were made in sequence, each for 3 minutes. Simultaneous arterial and mixed venous blood samples were withdrawn anaerobically into heparinized syringes between the 1½ and 2½ min of each gas collection. Oxygen and carbon dioxide concentrations of the expired gas were determined in duplicate with a Scholander 0.5 ml gas analyzer. Blood samples were analyzed immediately for pHi, pCO2, and pO2 in duplicate with standard electrodes. Oxygen content in each blood sample was analyzed in duplicate with a direct reading galvanic cell system ("Lex - O2 - Con.", Lexington Instruments). Total expired volume of ventilation from each Douglas bag collection was measured with a Tissot spirometer.

Oxygen uptake, derived from the expired gas analysis, and arteriovenous oxygen content difference as measured with the galvanic cell analyzer, were used for determination of cardiac output according to the Fick principle. The "ideal" alveolar oxygen pressure (PiO2) was calculated from the alveolar air equation, and the "ideal" arterial oxygen saturation was determined at measured pH and calculated base excess of the arterial blood using a polynomial equation fitted to the oxyhemoglobin dissociation curve. The ratio of venous admixture (Qs) to total blood flow (Qt) was calculated from the equation:

\[
\frac{Qs}{Qt} = \frac{\text{CAiO}_2 - \text{CaO}_2}{\text{CaO}_2 - \text{CVO}_2}
\]

where CAiO2, CaO2 and CVO2 are the ideal, arterial and mixed venous oxygen content calculated from the oxyhemoglobin dissociation curve. Calculated rather than measured arterial and mixed venous oxygen contents were used for the calculation of venous admixture in order to minimize the errors in the Riley analysis that might occur when oxygen contents were not uniformly derived. The dead space to tidal volume ratio (VD/VT) was calculated from the modified Bohr equation, a correction being made for the 18 ml dead space of the valve. Alveolar arterial pO2 difference (A-aDO2) was obtained by subtracting measured arterial pO2 from the "ideal" alveolar pO2. Alveolar ventilation and ventilation perfusion ratios (VA/Q) were calculated in the standard manner. In practice, all measurements were processed in a remote time sharing computer using software specifically developed for respiratory gas exchange analysis.

The mean of each pair of observations from the control and post-nitroglycerin studies was recorded. For statistical analysis of the results, Student's t-test for paired values was used and the mean values were expressed with standard error of the mean (± SEM).

### Results

Each blood gas or cardiac output value represented the mean of two determinations. For the PaO2 values the reproducibility of each determination was ± 4% and for the cardiac indices it was ± 11%.

As no significant difference in hemodynamic response or pulmonary gas exchange was observed in any subset of patients, i.e., normal, coronary artery disease cases and others, the results are presented for the entire group.

### Hemodynamic Changes

After sublingual administration of nitroglycerin the heart rate increased from a mean of 68 ± 2 to 75 ± 2 beats per minute (P < 0.001). The mean arterial pressure (MAP) fell from 105 ± 3 to 98 ± 5 mm Hg (P < 0.05), the mean pulmonary artery pressure decreased from 19 ± 2 to 12 ± 2 mm Hg (P < 0.001), and the pulmonary artery diastolic pressure decreased from a mean of 13 ± 1 to 9 ± 1 mm Hg (P < 0.001). The cardiac index decreased in 11, increased in five, and remained essentially unchanged in three patients. The overall change was a slight but statistically insignificant decrease from a mean of 2.6 ± 0.1 to 2.4 ± 0.14 L/min/m². The peripheral vascular resistance did not change significantly, although the total pulmonary vascular resistance fell from a mean of 314 ± 46 to 215 ± 45 dynes sec cm⁻⁵ (P < 0.001). The hemodynamic changes are shown in figures 1 and 2.

### Ventilation and Blood Gas Changes

Total and tidal ventilation, pCO2, arterial pH, base excess, and overall VA/Q did not change significantly following sublingual nitroglycerin. However, the dead space to tidal volume ratio (VD/VT) increased slightly from a mean of 32 ± 1.9 to 35 ± 1.7% (P < 0.05).

The arterial PO2 (PaO2) ranged from 64 to 96 mm Hg.
with a mean of 80 ± 3 mm Hg in the control state, and decreased to a mean of 72 ± 2 mm Hg following administration of sublingual nitroglycerin (P < 0.001). There was no clinical evidence of chronic obstructive pulmonary disease and, therefore, relatively low control PaO₂ in some patients probably resulted from chronic heavy smoking. The mixed venous PO₂ (PVO₂) ranged from 32 to 42 mm Hg in the control state and did not change significantly. However, the calculated mean venous admixture, which was 8.8 ± 1% in the control state, increased significantly to 12.6 ± 1.5% (P < 0.001). The alveolar-arterial PO₂ difference increased from a mean of 26.8 ± 2 to 35.7 ± 2.9 mm Hg (P < 0.001). The important ventilation and blood gas changes are presented in figures 3 and 4. The simultaneous changes in venous admixture and PaO₂ are shown in figure 5. A high correlation (r = −0.8) between increase in venous admixture and concomitant decrease in PaO₂ was noted following sublingual nitroglycerin.

**Relationship between Hemodynamic and Blood Gas Changes**

No consistent correlation, positive or negative, between hemodynamic and blood gas changes after nitroglycerin was observed. For example, changes in PaO₂ could not be related to those in cardiac indices, PVO₂, or left ventricular filling pressure. Thus no subset could be identified based on hemodynamic or etiologic factors that would be predictive of the observed response of PaO₂ to nitroglycerin administration.

