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THE EFFECT OF CAFFEINE ON HEART RATE, RHYTHM AND BLOOD PRESSURE

The University of Arizona M.S. 1986

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THE EFFECT OF CAFFEINE ON HEART RATE, RHYTHM AND BLOOD PRESSURE

by

JERENE MARY MAUNE

A Thesis Submitted to the Faculty of the

COLLEGE OF NURSING

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

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STATEMENT BY AUTHOR

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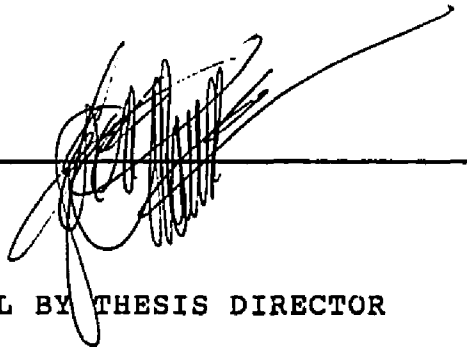
SIGNED 

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12/15/86

Date

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ABSTRACT

Ten young, healthy, non-smoking, females who were not on any regular medications and were regular caffeine consumers (at least 80 mg per day) were recruited to participate in a double-blind, cross-over study to evaluate the effect of a single 200 mg dose of caffeine on heart rate, rhythm and blood pressure. Cardiovascular parameters were monitored over 60 minutes after either placebo or the 200 mg caffeine was administered on two separate occasions. When the data were analyzed, there was a trend toward significance in heart rate in relation to time only and no significant findings in either systolic or diastolic blood pressure comparisons. No supraventricular or ventricular ectopics were noted in any of the subjects.

CHAPTER 1

INTRODUCTION

This research was a replication of a previous nursing study on the cardiovascular effects of caffeine by Newberg (1982). Literature specifying the controversies surrounding the cardiovascular response to caffeine are reviewed.

Overview of the Problem

Caffeine, a common methylxanthine popular for its central nervous system stimulation properties, is found in many beverages including sodas, coffee, and tea. The average amount of caffeine consumed per person in coffee is estimated to be 181 milligrams (mg) per day; in tea, 11 to 14 mg per day; and in soft drinks, 0 to 58 mg per day (Wells, 1984).

The physiological effects of caffeine in the body have been studied extensively. Research has revealed that caffeine affects the central nervous system,

gastrointestinal secretions, cardiovascular (C-V) function, and metabolism (Goodman, 1980; Curatolo, 1983). Because of its purported effects on the C-V system, patients with cardiac disease are frequently advised to eliminate coffee from their diets or change to decaffeinated coffee and other beverages. A decaffeinated regimen is based on studies that demonstrate ingestion of caffeinated coffee causes arrhythmias (Dobmeyer, 1984) and increased heart rate and blood pressure (Horst, 1930; Smits, 1985). However, other studies show that caffeine results in decrease in heart rate (Charney, 1984), biphasic heart rate response (Robertson, 1978; Pincomb, 1985), and no blood pressure changes (Robertson, 1981).

The controversy surrounding the cardiovascular effects of caffeine is confusing to the general public. Part of the reason for the confusion has been the lack of emphasis on reporting in the literature whether the healthy subjects were regular coffee consumers or non-users. The observation of physiologic tolerance to caffeine consumption was introduced as early as 1928 (Eddy, 1928). Tolerance is defined as the length of time someone needs to ingest caffeine before physiologic stimulant responses are attenuated. It is known that tolerance develops to the diuretic effect of caffeine (Eddy, 1928). Tolerance to central nervous

system caffeine effects was noted as early as 1968 (Colton, 1968). Uncertainty exists as to whether people develop tolerance to caffeine or become dependent on it. There is more evidence for a withdrawal syndrome from caffeine than for development of caffeine tolerance (Gilbert, 1976), and physical dependence may be more prevalent than tolerance (Goldstein, 1969). Sensitivity to methylxanthines varies widely and it is not known whether moderate users are more symptom free because they have developed a tolerance or because they are initially less sensitive than low users (Wells, 1984). Therefore, more studies are needed on the physiologic responses to caffeine in persons who consume caffeine habitually (Curatolo, 1983; Robertson, 1981).

Purpose

The purpose of this research was to investigate the effects of a single dose of caffeine on cardiovascular responses in healthy subjects who consumed caffeinated coffee regularly. The cardiovascular responses were heart rate and rhythm and blood pressure (B/P).

