# Polyvinylchloride Containers do not Influence the Hemodynamic Response to Intravenous Nitroglycerin

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**ABSTRACT**

*In-vitro evidence of sorption of nitroglycerin (NTG) to polyvinylchloride (PVC) containers suggests that these containers may deliver less nitroglycerin to the patient than glass containers. Sorption of NTG to the PVC container may result in hemodynamic changes in the patient when a fresh solution of NTG is prepared and administered from a PVC container. This study was designed as a prospective, randomized trial to measure the hemodynamic response in patients receiving NTG in glass or PVC containers, during the first hour after a container exchange. Patients admitted to the coronary care unit in a University hospital with chest pain considered to be due to unstable angina or acute myocardial infarction were eligible. Patients who received other vasoactive drugs within one hour of container exchanges were excluded. Systolic and diastolic blood pressures, and heart rate were measured at baseline and at intervals for one hour following a container exchange. Twenty patients completed the study. There were no significant changes with time in either group (ANOVA, p>0.05) with respect to systolic, diastolic, or mean arterial blood pressure or heart rate. No chest pain occurred during the 60 minutes following the container exchange in either group. We conclude that NTG can be administered safely and effectively in PVC containers to patients with unstable angina or acute myocardial infarction. However, it remains possible that changes in hemodynamic status could occur in patients on NTG if a change in container type (i.e., from PVC to glass or vice versa) is made during the course of therapy.*

**Key Words:** *nitroglycerin, polyvinylchloride, sorption*

**RÉSUMÉ**

*L'adsorption de la nitroglycérine au chlorure de polyvinyle (PVC), comme l'ont démontré les essais* in vitro, *suggère que les contenants faits de ce matériau peuvent entraîner l'administration d'une plus petite quantité de médicament que les contenants en verre. L'adsorption de la nitroglycérine peut amener des modifications hémodynamiques chez le patient quant on prépare et administre une solution fraîche de nitroglycérine dans un contenant en PVC. La présente étude, un essai prospectif randomisé, devait établir la réaction hémodynamique des malades recevant de la nitroglycérine au cours de la première semaine suivant la substitution des contenants en verre ou en PVC. Ont participé à cet essai des personnes alitées au service de soins coronariens d'un hôpital universitaire à la suite de douleurs à la poitrine attribuables de l'angine instable ou à un infarctus myocardique aigu. Étaient exclus les patients qui avaient reçu d'autres médicaments vasoactifs dans l'heure précédant la substitution des contenants. La pression artérielle systolique et diastolique et le rythme cardiaque ont été établis au départ, puis à intervalles d'une heure après l'échange des contenants. Vingt personnes ont terminé l'étude. On n'a relevé aucune variation significative avec le temps chez les deux groupes (ANOVA, p>0,05) pour ce qui est de la pression artérielle systolique, diastolique ou moyenne, ou le rythme cardiaque. La substitution des contenants n'a entraîné aucune douleur à la poitrine au cours des 60 minutes suivant l'échange. On en conclut que l'administration de nitroglycérine dans des contenants en PVC ne pose aucun danger pour les personnes atteintes d'angine instable ou d'infarctus myocardique aigu. Toutefois, il se peut que l'état hémodynamique des personnes à qui on administre ce médicament subisse des modifications quand on change de contenant au cours du traitement (à savoir quand on passe un contenant en PVC à un contenant en verre, ou vice versa).*

