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OINTMENT APPLICATIONS ON PULSE RATE AND
SYSTOLIC BLOOD PRESSURE.

THE UNIVERSITY OF ARIZONA, M.S., 1982
THE EFFECT OF SURFACE AREA
OF NITROGLYCERIN OINTMENT APPLICATIONS
ON PULSE RATE AND SYSTOLIC BLOOD PRESSURE

by

Kathy Ann Van Robays

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COLLEGE OF NURSING
In Partial Fulfillment of the Requirements
For the Degree of
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STATEMENT BY AUTHOR

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This thesis has been approved on the date shown below:

ALICE JEAN LONGMAN
Associate Professor of Nursing
For countless reasons this thesis is lovingly dedicated to my parents.
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ABSTRACT

This study's purpose was to determine the effect of surface area of application of nitroglycerin ointment on pulse rate and systolic blood pressure. The theoretical framework was based on the unique barrier properties of the skin and the systemic effects of nitroglycerin ointment.

Fifteen healthy subjects completed a two-day experiment. Nitroglycerin ointment (1.5 inch) was applied to either a 5.0 cm² or 20 cm² area of the chest in two treatment sessions and each subject received both applications. Pulse rate (Grass polygraph) and blood pressure (arm-cuff sphygmomanometer) were monitored for three hours and subjective sensations (the Distress Rating Scale) were evaluated.

There was not a significant statistical difference in decreases in systolic blood pressure and increases in pulse rate between the two treatment sessions. The findings indicated that there was a trend for the 20 cm² application to produce more significant clinical change in cardiovascular response. Minimal variability was found in subjective sensations between treatments.
CHAPTER I

INTRODUCTION

Heart disease is a fact of life in today's technological society. In the United States, cardiovascular disability is responsible for alterations in life style for over 40 million persons. Despite research and medical advances in the field of cardiology, more Americans die from diseases of the heart and blood vessels than from all other forms of death combined (American Heart Association, 1981).

Innovative treatment modalities such as coronary artery bypass surgeries, chemical regimens, dietary controls, and exercise programs, strive to decrease mortality and morbidity from cardiovascular diseases. Persons suffering from specific heart diseases often benefit from at least symptomatic relief through various therapeutic approaches.

The clinical actions of topically applied nitrates for the treatment of periperal circulatory disorders were first investigated by Lund in 1948 (Armstrong, Armstrong and Marks, 1980). Findings from Lund's study indicated that topical nitroglycerin could be used to treat circulatory insufficiencies, specifically Raynaud's disease.

Nitroglycerin ointment was introduced in the United States by Davis and Wiesel (1955) who documented its benefits in the treatment
of patients with angina pectoris. The investigators concluded that nitroglycerin ointment (NTGO) could be an adjuvant therapy in the management of coronary insufficiency. Following Davis and Wiesels's research, the therapeutic benefits of NTGO remained unnoticed until it was reintroduced in the 1970's to cardiovascular protocols.

Today, the vasodilatory effects of NTGO are commonly used for patients with angina pectoris (Reichek, Goldstein, Redwood, et al., 1974; Davidov and Mroczek, 1976; Burgess, 1979), and recently, clinical benefits have also been demonstrated in the treatment of congestive heart failure (Taylor, Forrester, Magnasson, et al., 1976; Meister, Engel, Guiha, et al., 1976a; Klausner, Chatterjee and Parmley, 1976; Franciosa, Blank, Cohn, et al., 1977; Chandraratna, Langerin, O'Dell, et al., 1978; Moskowitz, Kinney and Zelis, 1979) and acute myocardial infarction (Epstein, Kent, Goldstein, et al., 1975; Armstrong, Mathew, Boroomand, et al., 1976).

Nitroglycerin ointment provides a cutaneous approach for the introduction of long-acting nitrates into the systemic circulation (Reicheck, et al., 1974; Francis and Hagan, 1977). It contains two percent nitroglycerin (NTG) in a lanolin-petroleum base for transcutaneous absorption (Bowman and Rand, 1980; Hansen and Woods, 1980). Nitroglycerin, a glycercyl ester of nitric acid, is available in topical forms and also in sublingual and oral tablets. There is little evidence to suggest that one nitrate preparation acts differently from another except with respect to the time of onset and duration of activity (Abrams, 1979).
In the past decade, long-acting nitrates have received considerable attention for their clinical value in the treatment regimen of patients with cardiac disease. Nitroglycerin ointment is exceptionally attractive because of its enhanced bioavailability by circumventing the gastrointestinal tract and portal circulation (Meister, Engel, Guiha, et al., 1976b; Armstrong, et al., 1980). The metabolic advantage of NTGO preparations is that they evade hepatic degradation on the first pass through the circulation. Because active nitrates are continuously absorbed transdermally, the vasodilatory action remains longer than for other nitrate preparations (Armstrong, et al., 1976; Zelis, Liedtke and Flaim, 1980).

While sustained systemic availability of NTGO is the primary goal of therapy, minimal information is known about the physical and physiological factors influencing transcutaneous absorption. The actual administration process for NTGO has not been emphasized or investigated to the same extent as the clinical indications or therapeutic benefit (Hansen, Woods and Ellis, 1979). Pharmaceutical companies' (Nitrong, Wharton Laboratories; Nitro-Bid, Marion Laboratories; Nitrol Ointment, Kremers-Urban) suggestions document such disparities in administering NTGO (Physicians' Desk Reference, 1981). All three companies suggest spreading the ointment over a thin uniform layer on the skin, however, only Marion Laboratories suggest a specific surface area, six in². Marion and Wharton Laboratories advise protecting the site with plastic wrap and securing it with adhesive tape. Kremers-Urban suggest that
the ointment be spread over the desired area of the skin every three hours. The outcome of this deficient knowledge promotes variation in present methods of applying NTGO. Therefore, discoveries which enhance transcutaneous absorption of NTGO may provide practical clinical contributions (Hansen, 1978; Horhota and Fung, 1979; Hansen, et al., 1979).

**Statement of the Problem**

What is the relationship between the total surface area used in NTGO applications and changes in systolic blood pressure and pulse rate in normal subjects?

**Purpose of the Study**

The purpose of this study was to determine the effect of surface area of application of NTGO on systolic blood pressure and pulse rate. By using the most effective application technique, nurses can properly apply the drug and consequently improve patient care outcomes.

**Significance of the Problem**

One of nursing's obligations is the dispensing of drug therapies. The uniqueness of topical NTG therapy requires special attention by nurses to promote optimal absorption and systemic effects. Present guidelines for applying NTGO are inconsistent. Few studies have been published which describe how alterations in total dose, site and completeness of absorption, intensity of effect, and duration of action affect the efficacy of therapy (Adkinson, 1977).
Important nursing implications of the actual method of measuring and applying NTGO have received minimal attention. Vague instruction and limited documentation allow considerable variability in NTGO applications (Hansen and Woods, 1980; Kirby and Woods, 1981). The clinical practitioner not only needs to be cognizant of potential adverse side effects with nitrate therapy, but also should be appreciative of the dynamics of transcutaneous absorption. Thus, before administering NTGO, the nurse should be attentive to such variables as: the condition of the skin, the site of application, the total surface area used, and the application of an occlusive dressing, all factors which may affect the efficacy of therapy.

With the high incidence of cardiovascular diseases, medical treatment regimens utilizing vasodilators are increasingly common. Included in therapies of angina pectoris and chronic congestive heart failure is the frequent use of NTGO.

The physician is primarily concerned with the prescription and therapeutic outcomes of treatment modalities. The nurse is concurrently attentive to the correct administration and observation of side effects of these modalities. The unusual characteristics of NTGO's dosage and application demand additional consideration in administration procedures for the nurse. It is vital for health care personnel and patients to know if transcutaneous penetration of NTGO is influenced by total surface area of the application site. Through continued research on NTGO therapy and application procedures, nurses can properly administer the preparation and teach the patient with cardiovascular disease.
Hypotheses

The following hypotheses were tested in this study:

1) A 1.5 inch dosage of NTGO placed on a 5.0cm$^2$ area of the right pectoral region will decrease systolic blood pressure and increase pulse rate in normal subjects.

2) A 1.5 inch dosage of NTGO placed on a 20cm$^2$ area of the right pectoral region will decrease systolic blood pressure and increase pulse rate in normal subjects.

3) The 20cm$^2$ application will produce a significantly greater decrease in systolic blood pressure and increase in pulse rate than will the 5.0cm$^2$ application.

Theoretical Framework

The theoretical framework is based on the unique barrier properties of the skin and the systemic effects of nitroglycerin ointment. The model for this framework is illustrated in Figure 1.

The Skin

The skin, the largest organ of the body, is under constant assault from various chemical and physical substances. The single most important function of human skin is its ability to act as a two-way barrier. Its selective permeability prevents the exodus of water, electrolytes and other body constituents and prevents the environmental admission of toxic or unwanted molecules, microorganisms or viruses (Baker, 1979; Horhota and Fung, 1979).
Skin Barrier

Systemic Availability

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Figure 1. Model of Theoretical Framework
Historically, the skin was thought to be totally impermeable to molecular entry. Modifications in this concept, however, suggest that the skin functions as a rate-controlling barrier. The local or systemic effects ensuing from transcutaneous entrance of synthetic chemicals, toxic gases, environmental hazards, cosmetics, and topical medications led to this revision. Scientific investigations in past decades have attempted to delineate which chemicals penetrate the skin barrier (Idson, 1975).

The selective barrier properties of the skin have established that it is a poor route for most systemic drug administration (Horhota and Fung, 1979). However, the selective permeability of the skin provides a valuable route for certain topical drug applications, particularly NTGO.