Significance to Nursing

Caffeine is frequently restricted in patients who experience a myocardial infarction. It is possible that these caffeine restrictions may not be necessary. Patients faced with acute injury to their hearts are engulfed in pain and fear for their well being and future lifestyle. They are pressured to make major lifestyle changes such as stopping smoking and beginning or increasing exercise. If caffeine restriction has no cardiovascular benefits, patients can continue its intake and can focus on modifying other activities necessary to improve their physical condition. Some people even report headaches as a withdrawal symptom from caffeine (Greden, 1980). Drinking a cup of coffee is a habit for many people, especially after meals or upon arising in the morning. It is familiar to people and becomes a sort of ritual. If patients must give up coffee drinking in addition to the other changes required e.g., stopping smoking, following a low sodium diet, and increasing exercise, the enormous amount of change on top of a severe injury that may have occurred to the heart can overwhelm a patient. Knowledge of what type of caffeine restriction is needed for cardiac patients is important to nurses as they work in concert with other health

professionals to teach and reinforce new habits and dietary regimens.

Newberg (1982) also cited the need to identify the effect of chronic caffeine use on cardiovascular responses to delineate the groups "at risk" to develop caffeinerelated symptoms. If an "at risk" group is identified, they can learn to modify their intake or abstain from the use of caffeine, thus eliminating or decreasing any side effects.

This study is important to the science of nursing by investigating whether caffeine tolerance exists and establishing which cardiovascular changes may or may not occur. If no increase in B/P or arrhythmogenic activity is related to caffeine intake in moderate doses, the findings will promote the idea of tolerance; however, the mechanism of such tolerance will need to be explored biochemically.

Summary

The controversies surrounding caffeine effects on the cardiovascular system are discussed. The health, age, prior caffeine use, and conditions under which subjects were studied must be known in order to generalize cardiovascular findings in response to caffeine that will be meaningful to the general public,

of which over 50 percent consume coffee. Nurses are in contact with patients who experience myocardial injury and are in a position to teach new dietary and lifestyle changes. Thus, nurses need to understand how the cardiovascular system of an individual who habitually consumes caffeinated coffee reacts when caffeine is consumed. The controversies indicate a need for further research on the physiologic effects of caffeine, especially in regular moderate users.

CHAPTER 2

THEORETICAL FRAMEWORK

As in the previous study by Newberg (1982), the possible relationship between caffeine, a metabolic stimulant, and cardiovascular changes are depicted in the theoretical framework (see Figure 1). The cardiovascular parameters discussed are heart rate, rhythm, and blood pressure. In this chapter findings on types of changes that have been observed in heart rate and rhythm and blood pressure in response to one or multiple doses of caffeine will be reviewed. The differences between habitual and acute caffeine consumption in relation to cardiovascular responses will also be emphasized.

The Effect of Metabolic Stimulants on Cardiovascular Changes

Various properties of caffeine and its metabolism in the human body in relation to the cardiovascular system will be discussed. As mentioned previously, caffeine, an alkaloid, is a methylxanthine and is