**Mots clés:** *adsorption, chlorure de polyvinyle, nitroglycérine*

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## INTRODUCTION

Intravenous nitroglycerin (NTG) is used for the treatment of myocardial ischemia, hemodynamic abnormalities associated with ventricular failure, hypertensive episodes, and induction of hypotension during surgical procedures.[1-5] A potential problem with the admixture and administration of NTG has been identified. Sorption (adsorption and absorption) of NTG to commonly-used polyvinylchloride (PVC) infusion systems has been documented and a number of *in vitro* studies have shown NTG to be extensively removed from solutions mixed in PVC containers.[6-19] Potential sources of sorption include infusion containers, calibrated burettes, in-line intravenous filter systems, and infusion pumps with PVC components.[7] The rate and extent of sorption is related to solution concentration, flow rate, surface area of plastic, and time of exposure.[7,10,19] Sturek et al[15] compared the loss of NTG from a 0.47 mg/mL solution stored in either glass or PVC containers for 50 hours. At the end of this period, there was an 83% decrease in NTG concentration in the PVC container while the loss from the glass container was only 13%. Another study,[7] reported that NTG solutions admixed in glass containers were stable for 48 hours at all temperatures, while those prepared in PVC containers showed NTG potency losses of between 38% and 86%, which were directly related to storage temperature. In light of this, specialized containers and tubing (e.g., polyolefin and glass) have been recommended when preparing NTG for intravenous infusion.[14,18,19] Despite the *in vitro* studies of the sorption of NTG to PVC, little information is available on the clinical consequences of this effect. Furthermore, the potential exists for adverse hemodynamic effects, which are related to the NTG administration procedure when NTG solutions are prepared, administered over a 12 to 24 hour period and then exchanged for a container of fresh solution. If the sorption process occurs over a period of several hours, the patient will be titrated to a NTG rate which reflects a reduced NTG concentration in solution. Clinical problems may occur in the first hour after a PVC container exchange when the patient may temporarily receive a higher concentration of NTG, before completion of the sorption process. The present study was undertaken to examine the hypothesis that clinically important disturbances in blood pressure would be seen in patients receiving NTG mixed in PVC containers, during the first hour after a container exchange.

## METHODS

### Patient selection

During a three-month period, thirty-nine patients were recruited into the trial and randomized to receive their NTG from either glass bottles or PVC bags. All were admitted to University Hospital (Shaughnessy site) Coronary Care Unit with chest pain considered to be due to unstable angina pectoris (UAP), or acute myocardial infarction (AMI). Of these patients, twenty (10 in each group) completed the study (15 UAP, 5 AMI). Of the excluded or withdrawn patients, seven (3 in the glass group and 4 in the PVC group) had their NTG infusion discontinued before any container changes occurred; nine (3 in the glass group and 6 in the PVC group) were excluded due to incomplete data collection and three (2 in the PVC group and 1 in the glass group) were excluded due to the administration of other hypotensive medications within one hour of the container exchange. Patient demographics at entry are summarized in Table I. The study protocol was approved by the Human Subjects Review Committee (University of British Columbia) and the Research Committee (University Hospital). Informed, written consent was obtained from each patient.

### Study design

The study was designed to detect changes in blood pressure and heart rate during the first hour after a container exchange in patients receiving NTG from PVC bags. Patients receiving NTG from glass bottles were considered a control group in whom no changes in hemodynamic status were expected in relation to a container exchange. The trial was randomized but could not be blinded due to the different containers utilized. On admission to the unit, patients were randomly assigned to receive NTG from either PVC bags (Baxter, Toronto, Canada) or from glass bottles (Abbott, Chicago, U.S.A.) for the entire treatment period. Infusions were prepared by diluting the contents of two 50 mg ampoules of NTG (Tridil®, Dupont, Scarborough, Canada) in 500 mL of 5% dextrose in either glass bottles or PVC bags to give a 200 µg/mL solution. A Plum® volumetric infusion pump (Abbott) was utilized to deliver the desired flow rate via Plumset® PVC infusion sets. Times of solution admixture and change of administration sets were recorded. NTG solutions were maintained at ambient temperature prior to administration. NTG infusions were initiated at 10 µg/min and were titrated as required by 10 µg/min every 10 minutes until pain control was achieved, while maintaining systolic blood pressure above 100 mm Hg. Expired containers were discarded and replaced with fresh solutions at various intervals between 8 and 35 hours after initiation of therapy or a previous exchange. Nurs-

