Readers' Comments
An Explanation for the Effect of Different Storage Conditions on Sublingual Nitroglycerin Tablet Stability

It is recommended that all patients with ischemic heart disease carry sublingual nitroglycerin (SL NTG) with them at all times in case of an anginal attack.[1] NTG is a volatile liquid and SL tablets must be dispensed in the original manufacturer's amber glass vial with a metal screw top cap to maintain the potency of the product.[2] Although the manufacturer clearly indicates an expiration date on the product package, the drug can volatilize once the container is opened and lose its potency. In fact, early published studies suggested that SL NTG tablets rapidly lose potency over time, especially at elevated temperatures, leading to the recommendation that patients replace their SL NTG supply at least every 6 months.[3–6] This recommendation, however, does not take into account the manner in which patients carry their medication.

A recent study published by the *Journal* demonstrated that SL NTG tablets remained stable through the expiration date stated on the package label when stored in the original glass vial at 25°C/60% RH (approximately 33 months). However, when stored in the original package at 40°C/75% RH, drug content decreased more rapidly and fell below compendial standards within 9 months.[7] In addition to these controlled conditions, we found that SL NTG degraded more rapidly when carried in pants pockets in comparison to product carried in a purse or backpack. In response to those findings, we hypothesized that the temperature inside a person's pants pocket is higher than inside a purse/carrying bag or ambient conditions and that the higher temperature adversely affects the chemical stability of nitroglycerin. The objective of this project was to determine the temperature in different environments in which SL NTG is routinely stored and carried.

Eight men and 8 women from the University of New Mexico College of Pharmacy were recruited to participate in the study. The study protocol was approved by the University of New Mexico Human Research Review Committee and all participants completed the study. Participants were given 3 small data logging devices (approximately 17 mm in diameter and 6 mm height; PyroButton, Opulus, Philadelphia, Pennsylvania). One device was placed in a pants pocket with the sensor closest to the body. Another device was placed in the participant's purse or carrying bag. The third data logger was placed on a desk or counter in close proximity to the study participant. The data logging devices were programmed to record temperature at 5 minute intervals over a 60-minute period. Participants were required to remain in their workspace during the recording period. After the recording period, the devices were collected and the data were downloaded into an Excel spreadsheet for subsequent analysis. Each participant was tested on 3 different days and the order of testing was randomized to eliminate bias.

Temperatures in the pants pocket were always higher than temperatures in both the purse/carry bag and ambient conditions. The average temperature from all study participants in the pants pocket was approximately 9°C higher than ambient conditions (30.28°C ± 2.01 vs 21.01°C ± 1.43), as shown in Figure 1. In contrast, the average purse/carrying bag temperature for all participants (23.25°C ± 1.28) was only about 2°C higher than the average ambient temperatures. Interestingly, the average temperature in the pants pocket for female participants was 32.3°C (range 29.86°C to 34.49°C), about 2°C higher than the 30.31°C average temperature for the male subjects (range 29.68°C to 30.85°C). Average purse/carrying bag temperatures for men and women was approximately the same (23.16°C and 23.25°C, respectively).

It is well known that nitroglycerin is volatile.[8] Figure 2 shows the reported vapor pressure of nitroglycerin as a function of temperature.[9] Vapor pressure is directly related to volatility, with higher vapor pressure indicative of greater volatility. The best fit quadratic equation for these data is $Y = 6.901 \times 10^{-3} - (5.803 \times 10^{-4})(X) + (1.48 \times 10^{-5})(X)^2$. Using the average temperature from the pants pocket (30°C), the purse/carrying bag (23°C) and the average ambient temperature (21°C), the calculated vapor pressure of nitroglycerin is 0.0028 Torr, 0.0014, and 0.0012 Torr, respectively. Although there is a small increase in the vapor pressure of nitroglycerin stored in the purse/carrying bag compared with ambient conditions, vapor pressure more than doubles when carried in a pants pocket. A higher vapor pressure is indicative of a more volatile material and these data correlate well with previous findings that showed sublingual nitroglycerin tablets lose potency more rapidly when carried in close proximity of the body.