**Discussion**

The hemodynamic response to a single sublingual dose of nitroglycerin in our patients was consistent with the known pharmacological actions of the drug. The heart rate increased, mean systemic and pulmonary arterial pressures decreased, and the left ventricular filling pressure fell with a significant reduction in total pulmonary vascular resistance. The cardiac index decreased slightly but not significantly and the systemic vascular resistance did not change. The latter was probably due to the fact that the vasodilator effect of nitroglycerin was predominantly on the venous capacitance bed and much less on the arteriolar resistance bed.

Associated with the above hemodynamic changes was a striking reduction in PaO₂ and an increase in percent venous admixture. There was, however, no simultaneous change in mixed venous PO₂, arterial pH, or base excess. In other words, the arterial hypoxemia was not associated with significant tissue hypoxia. The cause of this fall in arterial oxygen pressure following sublingual nitroglycerin remains speculative. Possible causes of arterial hypoxemia include: a) decrease in alveolar ventilation, b) limitation of diffusion, c) disturbance of ventilation-perfusion relationship, and d) increase in true shunt flow.

Because there was no significant change in alveolar ventilation or PCO₂ following sublingual nitroglycerin, alveolar hypventilation was unlikely to be responsible for the fall in PaO₂ in these patients. Limitation of diffusion as a cause of arterial hypoxia is not considered a factor of great importance in resting pulmonary gas exchange. Furthermore, none of our patients had any interstitial lung disease likely to interfere with pulmonary gas exchange by causing diffusion defect even at rest. Hence, the observed reduction in PaO₂ following sublingual administration of nitroglycerin resulted either from worsening of ventilation-perfusion relationship or from an increase in true intrapulmonic shunt flow or both.
Increase in venous admixture and alveolar-arterial $\text{PO}_2$ difference would favor either mechanism of reduction in arterial oxygen pressure. An increase in venous admixture and decrease in $\text{PaO}_2$ were observed in previous studies when pulmonary blood flow had been increased by isoproterenol infusion\textsuperscript{18} or by nitroprusside administration.$^{1,2}$ As no significant change in cardiac output occurred following sublingual nitroglycerin in the present study, it is conceivable that there was a redistribution of pulmonary blood flow following sublingual vasodilator administration causing either an increased perfusion of poorly ventilated pulmonary units or opening up of intrapulmonic shunts or both. This conclusion is supported by the correlation between the increase in venous admixture and simultaneous decrease in $\text{PaO}_2$ presented in figure 5.

Differentiation between these two causes of arterial hypoxia, ventilation-perfusion imbalance versus true shunt flow is generally made by calculating shunt flow with the subject breathing pure oxygen. However, there is now evidence that breathing pure oxygen produces or increases shunt flow by causing absorption collapse of pulmonary units with low ventilation-perfusion ratios.$^{14,17}$ Such an effect might be magnified in the face of nitroglycerin-induced redistribution of pulmonary blood flow. Under

**Figure 3.** Changes in ventilation following sublingual nitroglycerin. $\text{VD/VT} = \text{dead space-tidal volume ratio}; A-a\text{DO}_2 = \text{alveolar-arterial } \text{PO}_2 \text{ difference}; C = \text{control}; N = \text{following sublingual nitroglycerin}.$

**Figure 4.** Changes in arterial ($\text{PaO}_2$), mixed venous ($\text{PVO}_2$) and venous admixture following sublingual nitroglycerin. $C = \text{Control}; N = \text{following nitroglycerin sublingually.}$ The $\text{PaO}_2$ decreased, the $\text{PVO}_2$ did not change significantly, and the venous admixture increased following sublingual nitroglycerin.
these conditions, there would be an increase in the number of lung units that are better perfused but poorly ventilated and, therefore, are liable to collapse with pure oxygen breathing. Because of these limitations and in order to keep the duration of the procedure within the limits of patient acceptance, no attempt was made to measure shunt flow. For the same reason, duration of arterial hypoxia following a single dose of sublingual nitroglycerin was not ascertained.

In the study of Konietzko et al. a decrease in VD/VT and no significant changes in PaO₂ or alveolar-arterial PO₂ difference were noted in coronary disease patients following intravenous administration of isosorbide dinitrate.¹⁴ In contrast, our patients (including those with coronary disease) showed an increase in VD/VT and alveolar-arterial PO₂ difference concomitantly with the fall in PaO₂ following sublingual administration of nitroglycerin. The reason for the discrepancy in findings between our studies and those of Konietzko et al. is unclear, but may be related to pharmacological differences between intravenous isosorbide dinitrate and sublingual nitroglycerin.

In the present study we intended to investigate the effects of nitroglycerin in all patients undergoing diagnostic catheterization. The list included not only those with coronary artery disease and normal subjects but also patients with cardiomyopathies and mitral regurgitation. That the changes in blood gases were noted in such a heterogeneous group of patients indicates that these changes resulting from the administration of nitroglycerin are general effects and are therefore not peculiar to any particular etiologic or hemodynamic subgroup.

Whatever the precise underlying mechanism, the administration of nitroglycerin sublingually results in an increase in venous admixture and arterial hypoxemia. Since the fall in PaO₂ is not associated with significant hemodynamic deterioration or with abnormalities in arterial pH, base excess, or mixed venous PO₂, there is no evidence of resultant important tissue hypoxia. Hence, we conclude that during measurement of blood gases in patients given nitroglycerin sublingually, caution should be exercised in the interpretation of the reduction in PaO₂ that might occur.

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