**Table I. Patient demographics on admission**

| Patient | Container Type | Sex | Age (years) | Weight (kg) | Admission Diagnosis* | Discharge Diagnosis* | Concurrent Medications+ |
|---|---|---|---|---|---|---|---|
| 1 | glass | F | 67 | 72 | UAP | UAP | C,B |
| 2 | glass | M | 64 | 95 | UAP | UAP | C,B |
| 3 | glass | F | 76 | 85 | UAP | UAP | C,B,N |
| 4 | glass | M | 75 | 65 | UAP | UAP | none |
| 5 | glass | M | 47 | 89 | CPNYD | UAP | C,B,A |
| 6 | glass | F | 64 | 64 | AMI | AMI | C,B,N,D |
| 7 | glass | M | 65 | 83 | UAP | UAP | C,B,D |
| 8 | glass | M | 57 | 66 | UAP | UAP | C |
| 9 | glass | F | 62 | 95 | CPNYD | UAP | C,N |
| 10 | glass | F | 76 | 67 | CPNYD | UAP | C,B,N,D |
| 11 | PVC | M | 43 | 80 | UAP | UAP | C,B |
| 12 | PVC | M | 69 | 60 | UAP | UAP | C,B |
| 13 | PVC | F | 60 | 96 | CPNYD | UAP | C |
| 14 | PVC | F | 79 | 65 | UAP | UAP | C |
| 15 | PVC | F | 76 | 67 | CPNYD | UAP | C,B,N,D |
| 16 | PVC | M | 47 | 89 | CPNYD | UAP | C,B,A |
| 17 | PVC | F | 64 | 64 | AMI | AMI | C,B,N,D |
| 18 | PVC | F | 79 | 71 | AMI | AMI | C,B,N,D |
| 19 | PVC | M | 73 | 47 | AMI | AMI | B |
| 20 | PVC | M | 62 | 84 | AMI | AMI | C,B,N,D,A |

* AMI — acute myocardial infarction
CPNYD — chest pain not yet diagnosed
UAP — unstable angina pectoris
\+ A — angiotensin converting enzyme inhibitor
B — beta blocker
C — calcium channel blocker
D — diuretic
N — nitrate

ing staff were instructed to flush the administration sets with new solution prior to restarting the infusion. No infusion set changes occurred within 24 hours of the observation period.

The hemodynamic parameters measured were systolic and diastolic blood pressure, and heart rate. All blood pressure and heart rate measurements were made utilizing a Dinamap$^{R}$ (Critikon Inc, Tampa, U.S.A.) vital signs monitor. Routine hemodynamic measurements and NTG infusion rates were recorded hourly during the study. Blood pressure and heart rate measurements were determined 5 minutes prior to the container exchange (baseline) and at 5, 10, 15, 30, 45 and 60 minutes after the exchange. The mean arterial pressure (MAP) was calculated by adding two times the diastolic blood pressure to the systolic blood pressure and then dividing the total by three. Patients were assessed after the first container exchange, only if their blood pressure fluctuations were within ±10 mm Hg during the hour prior to the exchange, otherwise they were evaluated at the next container exchange at which this criterion was met. In cases where data collection during the first container exchange was deemed incomplete or patients received, within one hour of the container exchange, other drugs which could have affected hemodynamic status during the assessment period (e.g., beta-blockers, calcium channel blockers, nitrates), the data from the next container exchange were obtained.

**Table II. Clinical indices on admission and at baseline***

| PARAMETER | STUDY GROUP+ | |
|---|---|---|
| | PVC | GLASS |
| **ADMISSIONS** | | |
| HR (bpm) | 73 ± 14 | 80 ± 20 |
| SBP (mm Hg) | 128 ± 10 | 129 ± 18 |
| DBP (mm Hg) | 77 ± 10 | 74 ± 13 |
| MAP (mm Hg) | 94 ± 10 | 92 ± 13 |
| **BASELINE** | | |
| HR (bpm) | 69 ± 14 | 73 ± 19 |
| SBP (mm Hg) | 124 ± 22 | 114 ± 17 |
| DBP (mm Hg) | 71 ± 10 | 63 ± 12 |
| MAP (mm Hg) | 88 ± 13 | 80 ± 13 |
| NTG Rate (µg/min) | 74 ± 44 | 111 ± 73 |
| NTG Rate (µg/kg/min) | 1.1 ± 0.6 | 1.4 ± 0.9 |