Previous research has been consistent in showing that the loss of SL NTG occurs more rapidly in higher temperature environments.[7,8] The findings of this research demonstrate that items carried in pants pockets are exposed to temperatures that are on average 9°C (16°F) higher than ambient temperatures and 7°C (13°F) higher than temperatures found in a purse or carrying bag. The markedly higher

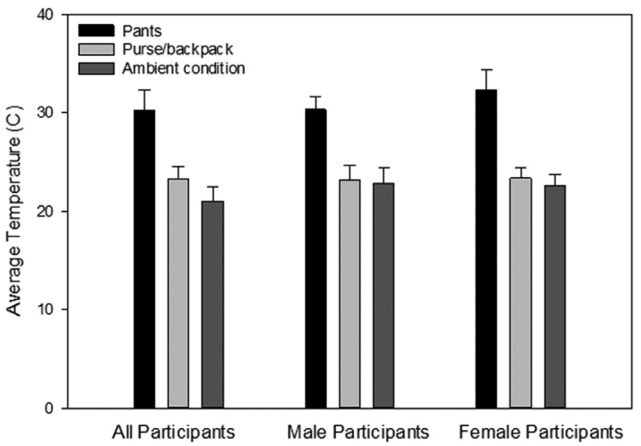

Figure 1. Average temperatures from study participants as a function of the location of the recording devices.

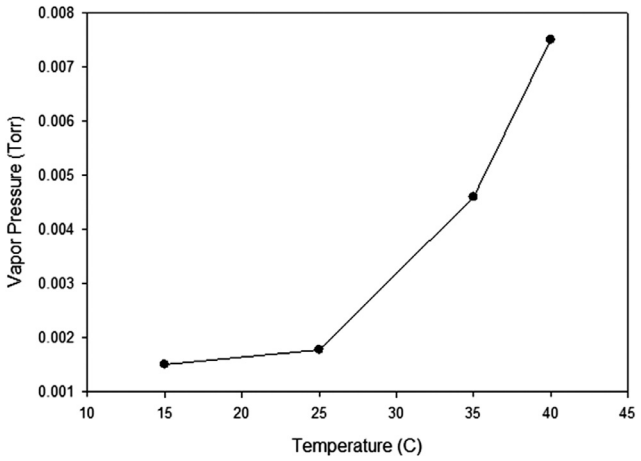

Figure 2. Influence of temperature on the vapor pressure of nitroglycerin. Data are from reference 9.

temperatures in pants pockets produce a suboptimal storage environment for SL NTG and may somewhat explain the preservation of SL NTG tablet potency when tablets were stored in carrying bags compared with pants pockets.[7]

Based on the results of this study and previous work,[7] SL NTG should be carried by patients in a purse or carrying bag rather than in a pants pocket. If this is not practical, then every effort should be made to carry SL NTG in a manner to minimize close contact with the body, for example, a loose pocket such as a jacket or shirt.

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Underlying Differences in the Treatment of Left Ventricular Thrombus With Non-Vitamin K Antagonist Oral Anticoagulants

We read with great interest the manuscript by Fleddermann et al "Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus."[1] The study included a considerable number of patients (n = 52) with left ventricular (LV) thrombus who were treated with non-vitamin K antagonist oral anticoagulants (NOAC), which doubled the number of cases currently published in the literature. Overall results for NOAC therapy in LV thrombus were promising, whereby majority (82.9%) of the patients reported resolution, whereas 1 patient had an embolic event and 4 had bleeding episodes. The advent and recent rise in usage of NOAC represents an attractive alternative to vitamin K antagonist (VKA). It provides various benefits such as lower bleeding risk, stable anticoagulation effect, fewer drug-drug interactions, which likely confers therapeutic advantage in the treatment of LV thrombus.[2] However, this is not a new concept, as a meta-summary by Leow et al[3] has previously been published, before the systemic review by Kajy et al[4] as cited by the authors. In that study (n = 36), thrombus resolution was met in 87.9% of patients, and there were minimal bleeding and no embolic events.

The patient population with LV thrombus is diverse and various precipitating factors could result in its formation. Although post-myocardial infarction (MI) was once the most common cause of LV thrombus, improvement in percutaneous coronary intervention and management of MI has resulted in its decline and has now been superseded by heart failure as the most common precipitating factor in the contemporary era.[5] This shift in epidemiology plays an important role in the research of LV thrombus treatment. First, based on the data kindly provided by Fleddermann et al, only 19.2% of patients (n = 10) were on concomitant NOAC and DAPT (also known as triple therapy). In contrast, 47.2% of patients were on triple therapy in the meta-summary abovementioned, 39.0% in the systemic review, and 38.0% in a study of post-MI LV thrombus patients by Maniwa et al.[6] The significantly lower rate of triple therapy use reported in this study could be due to the decreasing incidence of post-MI LV thrombus and may result in a falsely lower rate of bleeding than expected. Hence, whereas initial reports of NOAC use in the treatment of LV thrombus are encouraging, the rate of bleeding complication should be interpreted while taking into context the proportion of patients on triple therapy.

Second, both the underlying cause of LV thrombus formation and patients' clinical characteristics could vary across studies. In particular, comorbidities such as cardiovascular risk factors, valvular abnormalities,