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# Extraction of Nitroglycerin by a Membrane Oxygenator

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## Abstract

This study examined the extraction efficiency of a membrane oxygenator for nitroglycerin (NTG). An *In-Vitro* cardiopulmonary bypass circuit was constructed to mimic clinical conditions. A NTG solution (150 ng/ml) was placed into the circuit via a glass cardiotomy reservoir and circulated at 5 L/min for 60 min. Analysis of NTG samples obtained during the study showed that the oxygenator initially extracted 70% of drug entering the device. A small increase in drug concentration was observed for the first 10 min, followed by a continual decrease. By 60 min only 20% of the original drug concentration remained. We conclude that the membrane oxygenator used during cardiopulmonary bypass is capable of substantially extracting NTG.

## Introduction

Hypertension occurring during cardiac surgery and cardiopulmonary bypass (CPB) is often treated with nitroglycerin (NTG).<sup>1,2</sup> This compound has been reported to avidly bind to numerous materials such as IV solution containers, tubing, and catheters made of polyvinylchloride (PVC) plastic.<sup>3-6</sup> We have recently shown a substantial loss of NTG to a bubble oxygenator as a result of

contact with the polyurethane sponge used to de-foam blood.<sup>7</sup> This reduced drug availability occurs despite the use of polyethylene IV tubing which does not adsorb NTG.<sup>8</sup> Since membrane oxygenators are also used during CPB, particularly during long cases, this study was conducted to determine the potential for NTG extraction by this type of blood oxygenator.

## Methods

A stock solution of NTG was prepared by adding an aliquot of a commercial NTG product<sup>a</sup> to a 2 L solution of normal saline, to yield a concentration of 150 ng/ml. This solution was placed in a silanized (silicon hydride) glass container. An *In-Vitro* CPB circuit was constructed to mimic clinical conditions (Fig. 1). A glass cardiotomy reservoir was the initial receptacle for the NTG solution. A 20 foot length of PVC surgical tubing<sup>b</sup> was connected to the reservoir to form a complete circuit. A membrane oxygenator<sup>c</sup> was connected to the tubing ten feet beyond the reservoir.

The roller pump generated a flow of 5 L/min and the solution was maintained at a temperature of 32°C. Samples (3 ml) for NTG analysis were obtained from the stock solution immediately after mixing and after the solution was placed in the reservoir. As the roller pump was started, a sample was taken from the inflow port prior to entrance

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<sup>a</sup> Tridil, American Critical Care, McGaw Park, IL 60085

<sup>b</sup> Tygon, Norton Company Health Care Products, Akron, OH 44309

<sup>c</sup> Sci-Med Kobolow Membrane Lung, Model 3500-3B (3.5 M<sup>2</sup>) Sci-Med Life Systems, Inc., Minneapolis, MN 55441

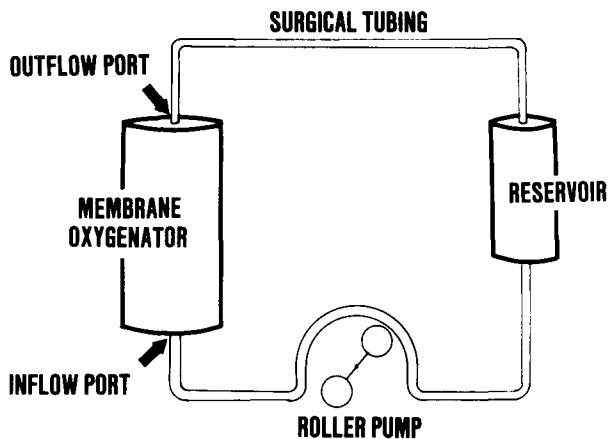


FIGURE 1. Experimental cardiopulmonary bypass apparatus circuit.

of solution into the oxygenator and from the outflow port after initial passage through the oxygenator. Additional samples were obtained simultaneously from the inflow and outflow ports at 2, 5, 10, 25, 45, and 60 min. Samples were collected from three-way stopcocks placed in the tubing 3–4 cm before and after the oxygenator. All NTG samples were collected in silanized glass vials and frozen at  $-20^{\circ}\text{C}$  until analysis. An appropriate volume of sample was extracted twice with spectrograde pentane. After combining the extracts and suitably diluting or concentrating the solution, a portion was injected onto a gas chromatographic column. A Varian 3700 dual column instrument was used, equipped with a  $9\text{mCi } ^{63}\text{Ni}$  electron capture detector together with a Chimadzu Chromatopac C-RIA recording data processor.<sup>9</sup> Concentrations of NTG were determined from a standard curve relating drug concentration to the area under NTG chromatogram relative to that of an internal standard (*o*-iodobenzyl alcohol) of known concentration. Using the internal standard method, the assay precision was  $\pm 6\%$  at NTG concentrations of 50, 100, and 200 ng/ml.