Transcutaneous absorption, the penetration of molecules into and completely through the skin from the external environment to blood and lymph, is governed by physiochemical properties (Baker, 1979). The principal rate-limiting function of the epidermis exists almost entirely in the stratum corneum. This thin membrane of keratinized, metabolically inactive epithelial cells, often referred to as the "dead" surface layer of the epidermis, presents the greatest resistance for molecular movement (Scheuplein and Blank, 1971). The fate of a topically applied drug, therefore, depends on the physiochemical interaction between the penetrant, its base, and the stratum corneum (Baker, 1979).

From existent research on transcutaneous absorption it is evident that the horny layer, or stratum corneum, acts like a passive
diffusion medium (Stuttgen and Scheuplein, 1979). Diffusion laws of physics pertinent to passive diffusion processes explain the skin's permeability phenomenon (Scheuplein and Blank, 1971; Stuttgen and Scheuplein, 1979).

The transport of molecules from the environment across the skin is a complex and difficult process. While transcutaneous absorption occurs through various routes, it primarily occurs between the cells of the stratum corneum or via the pilosebaceous follicles. Through transcellular absorption drugs applied topically to the skin reach the orifices of the sweat glands and hair follicles. The sebaceous glands, attached to hair follicles, empty secretions into the follicular canals near the skin surface. Medications easily penetrate these stratified squamous epithelial lined canals and duct systems (Idson, 1975).

Once a substance passes through this superficial barrier, there seemingly is no resistance to its penetration of the epidermis, dermis, and lastly, microcirculation. Schaefer (in Stuttgen and Scheuplein, 1979) concluded that all foreign material which successfully pervades the stratum corneum will almost entirely be taken up by cutaneous blood and lymph systems. This final phase, molecular entry into the systemic circulation, is mediated by an effective blood flow, interstitial movement, condition of the lymphatics, and perhaps molecular combination with dermal constituents (Idson, 1975).

The various factors influencing barrier integrity affect the efficiency of transcutaneous absorption. Intactness and hydration of the stratum corneum are crucial among parameters affecting transcutaneous
transport. Removal of the stratum corneum or damage to the cell membrane compromises osmotic functions wherein water diffuses outward, even under optimal conditions (Scheuplein and Blank, 1971; Idson, 1975; Baker, 1979).

The efficiency of the skin's barrier property predicts the success of transcutaneous absorption. The absence of homogeneity in this exclusive property over the entire body surface suggests another variable (Marzulli, 1962; Hansen, et al., 1979). Regional variations in structure and chemistry of the stratum corneum influence its permeability. Anatomical absorption rates are largely contingent on different thicknesses of the biological membrane (Marzulli, 1962; Baker, 1979).

The Drug

The chemical properties of the drug and its vehicle also regulate the efficacy of molecular permeation. The solubility of the penetrant greatly influences its success in perforating the skin's barrier. The epidermal cell membrane is largely an aggregate of densely packed cells in a lipid and protein milieu, generally a lipid-soluble matrix (Scheuplein, 1965). The Meyer-Overton theory of absorption recognizes the cell membrane's lipid-water solubility pattern. According to this theory, substances soluble in lipids pass through the cell membrane due to the membrane's lipid content while water-soluble substances pass following the hydration of protein molecules in the cell wall. This theory suggests that the cell is permeable to both
l lipid and water-soluble substances (Idson, 1975). The degree of water-solubility a substance exhibits not only determines the amount of drug released at the absorption site, but also the rate of permeation through the skin (Katz and Shaikh, 1965; Baker, 1979).

Other factors, polarity and molecular weight, also affect diffusion across the stratum corneum. Polar and nonpolar molecules diffuse through the skin by different mechanisms. Often nonpolar molecules' diffusion rates are greater than for corresponding polar molecules (Blank, Scheuplein and Marfarlane, 1967). Scheuplein (1965) first concluded that molecular weight influenced the diffusion rate of substances. The permeability constant is influenced by the interaction between molecular weight, temperature and solubility factors (Blank, et al., 1967).

Increasing drug concentration to saturation levels within its carrier increases the amount of drug transcutaneously absorbed per unit surface area. The degree of the drug's saturation solubility within the carrier places an upper limit on the activity that can be achieved from the active agent (Coldman, Paulsen and Higuchi, 1969; Idson, 1975; Horhota and Fung, 1979). Magnifications in drug concentration may not only be costly and wasteful, but occasionally a supersaturated concentrated substance may produce significant decreases in penetration rates or create caustic effects on the skin's integrity (Idson, 1975; Baker, 1979). These adverse effects have stimulated investigation into improving the vehicle, the substance carrying the active ingredient, which will be dissolved or dispersed on the skin's
surface (Baker, 1979). The essential requirement for topical therapy is that a drug embodied in a medicinal preparation reaches the skin surface at a satisfactory rate and in adequate amounts (Stroughton, 1965; Coldman, et al., 1969; Idson, 1975). The vehicle should not only be compatible but have a low affinity to the active agent, and lastly, avoid trauma to the skin surface (Stroughton and Fritsch, 1964; Munro and Stroughton, 1965; Poulson, Young, Coquilla, et al., 1968; Baker, 1979; Horhota and Fung, 1979).

Following the application of a topical agent to the skin, the effects of temperature and time on absorption must be considered. Drug transport optimally occurs within a narrow temperature range (Scheuplein, 1965). Specific time intervals for total exposure are important to selectively influence greatest absorption.

The mathematical analysis of variables affecting the release of solid drugs suspended in a vehicle is illustrated in Figure 2 (Horhota and Fung, 1979). As can be seen, the equation suggests that several variables can be used to approximate the penetration of the skin's barrier by a drug dissolved in a topical vehicle (Poulsen, et al., 1968). The model assumes that the skin represents a semipermeable diffusional barrier for drug transfer. When the effective partition coefficient, drug concentration, diffusibility of the drug through the barrier, and effective barrier thickness remain constant, the equation addresses the role of surface area of application in determining transcutaneous absorption rates.
\[ \frac{dQ}{dt} = KC_v \frac{DA}{T} \]

\( \frac{dQ}{dt} \) = steady state of penetration of the skin barrier

\( K \) = effective partition coefficient of the drug's dissociation between its vehicle and the skin barrier

\( C_v \) = drug concentration dissolved in the vehicle

\( D \) = diffusibility of the drug through the barrier

\( A \) = surface area of application of the vehicle

\( T \) = effective thickness of the skin barrier

Figure 2. Quantitative Relationship Between Drug Transfer and Several Variables
With the objective of enhancing the absorption of a topically applied drug, it is obvious that the pharmaceutical formulator can manipulate only certain aspects of the equation. These are the partition coefficient \( K \) and drug concentration \( C_v \) (Poulsen, et al., 1968). Specifically, diffusion should be improved when drug concentrations approach saturation levels and when vehicles with low affinity to the penetrant are used. In the product term \( KC_v \), attempts toward elevating drug delivery should increase the drug's thermodynamic activity within the vehicle (Horhota and Fung, 1979).

An easily maneuverable variable affecting the efficiency of topical drug transport is the surface area of application of the vehicle \( A \). The size of the surface area and locality play a dominant role in determining the rate of absorption, magnitude of effect, and duration of action (Stuttgen and Scheuplein, 1979; Zelis, et al., 1980). Specifically, the sustained therapeutic activity of NTGO is influenced by the continuous absorption from a sizeable deposit on the skin (Meister, et al., 1976a).

Various researchers suggest applying NTGO to a substantial area over the skin, particularly the anterior chest wall. Lastly, to enhance the skin's permeability by increasing hydration and temperature factors, a plastic covering is then placed over the application site (Armstrong, 1977; Abrams, 1977; Hansen and Woods, 1980). The dressing serves to augment absorption and prevent medication delivery onto one's clothing (Abrams, 1977; Hansen and Woods, 1980).
Nitrates—Mechanism of Action

Even though nitrates have been used for more than a century, controversy still exists on the exact mode of action within the cardiovascular system (Haradarson and Wright, 1976). The actual clinical and hemodynamic improvement produced by nitrates is contingent upon their effects on heart rate, end diastolic volume, and ejection fraction (determined by dividing end diastolic volume into stroke volume) (Gould, Reddy, Zen, et al., 1980).

The primary mechanism for effects of nitrates on the system are systemic venodilation and coronary artery dilation. A less potent effect of nitrates is arterial dilation which reduces arterial afterload pressure (Williams, et al., 1977; Dobbs and Povalski, 1977). To summarize the events precipitated by nitrate therapy, NTG decreases peripheral vascular resistance which results in an increase in ejection fraction and cardiac output, with a decrease in end diastolic volume and pulmonary capillary pressure (Forrester, 1976). Nitrates therefore improve the efficiency of pump action.

Specifically, NTG exerts its effects by means of dilating smooth muscle in blood vessel walls. Although it is normally known to be a generalized vasodilator, its selective action is more pronounced on the large venous capacitance vessels than on the arterial resistance system. Venous pooling created by a decreased systemic venous tone redistributes blood away from the central circulation, thereby reducing right and left atrial pressure (Mason and Braunwald, 1965; Ferrer, Bradley, Wheeler, et al., 1966; Campion, et al., 1970; Taylor, et al., 1976; Dobbs and

The vasodilator's favorable influence is its dual reduction in preload (venous filling pressure) and afterload (arterial impedance) (Dobbs and Povalski, 1977). The decrease in left ventricular and diastolic volume and pressure therefore contributes to the low ventricular wall tension and concomitant oxygen requirement. The diminished wall tension also produces an improved ventricular contractility (Wayne, 1977a). The diminished peripheral vascular resistance decreases systolic flow impedance which simultaneously increases stroke volume and ejection fraction (Ferrer, et al., 1966; Campion, et al., 1970; Armstrong, et al., 1976; Taylor, et al., 1976; Mason, 1978; Dobbs and Povalski, 1977). While venous tone is diminished and the blood volume is redistributed, a subsequent decrease in central venous pressure is measureable. In the arterial system, vasodilation consequently decreases the systolic blood pressure in the absence of an equivalent change in diastolic pressure. These arterial pressure changes decrease the mean arterial pressure and suggest a reduction in afterload (Armstrong, et al., 1976; Abrams, 1977).