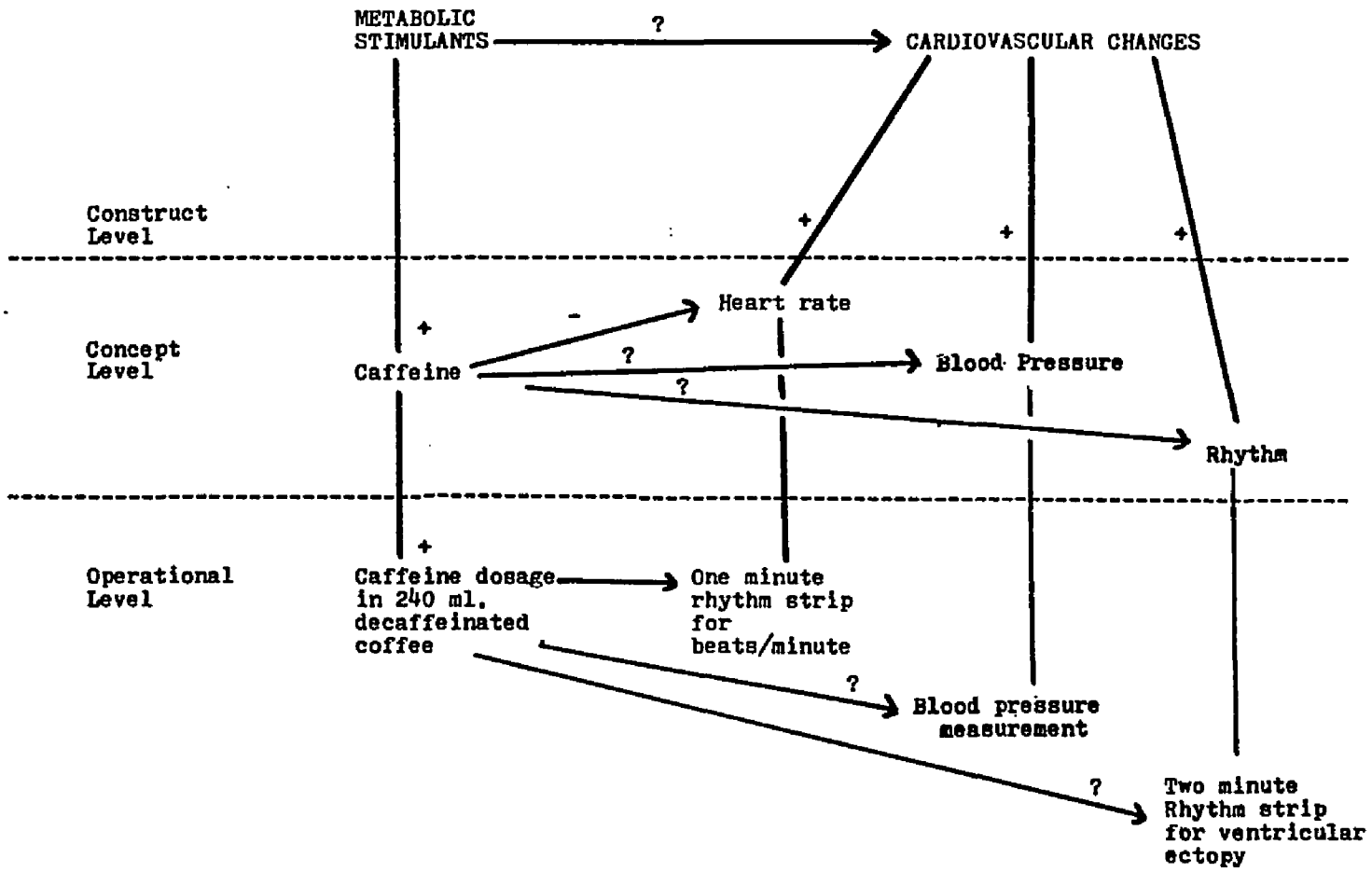

Figure 1. Model of Caffeine and Cardiovascular Responsiveness in Caffeine-Habituated Subjects (Newberg, 1982).

structurally related to uric acid. After ingestion, the methylxanthines are widely and evenly distributed in the body (Fredholm, 1980). Caffeine selectively inhibits blood flow to different vascular beds, lowering cerebral and renal blood flow. The average daily caffeine intake in the United States is 200 mg per person or 5 mg per kilogram per day (Callahan et al., 1982). Greden, et al. (1978) classified low caffeine consumption as approximately 249 mg/day, moderate consumption at 250 to 749 mg/day, and high consumption at greater than 750 mg/day. More than 99 percent of an orally administered dose of caffeine is absorbed in about 45 minutes (Bonati, 1982). There is no difference in the time to peak serum caffeine concentration between habitual caffeine users or abstainers (Colton, 1967).

Substantial inter- and intra-individual variation exists in peak caffeine plasma time and concentration after a single dose of caffeine. After oral administration, the plasma concentration has been found to peak at an average of 30 (Whitsett, 1984) to 60 minutes (Robertson, 1981), with a range of 15 to 120 minutes. Robertson (1981) measured peak plasma levels and found that after oral consumption of the same dose of caffeine, subjects peak plasma levels ranged from 3.8 to 14.8 mcg/ml. Dobmeyer (1983) gave 200 mg

caffeine both orally and intravenously as caffeine citrate. Maximum plasma caffeine concentration after oral administration was 3.2 ± 0.4 mcg/ml at 30 minutes post dose, and after intravenous administration maximum plasma caffeine concentration was 5.3 ± 7 mg/ml at 10 minutes post infusion. Impaired liver function greatly prolongs a patient's caffeine plasma half-life (Wahllander, 1968). Other common factors that can influence plasma caffeine half-life are cigarette smoking, pregnancy, and oral contraceptive pills (Kalow, 1985). There are also ethnic differences in caffeine metabolism (Kalow, 1985). Orientals have a different metabolic pathway in the liver.