* — 5 minutes prior to container exchange
\+ — data are presented as mean ± s.d.
there were no significant differences between groups with respect to any of the indices (t-test, $p<0.05$)

### Data Analysis

Group comparisons of demographic and baseline clinical data were performed using the unpaired Student's t-test. The effect of container exchange within each group was evaluated using one way ANOVA with repeated measures for the baseline and post-exchange hemodynamic data. Results were considered statistically significant at the 5% level ($p < 0.05$).

## RESULTS

The patients' clinical indices on admission to hospital and at baseline (5 minutes prior to container exchange) are summarized in Table II. There were no significant differences in blood pressure or heart rate between the two groups at either time. Although the baseline mean NTG infusion rate (absolute and weight-adjusted) was higher in the group using glass bottles, there was considerable inter-individual variability, and this difference was not statistically significant. In comparison to the baseline measurements, there were no significant differences within either group in systolic (SBP) or diastolic (DBP) blood pressures (Figure 1), or mean arterial pressure over the first hour after the exchange. There also were no significant changes in heart rate over the same time period (Figure 2). The mean time between preparation and administration of the NTG solutions was 13 ± 17 minutes, and was the same in both groups.

No chest pain developed during the 60 minutes post-container exchange in any of the patients.

## DISCUSSION

The therapeutic benefits of NTG in the treatment of ischemic heart disease are well established. It is an effective peripheral vasodilator which reduces left ventricular filling pressures (preload) with a subsequent reduction in myocardial

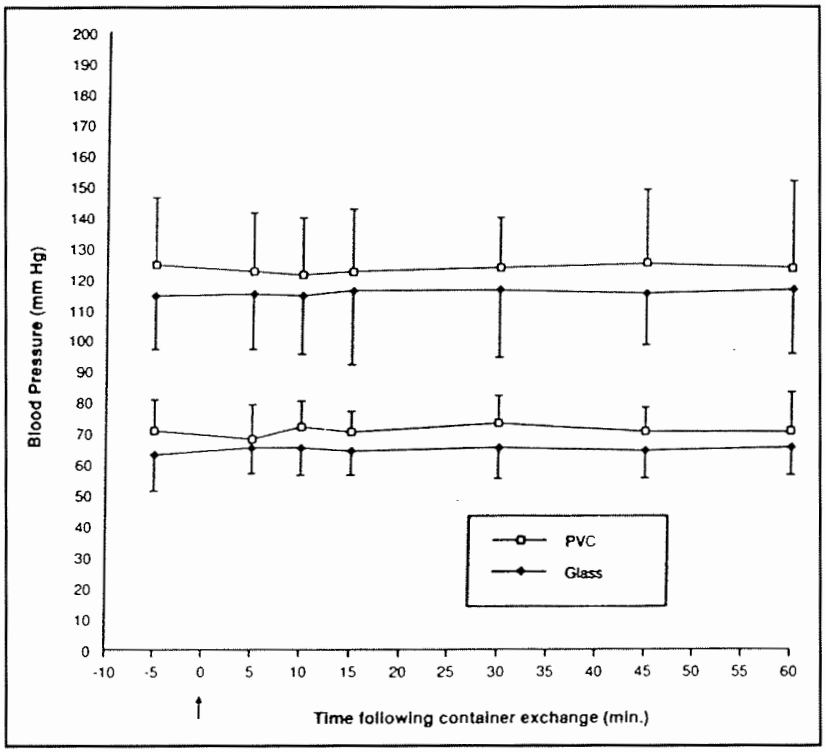


**Figure 1: Diastolic and systolic blood pressure 5 minutes prior to and during the 60 minutes after container exchange. Data are shown as mean value ± s.d. The arrow indicates the time of container exchange.**