The intrinsic mechanism of the myocardium to adapt to elevated filling pressure by appropriate alterations in cardiac contractility is referred to as the Frank-Starling "law" of the heart. The diastolic
filling pressure determines myocardial fiber length prior to contraction. The elevation of filling pressures within its physiologic limits elevates left ventricular performance which is evidenced by an increased left ventricular stroke volume. Further increase in filling pressures beyond this level does not result in improved cardiac performance since maximal shortening of myocardial filaments has been attained (Jensen, 1980). Therefore, if filling pressures are maintained on this plateau, a vasodilator augments stroke volume by reducing the resistance to ejection. The benefit of NTG therapy to patients with high filling pressures is the decreased left ventricular end diastolic pressure accompanied by an elevated stroke volume (Parmley and Chatterjee, 1976).

The vasodilatory effects of NTG not only vary in the venous and arterial systems, but are also nonuniform in regional circulations. Reflex sympathetic discharge is largely responsible for the body's response to NTG which manifests diverse effects even in isolated circulations. The arteriolar dilation can be concealed in a reflex vasoconstriction in circulations under extensive neurogenic control. It is generally accepted that the splanchnic and renal circulation promptly vasoconstricts, and secondly, renal blood flow decreases subsequent to the decline in mean arterial pressure (Ferrer, et al., 1966; Abrams, 1979; Zelis, et al., 1980).

Researchers conclude that the system's response to NTG depends on the stimulation of a specific nitrate receptor site in the vascular wall. The active nitrate molecule reacts with a sulphydryl group at
the receptor to release the nitrate ion which initiates vascular relaxation (Abrams, 1977).

Another aspect of nitrates which deserves attention is its effect on the coronary circulation. Nitroglycerin acts predominantly on the large epicardial arteries, preferentially dilating the conducting vessels rather than the small arteriolar resistant vessels. Decreasing the resistance of the conducting vessels without a reduction in arterial pressure shunts blood to ischemic areas. Large coronary collaterals effectively dilate in response to nitrate therapy during myocardial ischemia (Mason and Braunwald, 1965; Dobbs and Povalski, 1977; Abrams, 1977).

The effect of NTG on coronary circulation appears to be from blocking calcium influx within the large coronary arteries. This unique effect proposes dissimilarities in ionic mediation of smooth muscle relaxation (Abrams, 1977). Following prolonged nitrate therapy these vessels manifest a heightened reaction to nitrate stimuli (Dobbs and Povalski, 1977).

Alterations in peripheral vascular resistance further influence myocardial perfusion. The reduction in systolic blood pressure not only minimizes intraventricular wall tension, but subsequently improves the endocardial perfusion gradient (Dobbs and Povalski, 1977). The action of nitrates on vascular smooth muscle produces an increased myocardial blood flow with a diminished oxygen consumption. The valuable result from NTG therapy is improved myocardial efficiency (Mason and Braunwald, 1965; Armstrong, et al., 1976).
Deleterious responses to nitrate therapy restrict the drug's clinical value. In a patient experiencing a decreased diastolic filling pressure, a reduction in systemic arterial pressure would yield a net decrease in stroke volume. To maintain an adequate cardiac output, reflex action stimulates an increase in heart rate and contractility. This compensatory tachycardia created by baroreceptor stimulation produces an increased adrenergic drive. The acceleration in heart rate elevates myocardial work and oxygen demands. In select patients this additional stress may decrease perfusion to ischemic areas; and, if sympathetic response is intense, the increased contractility amplifies left ventricular end diastolic pressure (Campion, et al., 1970; Parmley and Chatterfee, 1976; Dobbs and Povalski, 1977; Zelis, et al., 1980). These adverse considerations have curtailed the eagerness to use nitrates during acute myocardial infarction. Nitroglycerin may however, be beneficial when myocardial infarction is complicated by congestive heart failure, wherein the reduction of heart size takes precedence over any adverse effects resulting from a fall in perfusion pressure (Zelis, et al., 1980).

When blood flow is inhibited by atherosclerotic plaques obstructing the vessel lumen, myocardial ischemia develops. The relative imbalance between the demand and availability of oxygen to the myocardium is manifested by the classical clinical sign of angina pectoris (Mason, et al., 1971; Dobbs and Povalski, 1977; Miner and Conti, 1978; Arnow, 1979a). These transient vasospastic attacks result from ineffective attempts of the myocardium to increase its oxygen supply (Burgess, 1979; Dobbs and Povalski, 1977). Pharmacological
interventions attempt to modify the painful attacks, either by decreasing oxygen demands or increasing the oxygen supply to the myocardium (Dobbs and Povalski, 1977). In the past, nitrates have received considerable attention for their significant relief of anginal attacks occurring both at rest and with exercise (Salerno, Previtali, Medici, et al., 1981). Investigators conclude that nitrates increase blood flow to potentially ischemic areas via collateral channels in patients with severe symptomatic multi-vessel involvement. The increased blood delivery to the myocardium improves cardiac oxygen consumption (Goldstein, Stinson, Scherer, et al., 1974).

Nitrates relieve angina pectoris by diminishing myocardial oxygen requirements via two mechanisms of action. With a reduced venous return to the myocardium the left ventricular wall tension is decreased. The lowered wall tension relieves elevated oxygen demands and improves ventricular wall motion. Secondly, the decreased coronary vascular resistance augments blood flow to ischemic areas (Brachfeld, Bozer and Gorlin, 1959; Leighninger, Rueger and Beck, 1959; Muller and Rorvik, 1958; Ganz and Marcus, 1972).

Clinical Effects of NTG

Variations in the duration of exercise capacity produced by different nitrate preparations reflect dissimilarities in NTG's rate of entry into the systemic circulation. The transcutaneous route permits gradual absorption of larger doses of nitrates than would be
tolerated if administered sublingually (Reichek, et al., 1974). Therefore, topical delivery maintains sustained effects on the cardiovascular system as compared to short-acting nitrates.

Following investigations into the clinical benefits of nitrates, investigators recommend longer-lasting nitrate preparations for patients with angina pectoris (Slutsky, Battler, Garber, et al., 1980). The advantageous effects of sustained released nitrates are the increase in exercise capacity and decreased workload of the heart (Abrams, 1977; Francis and Hagan, 1977), the decrease in frequency of attacks (Miner and Conti, 1978; Davidov and Mroczek, 1977), and the improved ST segment response on the electrocardiogram (Davidov and Mroczek, 1976).

The therapeutic effects of topical nitrates have extended its application to include patients with acute and chronic congestive heart failure. Investigations demonstrate NTG0's ability to decrease left ventricular filling pressure which concomitantly improves ventricular dimensions. The reduced peripheral vascular resistance and increased capacitance decreases systolic, mean, and diastolic arterial pressure which facilitates a decrease in ventricular size. The decline in ventricular size decreases myocardial tension, improves oxygen consumption (Williams, Glick and Braunwald, 1965) and minimizes oxygen demands (Hardarsen and Wright, 1976; Abrams, 1977; Slutsky, et al., 1980).

Topical nitrates enhance cardiac performance during heart failure through an interplay of events on the cardiac cycle.
Peripheral vasodilators elevate the cardiac index and decrease pulmonary capillary pressure via diminished blood return to the heart and improved ventricular performance (Forrester, 1976). The reduced left ventricular end diastolic pressure and pulmonary capillary wedge pressure relieve the signs and symptoms of pulmonary congestion. This relief in symptomatology proposes NTGO's utilization to prevent episodes of proxysmal nocturnal dyspnea (Arnow, 1979b; Parmley and Chatterjee, 1980; Klausner, et al., 1976; Burgess, 1979).

Finally, based on the significant improvement in left ventricular function and reduction in myocardial oxygen consumption, NTGO therapy can be effective with patients following an acute myocardial infarction. Therapy may also be a valuable adjunct in a myocardial infarction complicated with congestive heart failure (Armstrong, et al., 1976).

In conclusion, the variables in Figure 2: partition coefficient, drug concentration, diffusibility of the drug, and barrier thickness were maintained constant for the purpose of this study. The surface area of NTGO applications was manipulated to determine its effect on the elevation of drug absorption. Following these manipulations, the relationship between the surface area of NTGO to the induced changes in pulse rate and systolic blood pressure was determined.
CHAPTER II
REVIEW OF THE LITERATURE

This chapter presents a selected review of the literature pertinent to the application of nitroglycerin ointment (NTGO) in specific clinical states. Various methods used to apply nitroglycerin ointment according to change in dosage, surface area, and site are presented.