## Results

The NTG measured in the cardiotomy reservoir was 97.4% of the stock solution and all subsequent measurements are reported using this value as the reference point. As the solution circulated through the circuit, there was substantial loss of NTG (Table 1). First-pass of solution through the surgical tubing resulted in a minimal (11.3%) loss whereas the oxy-

TABLE 1  
Loss of Nitroglycerin to CPB Circuit

Time (min)	Inflow Port* Sample (%)	Outflow Port Sample (%)
0	88.7 <sup>+</sup>	26.5 <sup>=</sup>
2	48.1	35.2
5	30.8	30.1
10	27.2	26.0
25	19.9	23.5
45	22.2	23.3
60	20.2	21.8

\* Expressed as % NTG relative to stock solution

<sup>+</sup> First pass of solution through tubing

<sup>=</sup> First pass of solution through oxygenator

genator extracted 70% of the drug concentration entering the inflow port. The drug concentration increased transiently for the first 10 min, then remained constant throughout the remainder of the study.

## Discussion

Previous studies document the ability of PVC plastic material to adsorb NTG, thus reducing drug delivery to the patient.<sup>3–6</sup> For example, up to 60% of drug may be lost after first-pass through PVC intravenous tubing.<sup>3</sup> The clinical significance of this interaction between drug and delivery device was recently reported when a patient required over 10 times the dosage of NTG after the intravenous tubing was changed from a polyethylene to PVC material.<sup>10</sup>

Using similar methodology, we recently reported that a bubble oxygenator can initially extract a substantial amount of NTG from solution.<sup>8</sup> It appears that NTG is lost to the polyurethane sponge used to defoam oxygenated blood since NTG has been shown to adsorb to polyurethane (written communication, D. M. Baaske, American Critical Care). We now report similar findings with a membrane oxygenator.

The In-Vitro CPB circuit used in this study was designed to mimic clinical conditions. The solution flowed at a rate similar to a normal cardiac output and was cooled to hypothermic conditions. The length of surgical tubing was similar to that used during cardiac surgery and the NTG concentration of 150 ng/ml is a plasma concentration believed achievable when the drug is used during CPB.

The first pass of solution through the tubing resulted in only an 11.3% loss of drug which is consistent with our previous findings.<sup>8</sup> This minimal loss is believed due to a rapid flow rate of drug and a small surface area of tubing relative to the volume of solution passing through the tubing. The majority of the drug loss occurred during initial passage through the oxygenator. The membrane oxygenator consists of a silicone rubber sleeve in which a homogenous silicone rubber membrane is wound in a spiral coil upon a polycarbonate spool. During CPB, venous blood flows into the inflow port, around the membrane for gas exchange, and exits through the blood outflow port. The probable site of loss is the membrane since NTG adsorbs to silicone rubber.<sup>11,12</sup>

After the initial loss of drug during first pass through the oxygenator, there was a transient increase in concentration followed by a plateau whereby only about 20% of the initial concentration remained at the end of the study (Table 1). The increased concentration observed during the first ten min of the study was apparently due to the incomplete emptying of solution from the cardiotomy reservoir during the initial passage. The solution from the outflow port of the oxygenator then mixed with the original stock solution remaining in the reservoir. After first pass of solution, only 26.5% of the original NTG concentration remained; an extraction ratio of 70%. This magnitude of drug loss, however, must be cautiously extrapolated clinically due to possible sequestration of drug from the oxygenator by plasma proteins and saturation of oxygenator extraction sites with prolonged administration. Despite this unknown quantitative drug loss, the interaction between drug and oxygenator may explain, at least

in part, the increased NTG requirements noted during CPB compared to the pre-bypass period.<sup>2</sup>

We conclude that the membrane oxygenator is capable of extracting NTG. Clinical studies of NTG during CPB should consider the possibility of the patient receiving a variable dosage of NTG even if the drug is administered through non-adsorbing polyethylene tubing.

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