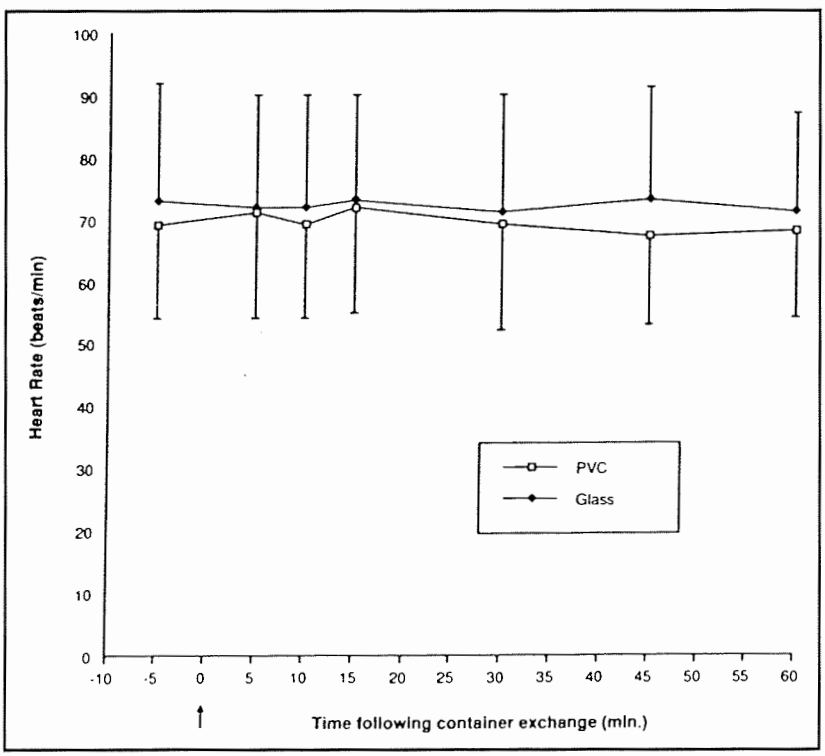


**Figure 2: Heart rate 5 minutes prior to and during the 60 minutes after container exchange. Data are shown as mean values ± s.d. The arrow indicates container exchange.**

oxygen demand.[22,23] NTG lowers blood pressure (systolic greater than diastolic) and, in some cases, the rapid drop in pressure produces a reflex increase in heart rate. Thus, blood pressure and heart rate provide useful end-points with which to monitor any potential container-related differences in clinical response to intravenous NTG. The present study was designed to detect changes in these two variables, as well as NTG infusion rates, during the first 60 minutes following a NTG container exchange. We found no significant change in blood pressure, heart rate, or NTG requirements in patients randomized to receive NTG mixed in either glass containers or PVC containers. If a change in pressure of 10 mm Hg or greater in either group had occurred, we estimate that the study had a probability of 80% (power = 0.8) of its detection based on the MAP at baseline.

The question of stability and potency of NTG solutions prepared in PVC containers has been previously investigated, but not in a clinical setting. A number of studies have demonstrated substantial sorption of NTG into the PVC components of infusion systems commonly employed in clinical practice.[6-19] This process is dependent on temperature, the time of exposure to the PVC, the surface area of PVC in contact with the NTG, and the concentration of the solution.[7,10,19] Many studies have addressed the question of NTG potency loss from PVC containers.[6-19] With the exception of a single study by Ludwig and Ueda,[24] the results have been consistent, showing a loss of NTG from solutions prepared in PVC bags compared to glass bottles.[6,7,8,15,18,20] Although Ludwig and Ueda[24] showed a considerable loss (18-26%) of NTG from a 5% dextrose in water solution admixed in PVC containers, they had a comparable loss of NTG from a similar solution mixed in glass bottles. This unusual observed loss of potency from the glass bottles may have been related to their procedure for sample collection. Samples were withdrawn through a short length of tubing of unknown composition which may have adsorbed some of the NTG.[14] Because of these studies, current recommendations are that NTG solutions be prepared in glass bottles and stored under refrigeration prior to use.[19] Despite the evidence of a significant loss of NTG potency from PVC infusion systems, to our knowledge, there have been no randomized clinical trials evaluating the clinical impact of container type on the hemodynamic response to NTG infusions. Our results indicate that, despite the reported loss of NTG potency in PVC containers, there is no discernable effect on the blood pressure or heart rate within 60 minutes of a container exchange.