Investigations of NTGO

Scientific investigators have focused their research on hemo-dynamic actions and clinical implications of NTGO. The therapeutic effectiveness of long acting nitrates has been evaluated in various ways: clinical studies of patients with angina pectoris (Davis and Wiesels, 1955; Mason, Zelis and Amsterdam, 1971; Reichek, et al., 1974; Parker, et al., 1976; Davidov and Mroczek, 1976; Reichek, 1976; Awan, Miller, Maxwell, et al., 1978; Salem and Singh, 1979); invasive studies of patients with congestive heart failure (Parmley, 1976; Parmley and Chatterjee, 1976; Taylor, et al., 1976; Meister, et al., 1976a; Chatterjee, Massie, Rubin, et al., 1978; Armstrong, et al., 1980); acute myocardial infarction (Williams, Ezra, Amsterdam, et al., 1975; Armstrong, et al., 1976); and investigations into changes in left

The lack of consistency in NTGO applications has been addressed by several authors (Adkinson, 1977; Hansen, et al., 1979; Zelis, et al., 1980; Hansen and Woods, 1980; Kirby and Woods, 1981). Based on previous research, Adkinson (1977) concluded that few studies have been published that describe how alterations in total dose, area of application and site of application, or the use of an occlusive dressing affect the rate and completeness of absorption, duration of action, and intensity of effect. Thus, dissimilarity exists in present application procedures of NTGO.

**Dosage of NTGO**

Reichek, et al., (1974) evaluated the effects of NTGO on the exercise capacity of 14 patients with angina pectoris with individually selected dosages. The smallest amount of NTGO was used to increase heart rate at least 10 beats per minute and/or decrease systolic blood pressure at least 10 mmHg while the patient was seated at rest for one hour post-application. A 15.2cm² area of the patient's back was utilized and covered with a plastic wrap. The patients exercised repeatedly on an upright bicycle ergometer during NTGO and placebo applications. Following NTGO applications, 10 patients were able to exercise at a higher work load, associated with an increase in resting heart rate and a decrease in systolic blood pressure while
electrocardiographic tracings documented ST segment depression. A significant increase in heart rate and a decrease in systolic blood pressure were observed at one and three hours following NTGO. These findings indicated that NTGO increased exercise capacity during the duration of the study (three hours) as compared to the placebo.

Taylor, et al., (1976) observed NTGO's hemodynamic effectiveness on 10 patients with severe chronic congestive heart failure. Applications of 1.5 to 4.0 inches (18.75 to 50 mg) were spread on the skin of the upper abdomen in a square equal to the length of dose from the tube and covered with the supplied applicator paper. Twenty minutes after the administration of NTGO, changes were measured in hemodynamic status, pulmonary capillary wedge pressure and cardiac index. On the basis of hemodynamic effectiveness and duration of action, Taylor and associates concluded that NTGO had potential value in the treatment of congestive heart failure due to ischemic heart disease.

Following clinical research of NTGO applications on 22 patients with acute myocardial infarction, Armstrong, et al., (1976) identified the need to determine an effective mode of administration considering variables affecting its efficacy, area of application, cutaneous blood flow, rate of evaporation, and dosage. Arbitrary NTGO applications were applied with doses varying from 0.5 to 1.5 inches with the average being one inch. Nitroglycerin ointment produced an early and sustained fall in myocardial oxygen requirements via reduction in preload and afterload, which together improved cardiac performance.
Significant hemodynamic changes occurred at 30 to 60 minutes with a peak at 90 minutes; data recorded demonstrated beneficial effects for 240 minutes. Contingent on these findings, the investigators postulated that NTGO therapy could provide a valuable therapeutic contribution in a myocardial infarction complicated by congestive heart failure.

Klausner, et al., (1976) investigated the response of NTGO therapy on 24 patients with chronic congestive heart failure. Seventeen patients had a 10 percent or greater increase in stroke volume after a mean dose of two inches was applied. The other seven patients did not respond to nitrate therapy even after larger doses (average 3.5 inches) were applied.

Wayne (1977b) conducted a double blind study utilizing 10 patients with both angina pectoris and previous myocardial infarction. Hemodynamic responses were evaluated following the administration of a placebo ointment, NTGO, and sublingual nitroglycerin. Three inches of two percent NTGO were applied over the skin of the lower chest. The hemodynamic action of NTGO was observed within 20 to 30 minutes, peaked at 90 minutes, and maintained significant effects for three hours. The interpretations of the data illustrated NTGO's action by improved diastolic filling, enhanced ventricle wall motion, elevated isovolumetric relaxation time, and decreased left ventricular ejection time, all factors which augment left ventricle function. The improvements in left ventricle performance and the absence of angina pain suggested that NTGO should be administered at regular intervals in patients with left ventricle dysfunction. The improvement in left ventricle
hemodynamics was significant for both sublingual and topical nitrates, but not the placebo ointment. The prolonged duration of effect following NTGO suggested its benefit for patients with angina pectoris.

In support of previous research, Davidov and Mroczek (1976) confirmed an increase in the duration of exercise in nine patients with angina pectoris during a graded exercise test after NTGO therapy. Two inches of NTGO were applied to the shoulder area. All of the subjects had a 50 percent or greater increase in exercise capacity lasting up to eight hours following the NTGO application. The results indicated that NTGO had valuable pharmacologic activity in patients with angina pectoris at one and three hours after application when compared to a placebo. Nitroglycerin ointment not only elevated subjects' exercise tolerance, but also decreased ischemic electrocardiographic changes.

The long-term effects of oral and topically administered nitrates on left ventricular function in 11 patients with previous myocardial infarction were assessed by Hardarson, et al., (1977). The amount of NTGO delivered was determined by first applying one inch (12.5 mg), and if within 30 minutes systolic blood pressure decreased 10 mmHg, the dose was satisfactory; without this effect the dose was increased by one inch until the effect was observed. The ointment was spread on a 54 cm² area of the right pectoral region, covered with the supplied wrap, and sealed with tape. The results documented improved left ventricular wall kinesis and decreased systolic blood pressure lasting four hours with both isosorbide nitrate and NTGO.
Chandraratna, et al., (1978) documented the effects of NTGO in seven patients with congestive heart failure, all previously refractory to standard treatment protocols. Applications were individually determined for each patient by increasing the dose by 0.5 inch increments until systolic blood pressure decreased 10 mmHg. The application covered a six in\(^2\) area, was protected with plastic wrap, and taped on four sides. The decrease in echocardiographic dimensions reflected a decrease in the end diastolic volume, contributing to a reduction in myocardial oxygen consumption. The pulmonary wedge pressure was also noted to decrease. The transmyocardial gradient (systemic artery diastolic pressure minus the pulmonary artery wedge pressure) indicated that coronary perfusion pressure had improved as a result of treatment. Sustained changes in cardiac performance for 4.5 to 7.0 hours indicated that NTGO was a useful agent for treatment of congestive heart failure.

Similarities between sublingual and topical nitrates were addressed by Miner and Conti (1978). Five centimeters of NTGO were applied to the skin of 22 patients with recurrent angina pectoris. The results indicated that the sublingual and topical nitrates produced similar decreases in end diastolic diameter with this patient population. The advantage of the ointment was that it produced changes which persisted for four hours. These findings confirmed the benefit of NTGO therapy for myocardial ischemia, and secondly, its potential as a prophylactic agent.

Utilizing an individually determined method in administering NTGO, Chandraratna, Chu, Schneider, et al., (1980) documented
hemodynamic alterations in 10 normal ambulatory subjects. Applications were individually selected for each subject by increasing the dose by 0.5 inch increments until systolic blood pressure decreased 10 mmHg. Based on the extended effects which lasted up to seven hours in doses varying from 0.75 to 2.5 inches, Chandraratna and associates concluded that this interval should be effective in symptomatic relief of angina pectoris.

To document disparities in present methods of administration of NTGO, Kirby and Woods (1981) investigated variations in the measurement of topical nitrates. The results indicated that there were significant differences in the method of measurement of NTGO among 48 nurses. The investigators concluded that the data suggested an unacceptable degree of inconstancy with current techniques in the measurement of doses of NTGO.

**Surface Area of Application**

Davis and Wiesels (1955), the founding fathers of NTGO, first applied the ointment to 17 patients with angina pectoris. Two percent NTGO was applied to the chest wall with a wooden applicator over an area five to eight inches in diameter. Following nitrate therapy, nine patients had a decrease in the number of anginal episodes, four patients had no decrease in angina but a general feeling of well-being, and four patients had no response. The investigators proposed that NTGO could be used as adjuvant therapy in the management of coronary insufficiency.
Meister, et al., (1976a) evaluated the effects of NTGO applications on 12 patients with congestive heart failure. Appreciable hemodynamic changes were observed within 15 minutes when one inch of two percent NTGO was applied to a six in$^2$ area of skin and covered with an occlusive dressing; changes lasted for the duration of the study (five hours). In this experiment the area of application was critical since there were no consistent hemodynamic changes when a three in$^2$ application was used. The six in$^2$ area decreased pulmonary wedge, pulmonary arterial and systemic systolic arterial pressure from 15 minutes to five hours after application. The systemic diastolic pressure decreased significantly at 30 minutes and remained depressed throughout the study. The prolonged hemodynamic changes suggest the benefit of vasodilatory therapy for ambulatory patients with congestive heart failure.

Observing vasodilatory effects of a placebo and sublingual oral, and topical nitroglycerin preparations, Shenory, Shiroff and Zelis (1976) determined onset, duration and peak activity within specific parameters. Two percent NTGO applied over a 10 cm$^2$ area of the chest induced arteriolar dilation comparable to the sublingual form, but greater than the oral nitrate.

Researchers the following year compared sublingual, oral and topical nitrate preparations on 17 patients with congestive heart failure. Franciosa, et al., (1977) applied a two-inch strip of NTGO over a two by three inch area on the abdomen and covered it with an occlusive dressing. Topical nitrates significantly improved cardiac
performance by such indices as an increased cardiac output and a decreased left ventricular filling pressure. The researchers concluded that topical nitrates could be useful for chronic congestive heart failure treatment due to its delayed onset and prolonged duration.

Following research on the effects of NTGO on seven patients with congestive heart failure, Moskowitz, et al., (1979) concluded that the drug could be given safely to improve supine hemodynamics without adversely affecting upright exercise performance. Two percent NTGO was spread over a six in² area of the abdomen and covered with plastic wrap; the mean dose was one inch. All of the patients showed an increase in cardiac performance. The simultaneous decrease in the ratio of arterio-venous oxygen difference with the cardiac index suggested an increase in circulatory reserve. The researchers concluded that NTGO could be an effective and safe agent for improving hemodynamics and symptoms in patients with congestive heart failure without impairing exercise performance.

More recently, Armstrong, et al., (1980) investigated the administration of NTGO in 14 patients with congestive heart failure. This study was more descriptive in discussing the application procedure. Utilizing convenient available sites, the anterior chest or flank area, researchers used a three in² application area and protected it with an occlusive dressing. When more than two inches of NTGO were applied, a second three in² site was employed. Patients were monitored for 240 minutes, and in select individuals, 480 minutes. The study confirmed
that NTGO provided prompt and sustained hemodynamic benefit in specific patients with congestive heart failure.

**Site of Application**

Hemodynamic alterations induced in 12 subjects with angina and eight subjects without angina following NTGO applications were observed by Parker, Augustine, Burton, et al., (1976). Three centimeters (15 mg) of two percent NTGO were applied to a 23 cm² area on the anterior chest wall and covered with plastic wrap. Following 15 minutes of nitrate therapy, the left ventricular end diastolic pressure and systemic pressure were decreased; reductions in brachial arterial mean pressure were also observed during the 60 minute experiment. Subjects reported a decline in the occurrence of chest pain; while those experiencing discomfort reported its delay in onset and decreased severity.

Following investigations into the effectiveness of NTGO, Hansen, et al., (1979) investigated variances in hemodynamic responses by applying NTGO in three separate sites: the middle forehead, inner aspect of the ankle, and left lower anterior chest. The protocol for determining dosage involved observing a 10 mmHg decrease in systolic blood pressure following nitrate delivery. Applications of 0.5 to 2.0 inches were placed on a 12 to 16 in² area on the appropriate placement site, covered with plastic wrap and taped on all four borders. The results revealed a faster, more sustained effect in hemodynamic parameters with the forehead site, followed with the chest, and lastly, the ankle region.
Lastly, Slutsky, et al., (1980) evaluated the effects of sublingual and topical nitroglycerin on left ventricular size and performance during supine bicycle exercise. Thirty-six persons were classified into various categories, two groups of normal subjects and two groups of patients with angiographically documented coronary heart disease. Two inches of NTGO were applied to the right anterior part of the chest. Both nitroglycerin preparations improved ventricular function during exercise. The ointment produced significantly prolonged effects compared to the transitory effects of the sublingual preparation. The researchers recommended topical nitrates for prophylactic therapy for patients with exertional symptoms of coronary heart disease.

In summary, this chapter has presented various methods of applying NTGO according to dosage, surface area, and site in select clinical situations: angina pectoris, congestive heart failure, and acute myocardial infarction. Evaluation of the effects of surface area of topically applied nitroglycerin ointment on decreasing systolic blood pressure and/or increasing pulse rate was the primary focus of this study.
CHAPTER III

METHODOLOGY

This chapter describes the research design, the setting, the sample, data collection instruments, and the data collection protocol.

Design of the Study

A quasiexperimental design was used to study the effect of surface area of nitroglycerin ointment (NTGO) applications on systolic blood pressure and pulse rate on healthy adult subjects. This design was chosen because of its practicality and feasibility in obtaining information for the problem being studied.

The Setting

A biological laboratory in the nursing department of a Southwestern university was the setting for this study. A private room without windows to the outside was used. Equipment in the room consisted of a reclining chair for the subject, a chair for the investigator, a sphygmomanometer, a pulse transducer which connected to the polygraph, and a television.

The Sample

The population for this study was drawn from volunteers willing to participate in the study. This convenience sample consisted of
sixteen subjects who met specific criteria. The criteria for the subjects were:

1) At least 18 years of age but less than 55 years of age.
2) Able to communicate using the English language.
3) No documented history of elevated intracranial pressure or intraocular pressure.
4) No documented history of cardiovascular disease.
5) No routine use of cardiovascular drugs.
6) No documented allergic response to nitroglycerin ointment, lanolin, or tape.
7) Willing to follow the instructions of the study.

To determine the subject's eligibility to participate in the study, potential subjects were interviewed two to three days before the experiment. Subjects who met the criteria were considered appropriate for the study. Following the initial screening session, each subject was given the following instructions: avoid strenous physical activity (defined as more exerting than walking at a normal pace) for two hours prior to the experiment; not ingest a heavy meal, an alcoholic beverage or a caffeine-containing beverage, or smoke a tobacco substance for two hours preceding the experiment; or bathe for at least two hours before reporting to the laboratory.

Protection of Human Rights

Approval from the Human Subjects Committee at the University of Arizona was obtained prior to the commencement of data collection.
Data were coded to protect each subject's privacy; analysis was done via computer using the coded data.

The purpose and nature of the study was explained to each subject and each subject was assured that withdrawal from the study would be permissible upon their request. Subjects who agreed to participate were told what their involvement would entail and that all information would remain anonymous and confidential with coded data. Prior to data collection each subject signed a witnessed consent form (Appendix B).

Treatment Groups

During the initial interview, subjects received code numbers from a table of random numbers (Zuwaylif, 1976) and were placed into two experimental groups, Treatment Group I or Treatment Group II. Data were collected on all subjects in two sessions.

1) On the first day (D₁) each subject in Treatment Group I received 1.5 inches of NTGO placed on a 20cm² area of the right pectoral region; on the second day (D₂) each subject received 1.5 inches of NTGO placed on a 5.0cm² area of the right pectoral region.

2) Each subject in Treatment Group II received 1.5 inches of NTGO placed on a 5.0cm² area of the right pectoral region on D₁; the following day, D₂, each subject received 1.5 inches of NTGO placed on a 20cm² area of the right pectoral region.

Data Collection Protocol

The following procedure was adhered to in determining physiological measurements. Data collection protocols were the same
on day one and day two. The total time of physiological recordings for each subject was seven hours. The time was divided into two, three and a half hour sessions.

1) Upon entrance to the biological laboratory each subject changed into a hospital gown and sat upright for 15 minutes. During this interval each subject signed the consent form (Appendix B) and completed the health questionnaire (Appendix C) and the Distress Rating Scale (Appendix D). The investigator then applied the blood pressure cuff above the right elbow (over the brachial artery) and mounted the pulse transducer to the tip of the right third finger. The right arm was positioned and supported on the chair’s arm rest so that the arm was at the level of the subject’s heart.

2) Baseline blood pressure by cuff sphygmomanometer and pulse rate by Grass polygraph were recorded on each subject by the investigator. Pulse rate was determined by multiplying the number of pulse rate markings in a 30 second interval by two. The recordings were coded with the subject’s identification number and labeled D1.

3) A 1.5 inch (22.5 mg) of NTGO was placed, but not rubbed, to the right pectoral region covering the appropriate surface area for the subjects in Treatment Group I and II. The application was accurately measured by following the tracings of a premeasured square stencil. A 20cm² (for the 20cm² application) or a 5.0cm² (for the 5.0cm² application) of plastic wrap was placed over the ointment and taped on all four borders.

4) Blood pressure and pulse rates were recorded every 15 minutes for the first hour. Then, these measurements were recorded
every 30 minutes for the two succeeding hours. Subjects were unable to see their blood pressure or pulse rate recordings during each session.

5) Subjects were seated upright throughout each session. Conversation was minimal due to the effect it could have on blood pressure and pulse rate. Sedentary activity such as reading, writing, or watching a non-violent television program was permitted during the procedure.

6) Following the subject's participation in the study, the plastic wrap was removed, the area wiped with an alcohol swab, and the equipment removed. Each subject then filled out the Distress Rating Scale (Appendix D), dressed, and left the laboratory.

7) On the next day, D2, the subject returned for the continuation of the study. The preceding protocol was repeated and the total surface area of application was changed according to the treatment group. The time of day (morning, afternoon or evening), application site (right pectoral region), and dosage of NTGO (1.5 inches) was kept constant. Data were coded with the subject's identification number and labeled D2.

Subjective and Physiologic Measurements

Pulse rate measurements were taken with a Graff Model D polygraph with 7 PIE preamplifiers and 7 DAF drive amplifiers. This instrument is commonly used for pulse rate determination. A biomedical engineer evaluated machine function prior to each subject's participation.
Blood pressure measurements were taken with a portable aneroid arm-cuff sphygmomanometer. To determine instrument validity the investigator checked blood pressure measurements for five trials on two individuals using the wall model and portable sphygmomanometer.

To determine investigator reliability, the investigator checked blood pressure measurements with two other nurses for five trials on five individuals. The primary investigator took all of the blood pressure and pulse rate measurements.

The Distress Rating Scale (Appendix D) was designed by the investigator. This Likert-type scale evaluated subjects' responses to potential sensations following NTGO delivery: headache, hypotension and nausea. Face validity of the scale had been assured through evaluation by five registered nurses with expertise in cardiovascular nursing.

Before each session subjects were instructed that should any unusual subjective feelings (headache or dizziness) occur during the data collection interval, they should be reported to the investigator. The time of onset, magnitude, and duration of adverse sensation was recorded on the data sheet (Appendix E). These subjective sensations were rated by the subjects on a scale from one to five; one, mild; five, severe.