The lack of clinical effect has a number of explanations. First, the rate of the sorption process of NTG to PVC containers is rapid and may have occurred before administration. Ingram and Miller[20] reported that when NTG was added to a 150 cc PVC (Viaflex$^{R}$) container, a decline in NTG potency of approximately 80% was observed, most of which occurred immediately after mixing. However, most studies indicate that sorption of NTG follows a first order process and a large percentage of the NTG loss appears to occur within the first few hours,[15,17] although few studies have investigated the rate of potency loss during the very early stages (less than 60 minutes) following admixture. In the present study, we attempted to minimize the time between the preparation of the NTG solutions and the container exchanges (mean 13 ± 17 minutes). However, it remains possible that sufficient time elapsed to permit completion of the majority of the NTG sorption process to the container or infusion set prior to administration. Therefore, the drug availability in the old and new solutions was equivalent and the clinical status remained stable after the container exchange.

Second, the PVC infusion sets, which were utilized in both groups, may have assumed the dominant influence on the overall sorption process, masking the potential specific impact of the PVC containers. Several studies have suggested that PVC infusion sets can reduce the potency of NTG solutions.[7,10,12,13,16,20] This effect may be flow dependent, with losses varying from 30% at the fastest flow rates to 80% at the slowest rates.[10,12] In accordance with normal practice at our institution, administration sets were utilized for 72 hours before being replaced and, as stated in the methods section, no sets were replaced within 24 hours of a container exchange. It is possible that the PVC infusion sets contributed to a loss of NTG potency, but it is also likely that this aspect of NTG sorption was already maximal (saturated) at the time of the flushing of the infusion sets with fresh solution and the container exchanges. These circumstances should have permitted detection of a specific container effect. A negative outcome to our study may have been less likely if the methodology had employed specialized administration sets made from a non-absorbing material, such as polyolefin. However, Young et al[21] compared the effects of NTG solutions prepared in glass bottles and administered through either PVC or polyolefin infusion tubing, and found no differences even at low flow rates. They concluded that it is unnecessary to use specialized administration sets when infusing NTG intravenously;

therefore, the choice of infusion sets was unlikely to influence the outcome of our study.

Third, pharmacological tolerance to the peripheral vasodilator effects of NTG leads to attenuation of the hemodynamic and anti-ischemic effects of NTG in patients with congestive heart failure or ischemic heart disease.[25] Tolerance may occur in as little as 12[28] to 24 hours[26,27] after initiation of therapy. In the present study, the average time between initiation of NTG therapy and container exchange was 30 hours [± 19 (sd) hours]. This is sufficient time for significant tolerance to develop.

In many institutions, glass bottles are considered the container type of choice for the intravenous administration of NTG because of concerns about potential sorption problems which had been reported from *in vitro* studies. We examined the hemodynamic responses of patients, randomly assigned to receive NTG from either glass bottles or PVC bags. No clinically important changes in hemodynamic status were observed in either group. Since patients in this study were assigned to either PVC or glass containers, the possibility remains that changes in hemodynamic status could occur in patients on NTG infusions whose container type is changed (i.e., from PVC to glass or vice versa) during their course of therapy. However our results do indicate that hospital procedures for administration of NTG can utilize the safer and more easily prepared PVC containers for the treatment of patients with unstable angina pectoris or acute myocardial infarction without causing instability in blood pressure or pain control. This policy was recently approved by our Pharmacy and Therapeutics Committee, and has now been integrated into routine clinical practice in our institution. We have thus far had no cases in which hemodynamic instability has occurred with the use of PVC containers.

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