Criteria for Termination of a Treatment Session

Criteria were determined for termination of a treatment session to protect the subject's right and ensure health safety. These were:
1) A treatment session could be terminated upon request by the subject.

2) If a subject's systolic blood pressure decreased by more than 30 mmHg, the session was terminated. If this effect occurred during the day one session, the subject was asked to return the next day for the D₂ treatment procedure.

3) If a subject's pulse rate approached 85 to 90 percent of one's maximal pulse rate (200 minus age), the session was terminated. If this effect occurred during the day one session, the subject was asked to return the next day for the D₂ treatment procedure.

Statistical Analysis of the Data

Statistical analysis of the data was done using descriptive and nonparametric statistics. Responses to the Distress Rating Scale and the incidence of reported subjective sensations were evaluated by the frequency of occurrence. Physiologic measurements, systolic blood pressure and pulse rate, were analyzed using a one-factor repeated measurements analysis of variance test to determine if changes occurred over time. Two-factor analyses of variance and a Hotellings t-squared test were used to determine if variation existed between the two treatments (Horowitz, 1974). The 0.05 level of significance was used as a decision criteria for these computations.
CHAPTER IV

PRESENTATION OF THE DATA

This chapter presents the results of the study. A summary of the characteristics of the sample and an analysis of subjective and physiologic measurements is presented.

Characteristics of the Sample

The sample consisted of 15 subjects who completed the requirements for data collection. One additional subject who withdrew before day two of the treatment protocol was not included in the data analysis.

Eleven of the subjects (73 percent) were female and four subjects (27 percent) were male. The 15 subjects ranged in age from 20 to 50 years with a mean age of 29.47 years. Eleven of the subjects (73 percent) were 20 to 30 years old.

Analysis of Physiologic Scores

Systolic blood pressure and pulse rate measurements were scored by computer. The Statistical Package for the Social Sciences computer programs (Hull and Nie, 1979) was used to determine if variations existed between the overall mean scores of each of the two testing days. To achieve this evaluation, a one-factor repeated measurements analysis of variance test was used to determine if changes occurred
between mean scores of the individual treatment sessions. Data were then analyzed to determine if the two treatments produced statistically significant cardiovascular change. A two-factor analysis of variance was used at each of the 10 time intervals to detect differences between treatments. To determine if there were consistent changes over time between the two treatments, the Hotellings t-squared test was used (Glass and Stanley, 1970; Horowitz, 1974).

Analysis of Pulse Rate

Pulse rate means for the 5.0cm² surface area are shown in Table 1. To determine if a change in pulse rate over time occurred, a one-factor repeated measures analysis of variance was used. The change in pulse rate measurements over time was significant at p=.0012.

Pulse rate means for the 20cm² surface area are shown in Table 2. Using a one-factor repeated measures analysis of variance, the change in pulse rate over time was significant at p=.0001.

Using a two-factor analysis of variance, no significant statistical variation was found in the mean scores of pulse rate at each time interval between the two treatment sessions. No consistent change occurred in pulse rate over time between the treatment sessions using a Hotellings t-squared test.

Analysis of Systolic Blood Pressure

Systolic blood pressure means for the 5.0cm² surface area are shown in Table 3. Using a one-factor repeated measures analysis of variance, the change in blood pressure was not significant at p=.1117.
Table 1. Pulse Rate Means For the 5.0 cm² Treatment Session

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Application</td>
<td>65.60</td>
<td>7.68</td>
</tr>
<tr>
<td>After Application</td>
<td>65.33</td>
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<td>After 30 Minutes</td>
<td>70.67</td>
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<td>After 45 Minutes</td>
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<td>9.28</td>
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<tr>
<td>After 60 Minutes</td>
<td>69.20</td>
<td>9.73</td>
</tr>
<tr>
<td>After 90 Minutes</td>
<td>69.47</td>
<td>11.35</td>
</tr>
<tr>
<td>After 120 Minutes</td>
<td>69.60</td>
<td>12.08</td>
</tr>
<tr>
<td>After 150 Minutes</td>
<td>68.93</td>
<td>11.71</td>
</tr>
<tr>
<td>After 180 Minutes</td>
<td>70.67</td>
<td>9.31</td>
</tr>
</tbody>
</table>

p = .0012
Table 2. Pulse Rate Means For the 20 cm² Treatment Session

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Application</td>
<td>69.60</td>
<td>8.85</td>
</tr>
<tr>
<td>After Application</td>
<td>69.47</td>
<td>8.73</td>
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<td>After 15 Minutes</td>
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<td>After 30 Minutes</td>
<td>80.13</td>
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<td>After 45 Minutes</td>
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<td>After 120 Minutes</td>
<td>76.27</td>
<td>13.02</td>
</tr>
<tr>
<td>After 150 Minutes</td>
<td>77.73</td>
<td>10.90</td>
</tr>
<tr>
<td>After 180 Minutes</td>
<td>76.93</td>
<td>12.19</td>
</tr>
</tbody>
</table>

p = .0001
Table 3. Systolic Blood Pressure Means For the 5.0 cm² Treatment Session

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Application</td>
<td>108.27</td>
<td>15.02</td>
</tr>
<tr>
<td>After Application</td>
<td>106.53</td>
<td>14.41</td>
</tr>
<tr>
<td>After 15 Minutes</td>
<td>103.73</td>
<td>14.56</td>
</tr>
<tr>
<td>After 30 Minutes</td>
<td>104.53</td>
<td>14.01</td>
</tr>
<tr>
<td>After 45 Minutes</td>
<td>103.73</td>
<td>11.75</td>
</tr>
<tr>
<td>After 60 Minutes</td>
<td>102.93</td>
<td>13.13</td>
</tr>
<tr>
<td>After 90 Minutes</td>
<td>102.67</td>
<td>14.61</td>
</tr>
<tr>
<td>After 120 Minutes</td>
<td>103.20</td>
<td>13.56</td>
</tr>
<tr>
<td>After 150 Minutes</td>
<td>104.13</td>
<td>14.05</td>
</tr>
<tr>
<td>After 180 Minutes</td>
<td>105.87</td>
<td>12.68</td>
</tr>
</tbody>
</table>

p = .117
Table 4 presents the systolic blood pressure mean scores for the 20cm² application. Using a one-factor repeated measures analysis of variance, the change in systolic blood pressure over time was significant at $p=0.0001$.

Using multiple two-factor analyses of variance, no significant statistical variation was found between the mean scores of systolic blood pressure at each time interval between the two treatment sessions. No consistent change occurred in systolic blood pressure over time between the two treatment sessions using a Hotellings $t$-squared test.

**Analysis of Subjective Responses**

At the termination of each treatment session subjects were asked to complete the Distress Rating Scale. Subjects' responses on the Distress Rating Scale which were rated from one (very good) to five (very bad) were evaluated for frequency of occurrence. Table 5 and Table 6 present subjects' responses after the 5.0cm² and 20cm² treatment session. Following the removal of the 5.0cm² application, six subjects rated their feeling state as either a two or three. Following the 20cm² application session, eight subjects rated their feeling state as either a two or three (Table 5). Subjects' responses did not relate to other symptomatology (headache, nausea, or lightheadedness), rather, responses were frequently associated with such experiences as hunger, fatigue, or boredom.

Eight subjects reported headaches at the conclusion of both treatment sessions. The intensity of the headache was equally distributed from mild to severe on the Distress Rating Scale (Table 5).
Table 4. Systolic Blood Pressure Means
For the 20 cm² Treatment Session

<table>
<thead>
<tr>
<th>Treatment Interval</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Application</td>
<td>108.53</td>
<td>12.68</td>
</tr>
<tr>
<td>After Application</td>
<td>108.27</td>
<td>14.71</td>
</tr>
<tr>
<td>After 15 Minutes</td>
<td>102.53</td>
<td>12.06</td>
</tr>
<tr>
<td>After 30 Minutes</td>
<td>100.27</td>
<td>12.33</td>
</tr>
<tr>
<td>After 45 Minutes</td>
<td>98.00</td>
<td>11.74</td>
</tr>
<tr>
<td>After 60 Minutes</td>
<td>97.47</td>
<td>12.18</td>
</tr>
<tr>
<td>After 90 Minutes</td>
<td>98.00</td>
<td>12.85</td>
</tr>
<tr>
<td>After 120 Minutes</td>
<td>100.00</td>
<td>10.58</td>
</tr>
<tr>
<td>After 150 Minutes</td>
<td>97.20</td>
<td>11.63</td>
</tr>
<tr>
<td>After 180 Minutes</td>
<td>100.40</td>
<td>12.63</td>
</tr>
</tbody>
</table>

p = .0001
Table 5. Frequency of Altered Feeling State and Headache After the 5.0 cm$^2$ and 20 cm$^2$ Treatment Sessions

<table>
<thead>
<tr>
<th>Treatment Session</th>
<th>Total Subjects</th>
<th>Feeling State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>very good</td>
</tr>
<tr>
<td>5.0 cm$^2$</td>
<td>6</td>
<td>3 3</td>
</tr>
<tr>
<td>20 cm$^2$</td>
<td>8</td>
<td>4 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Session</th>
<th>Total Subjects</th>
<th>Intensity of Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mild</td>
</tr>
<tr>
<td>5.0 cm$^2$</td>
<td>8</td>
<td>2 3 2 1</td>
</tr>
<tr>
<td>20 cm$^2$</td>
<td>8</td>
<td>2 3 1 2</td>
</tr>
</tbody>
</table>
Table 6. Frequency of Nausea and Lightheadedness After the 5.0 cm$^2$ and 20 cm$^2$ Treatment Session

| Treatment Session | Total Subjects | Intensity of Nausea
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mild severe</td>
</tr>
<tr>
<td>5.0 cm$^2$</td>
<td>4</td>
<td>2  2</td>
</tr>
<tr>
<td>20 cm$^2$</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

| Treatment Session | Total Subjects | Intensity of Lightheadedness
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1  2  3  4  5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mild severe</td>
</tr>
<tr>
<td>5.0 cm$^2$</td>
<td>3</td>
<td>1  2</td>
</tr>
<tr>
<td>20 cm$^2$</td>
<td>3</td>
<td>1  1  1</td>
</tr>
</tbody>
</table>
Four subjects reported a feeling of nausea on the Distress Rating Scale after the 5.0 cm$^2$ treatment session, whereas, two subjects reported its presence after the 20 cm$^2$ application. The degree of nausea was primarily within the lower limits or the mild range of the scale (Table 6).

The occurrence of lightheadedness was reported by three subjects after both treatment sessions. The degree of the sensations were uniformly distributed on the Distress Rating Scale; subjects rated the lightheadedness from one (mild) to three (Table 6).

In addition, subjects reported some adverse reactions occurring during treatment sessions. During the 5.0 cm$^2$ treatment session, eight subjects reported the onset of a headache within 15 to 150 minutes following the nitroglycerin application. The larger surface area, however, produced an earlier onset of a headache since 10 subjects reported its presence within 30 minutes after nitrate therapy.

Evaluation of subjects' sensation of nausea and lightheadedness during the experiment was essentially equal and infrequent for both treatment sessions. Only one subject experienced nausea during the 5.0 cm$^2$ treatment session, while two subjects reported lightheadedness during the 20 cm$^2$ application.
CHAPTER V
DISCUSSION OF THE FINDINGS

This chapter presents a discussion of the findings of the study in relation to the theoretical framework and the review of literature.

Findings in Relation to the Theoretical Framework

The unique barrier properties of the skin and the drug itself determine the systemic effects of nitroglycerin ointment (NTGO). In the past, the skin was thought to be impermeable to molecular entry. Differentiation in this concept now suggests that the skin functions as a rate-controlling barrier. The selective permeability of the skin provides a valuable route for certain topical drug applications, particularly, NTGO.

With the objective of enhancing the absorption of a topically applied drug, the pharmaceutical formulator can manipulate only certain aspects of the drug and the vehicle in which it is carried. An easily maneuverable variable affecting the efficiency of topical drug transport is the surface area of application of the drug. Investigators, through study and experimentation, generally agree on the interplay between the surface area and locality of the drug in determining the rate of absorption, intensity of effect and duration of action.
Research on the therapeutic effectiveness of NTGO, especially in clinical studies of patients with cardiac disease, have supported suggestions by various investigators that the ointment be applied over a substantial area of skin. Although there are several methods of measuring and applying NTGO, there is general agreement that the sustained therapeutic activity of NTGO is influenced by the continuous absorption from a sizeable deposit on the skin (Meister, et al., 1976a).

Nitroglycerin is normally known to be a generalized vasodilator, however, its selective action is more pronounced on the large venous capacitance vessels than on the arterial resistance system. The vasodilator's favorable influence is its dual reduction in preload and afterload (Dobbs and Povalski, 1977). In the arterial system, vasodilation consequently decreases the systolic blood pressure in the absence of an equivalent change in diastolic pressure (Armstrong, et al., 1976; Abrams, 1977).

To maintain cardiac output with the reduction in systemic arterial pressure, reflex action stimulates an increase in heart rate and contractility. This compensatory tachycardia results in an elevation of myocardial work and oxygen demands (Campion, et al., 1970; Parmley and Chatterjee, 1976).

This study's goal was to determine the effect of surface areas of application of NTGO on systolic blood pressure and pulse rate. By using the most effective application technique, nurses can properly apply NTGO and consequently improve patient care outcomes.
The pulse rate mean scores obtained during the 5.0cm$^2$ treatment session demonstrated a statistically significant increase in pulse rate (p=.001). The change, however, offers minimal clinical significance since the increase was less than five beats per minute. No significant statistical difference was found between the original systolic blood pressure mean scores and the scores following nitrate therapy. Therefore, the measured cardiovascular response was not clinically significant with the 5.0cm$^2$ application of NTGO.

The pulse rate mean scores measured during the 20cm$^2$ treatment session were statistically significant (p=.0001). The increase in pulse rate was more than 10 beats per minute, however, the increase was not maintained throughout the treatment session. The systolic blood pressure mean scores were also statistically significant (p=.0001). The decrease in mean scores offers limited clinical significance since the reduction in systolic blood pressure was not maintained at a minimal decrease of 10 mmHg following NTGO therapy. The larger surface area of nitrate application produced a general cardiovascular change with these subjects.

Referring to the mathematical analysis of variables affecting the release of drugs suspended in a vehicle (Figure 2) (Horhota and Fung, 1979), transdermal drug absorption was manipulated by the surface area of application. The present study did not produce a significant statistical change between the two treatment sessions. There was a trend for the larger area of application to enhance the transcutaneous
absorption of active nitrates as evidenced by significant statistical change with pulse rate and systolic blood pressure and a trend for significant clinical change in cardiovascular response.

Findings in Relation to the Review of Literature

The lack of consistency in NTGO applications has been documented by several authors (Adkinson, 1977; Hansen, et al., 1979; Zelis, et al., 1980; Kirby and Woods, 1981). There have been no specific studies published that uniquely determine the effect of the size of the surface area of application on healthy subjects. Considerable clinical experimentation with patients with cardiac disease or healthy subjects has evaluated NTGO on its physiological effects, while few studies evaluate the physical and physiological factors influencing transcutaneous absorption.

An investigation which utilized surface areas comparable to this study's was conducted by Meister, et al. (1976a). In patients with congestive heart failure, no consistent hemodynamic changes occurred when one inch of NTGO was applied to a three in \(^2\) application area. Following a six in \(^2\) application, hemodynamic benefits occurred within 15 minutes and lasted up to five hours.

The findings of this study are consistent in part with Meister's, et al., (1976a) research since no significant clinical change in cardiovascular response occurred with a small surface area of application. Meister and associates also documented hemodynamic benefits with a larger area of application, whereas, no consistent
cardiovascular response was observed with the 20cm² application in the present study. Another variation between the two investigations which may explain the discrepancy with subject response was the subject population. Meister used a patient population whereas the investigator in this study used a healthy subject population.

Previous investigations utilizing normal subjects were evaluated to determine appropriate dosage and NTGO's effect on healthy individuals. Hansen, et al., (1979) investigated variations in hemodynamic responses by applying NTGO in three separate sites: the middle forehead, inner aspect of the ankle, and left lower anterior chest. The protocol for determining dosage involved observing a 10 mmHg decrease in systolic blood pressure following nitrate delivery. Applications of 0.5 to 2.0 inches were placed on the appropriate placement site. The results revealed a faster, more sustained effect in hemodynamic parameters with the forehead site, followed with the chest, and lastly, the ankle region.

The following year, Chandraratna, et al., (1980) documented hemodynamic alterations in 10 healthy ambulatory subjects. Applications of 0.75 to 2.5 inches were applied to a six in² area. Contingent upon prolonged cardiovascular changes which lasted up to seven hours, the investigators concluded that this interval could be effective in symptomatic relief of angina pectoris.

Based on investigations by Hansen, et al., (1979) and Chandraratna, et al., (1980), the median dosage of NTGO for healthy individuals was 1.5 inches. Therefore, to alleviate the variable in
the amount of medication used, 1.5 inch of NTGO was selected for the subjects in this study.

The desired cardiovascular response from NTGO therapy, a 10 mmHg decrease in systolic blood pressure and/or a 10 beat increase in heart rate (Hardarson, et al., 1977; Chandraratna, et al., 1978; Hansen, et al., 1979; Chandraratna, et al., 1980) was not achieved during the 5.0cm² treatment session in the present study. This response was achieved with the 20cm² application, however, its magnitude was not consistently maintained throughout the treatment session. Many individual subjects did respond to nitrate therapy, however, the large variability between subjects produced no general clinical or statistical significance between treatment sessions. Therefore, the dosage of NTGO, 1.5 inch, was possibly inadequate for a majority of the subjects.

The statistical and clinical significance of the mean scores does not indicate a significant difference between the two treatment sessions. Would comparable studies of similar design substantiate the need to apply NTGO to a liberal sized, uniform layer on the skin? Would a larger subject population show a difference in cardiovascular response with the two surface areas of applications? Measuring the effects of surface area of NTGO on systolic blood pressure and pulse rate does indicate a trend toward supporting previous research that a large area of application produces a more significant cardiovascular response.
CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

This chapter presents the conclusions of the study, nursing implications, and recommendations for future research.

Conclusions

The purpose of this study was to determine the effect of surface areas of application of nitroglycerin ointment (NTGO) on systolic blood pressure and pulse rate. Discoveries which enhance transcutaneous absorption of nitroglycerin may provide practical clinical contributions.

From the data presented in the preceding chapters, the following conclusions are formed:

1) The data indicated that there was not a significant decrease in systolic blood pressure with the 5.0cm² application of NTGO. The 5.0cm² application did produce a statistically significant increase in pulse rate, however, its clinical significance was minimal. Based on these data, the hypothesis, a 1.5 inch dosage of NTGO placed on a 5.0cm² area of the right pectoral region will decrease systolic blood pressure and increase pulse rate in normal subjects, was not supported.
2) The data indicated that there was a significant decrease in systolic blood pressure and increase in pulse rate with the $20\text{cm}^2$ application of NTGO. Based on these data, the hypothesis, a 1.5 inch dosage of NTGO placed on a $20\text{cm}^2$ area of the right pectoral region will decrease systolic blood pressure and increase pulse rate in normal subjects, was accepted.

3) The data indicated that there was not a significant statistical difference in decreases in systolic blood pressure and increases in pulse rate between the $5.0\text{cm}^2$ and $20\text{cm}^2$ treatment sessions. Based on these data, the hypothesis, the $20\text{cm}^2$ application will produce a significantly greater decrease in systolic blood pressure and increase in pulse rate than will the $5.0\text{cm}^2$ application, was not supported.

4) The data indicated that there was minimal variability in subjects' subjective experience of nausea and lightheadedness between the $5.0\text{cm}^2$ and $20\text{cm}^2$ application.

5) The data indicated that the variability existing with subjects experiencing a headache was that the onset was more prompt with the $20\text{cm}^2$ application than the $5.0\text{cm}^2$ application.

**Implications**

This investigation may provide further insight into more effective application techniques to achieve the desired therapeutic effectiveness with NTGO. For patients with cardiovascular diseases such as: coronary artery disease, chronic congestive heart failure, or
myocardial infarction, failure to sustain the optimal level of preload
and afterload reduction because of improper dosage, measurement, or
application of NTGO could consequently induce serious deterioration of
the patient's condition.

One of nursing's obligations is the dispensing of drug
therapies. The uniqueness of NTGO requires special attention by
nurses to promote optimal absorption and systemic effects. A com­
prehensive understanding of the multiple factors which determine the
efficacy of NTGO therapy may influence the nurse to provide appropriate
interventions in the measurement and application of NTGO. A standardized
method of administration or a single unit-dose of NTGO has recently
become available (1982). The single unit-dose is beneficial to both
nurses responsible for administration of medications and patients with
cardiac disease.

Few research studies specifically investigate the importance of
the size of the surface area of NTGO applications. While this study had
a small sample size and limitations to generalization to patients with
cardiovascular disease, it provides an attempt to determine the effect
of surface area on drug absorption and systemic effects. The observed
response of the subjects in this study indicates a trend that healthy
subjects may have more clinical response from NTGO applied to a large
surface area than a small area. Through additional research, delineation
of appropriate guidelines for dosage, measurement, and administration of
NTGO may emerge that influence nursing care interventions.
Recommendations

Recommendations for further study include:

1) Conduct a study with a larger, homogeneous sample of subjects with specific medical cardiovascular disease symptoms.

2) Collection of data for a longer time interval following the application of the drug to determine if there is significant alteration in hemodynamic measurements.

3) Replication of design using different instruments used to measure hemodynamic status and with various methods used to apply the drug.

4) Exploration to compare scores with other variables in measurement and application techniques (e.g., site of application, size of surface area, dosage of medication, or presence of an occlusive dressing).
APPENDIX A

THE UNIVERSITY OF ARIZONA
TUCSON, ARIZONA 85724

HUMAN SUBJECTS COMMITTEE
ARIZONA HEALTH SCIENCES CENTER

TELEPHONE: 435-4711 OR 435-1275

6 November 1981

Kathy A. VanRobays, R.N.
College of Nursing
Arizona Health Sciences Center

Dear Ms. VanRobays:

We are in receipt of your project, "Comparison of Two Nitroglycerin Ointment Applications on Pulse Rate and Blood Pressure", which was submitted to the Human Subjects Committee for review. The study's procedures pose no more than minimal risk to the subject's involved. Regulations issued by the U.S. Department of Health and Human Services (45 CFR Part 46.110) authorize approval through the expedited review procedures, so that full Committee review is not required. A brief summary of the project is submitted to them for their information and comments, if any, after administrative approval has been granted. Your project is approved effective 6 November 1981.

Approval is granted with the understanding that no changes will be made in either the procedures followed or in the consent form to be used (copies of which we have on file) without the knowledge and approval of the Human Subjects Committee and the Departmental Review Committee. Any physical or psychological harm to any subject must also be reported to each committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Milan Novak, M.D., Ph.D.
Chairman

cc: Ada Sue Hinshaw, R.N., Ph.D.
Departmental Review Committee
APPENDIX B

SUBJECT CONSENT FORM

Project Title: The Effect of Surface Area of Nitroglycerin Ointment Applications on Pulse Rate and Systolic Blood Pressure

I, Kathy Van Robays, R.N., am conducting a study to facilitate the understanding of the effects of surface area of application of nitroglycerin ointment on pulse rate and blood pressure. The results of this study will be used to evaluate application procedures to maintain optimal effectiveness of nitroglycerin ointment therapy.

To be considered for the study, you must be between the ages of 18 and 55 years, must not be taking any cardiovascular medications, or have a history of cardiovascular disease. To evaluate your eligibility you will fill out a questionnaire which includes: age, sex, and pertinent health history. If you agree to participate in this study you will report to the Biological Laboratory, room 224, of The University of Arizona College of Nursing Building on two consecutive days; each session will last three and a half hours. These sessions will be at the same time each day and will be individually arranged.

For two hours before reporting to the laboratory you will be asked: to avoid strenuous activity (defined as walking faster than at a normal pace); not to ingest a heavy meal, an alcoholic beverage, or a caffeine-containing beverage; not to smoke a tobacco substance; or not to bathe. Upon arrival at the laboratory you will change into a hospital gown and be seated upright for 15 minutes. During this interval you will fill out the "Distress Rating Scale" which assesses possible sensations you may be experiencing; lightheadedness, headache, or nausea. The investigator will place a blood pressure cuff above your right elbow and a pulse transducer on your right third finger; your blood pressure and pulse will then be taken.

Nitroglycerin ointment, a drug commonly used for patients with cardiovascular disease, will be used for the study. A 1.5 inch dosage (22.5 mg) will be applied over a 20 cm² or a 5.0 cm² area of your chest, covered with plastic wrap, and taped on all four borders. Your blood pressure and pulse rate will be taken every 15 minutes for one
hour, then, every 30 minutes for the succeeding two hours. Following the third hour, the plastic wrap will be removed, the area wiped with an alcohol swab, and the equipment removed. You will fill out the "Distress Rating Scale", dress, and be permitted to leave the laboratory.

The next day you will return to the laboratory at the same time; the instructions and procedure will be the same as day one. The 1.5 inch dose of nitroglycerin ointment will be applied to the alternate surface area of the chest from day one, either a 20 cm² or 5.0 cm² area. The pulse rate and blood pressure measurements will again last for three hours, and, you will complete the "Distress Rating Scale" before and after the experiment.

You will be seated upright throughout each session. Conversation will be minimal due to the effect it may have on blood pressure and pulse rate. Sedentary activity such as: reading, writing, listening to a radio, or watching television, will be permitted during the procedure.

Individual risks are minimal; possible side effects may be a transient headache, dizziness, tachycardia (fast heart rate), or flushing. All of the side effects should resolve upon removal of the application. The primary investigator, a registered nurse, will be with you during the duration of the procedure. In the event of a medical emergency, acute, immediate medical treatment will be initiated following contact with Dr. Paul Fenster at the Health Science Center. With the occurrence of extended medical treatment, monetary compensation is not available for hospitalization or wages lost because of injury.

Your voluntary participation in this study will be of no cost to you; and you will not receive any monetary remuneration. Your personal benefit is minimal. The benefit to nursing and medical care will be valuable by facilitating the identification of the most therapeutic surface area for nitroglycerin ointment applications.

At any time you are free to withdraw from the study without changing your relationship with the institution or any persons. I will be available during each session to answer any questions that you might have pertaining to the study.

The information received will remain confidential. You will be assigned a number and the information will be coded by number for computer data analysis. Only the
primary investigator will have access to the data. At some future
time this study may be published in medical and/or nursing literature;
confidentiality of the information will be maintained during publication.

The nature, demands, risks, and benefits of this study have
been explained to me and I understand what my participation involves.
I understand that I am free to ask questions or withdraw from this
study at any time without affecting my relationship with the institu­
tion or any persons.

I understand that this consent form will be filed in an area
designated by the Human Subjects Committee with access restricted to
the principal investigator or authorized representatives of the
College of Nursing.

A copy of this consent form is available to subjects upon
request.

Subject's Signature

Date
Appendix C

HEALTH QUESTIONNAIRE

Please fill in the following blanks:

Age: __________

Sex: Male _______ Female _______

Please answer the following questions by placing a check (✓) under the appropriate column on the right.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a documented history of heart or blood vessel disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Are you taking any heart or blood vessel medications?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you have a documented history of glaucoma or increased eye pressure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you have a documented history of increased intracranial pressure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Have you ever had a skin rash to tape, lanolin or nitroglycerin ointment?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number __________

65
Appendix D

DISTRESS RATING SCALE

Please circle your response to each question which most describes your feeling state right now.

1. I am feeling: 1 2 3 4 5
   Very Good
   Very Bad

2. I presently have a headache: YES NO
   The headache is: 1 2 3 4 5
   Mild Severe

3. I am currently feeling nauseated: YES NO
   The nausea is: 1 2 3 4 5
   Mild Severe

4. I am currently feeling lightheaded: YES NO
   The lightheadedness is: 1 2 3 4 5
   Mild Severe

Number_______
Day___________
Time__________
Appendix E

DATA SHEET

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Treatment Group</th>
</tr>
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<tbody>
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Day

<table>
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<th>Time</th>
<th>Pulse Rate</th>
<th>Blood Pressure</th>
<th>Additional Comments</th>
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<tr>
<td>after application</td>
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<td></td>
</tr>
<tr>
<td>15&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60&quot;</td>
<td></td>
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</tr>
<tr>
<td>90&quot;</td>
<td></td>
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<td>120&quot;</td>
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