After ingestion, caffeine undergoes hepatic metabolism by successive demethylation to dimethyl- and monomethylxanthines, by oxidation to methyl- and monomethylxanthines, and by oxidation to methyl- and monomethyluric acids (Levy, 1982). Less than one percent of a caffeine dose appears in the urine in its native form (Cornish, 1957). The predominant metabolic pathway of caffeine in man is through 1,7 dimethylxanthine (paraxanthine) (Bonati, 1982).

Mechanism of Caffeine Action

The effects of caffeine on the cardiovascular system cannot be stated with certainty. Several theories exist. Currently those in the forefront are (1) antagonism of adenosine receptors, (2) inhibition of phosphodiesterases, and (3) extraneuronal uptake of catecholamines. Most of caffeine's pharmacologic effects are believed to be caused through antagonism of adenosine receptors (Fredholm, 1980). Adenosine receptor antagonism, the most prevailing theory, will be discussed in greater detail. Adenosine, a vasodilator substance, is a product of ATP breakdown in the cell and is released at times of oxygen deficiency (Guyton, 1986). It is a very important vasodilator for controlling local blood flow. The adenosine mechanism may control blood flow in skeletal muscle and other tissues of the body as well as in the heart and cerebral circulation. Adenosine also slows the discharge of cardiac pacemaker cells. Adenosine exerts negative inotropic and chronotropic effects in the heart and reduces cardiac oxygen uptake (Fredholm, 1980). Adenosine production is enhanced by catecholamines. A study of adenosine receptors in rats demonstrated that caffeine blocks adenosine receptors and thus inhibits the physiological effects of circulating adenosine (Borstel, 1985). There are two

adenosine receptors: A1, a high affinity receptor, and A2, a low affinity receptor. The alkylxanthine caffeine binds to both of these receptors to block adenosine's depressant actions. The resulting central nervous system stimulation following caffeine ingestion is biochemically, behaviorally, and electrophysically consistent with adenosine receptor antagonism.

Caffeine is also suspected to have a direct effect on the heart (Meyers et al., 1980). The effect appears to be related to caffeine's inhibition of the phosphodiesterase enzyme system (Balazs, 1981). Phosphodiesterase, also known as cyclic nucleotide phosphodiesterase, is an enzyme which mediates the catabolism of cyclic adenosine monophosphate (c-AMP) (Charney, 1984). An intra-cellular hormonal mediator, c-AMP causes the hormonal effects inside the cell and is the mediator for adrenocorticotropin, thyroid-stimulating hormone, luteinizing hormone, follicle stimulating hormone, vasopressin, parathyroid hormone. glucagon, catecholamines, secretin, and the hypothalmic releasing hormones to stimulate their target organs (Guyton, 1986). Various functions are elicited in different target cells such as (1) initiating synthesis of specific intracellular chemicals, (2) causing muscle contraction or relaxation, (3) initiating secretion by the cells, (4) altering the cell permeability, etc.

Thus, the blockage of c-AMP destruction results in accumulation of c-AMP in the body with a subsequent increase in its activity in the body (Balazs, 1981). This theory can explain why caffeine affects so many cells of the body and why methylxanthines are capable of potentiating the actions of several hormones (Fredholdm, 1980). One problem with the phosphodiesterase theory is that therapeutic levels of caffeine in the human body fail to affect phosphodiesterase levels (Fredholm, 1980).

Methylxanthines may also reduce the uptake and/or metabolism of cathecholamines in non-neuronal tissues, resulting in an accumulation of catecholamines (Rall, 1980). Release of endogenous catecholamines contributes to cardiac methylxanthine effects (Fredholm, 1980). Caffeine also exerts similar direct cardiac effect as catecholamines (Balazs, 1981). Kalsner (1975: 1702) found that "the methylxanthines enhance beta-adrenergic receptor-mediated responses via a blockade of catecholamine uptake, giving rise to an increased concentration of agonist receptors." It must be noted, however, that Kalsner used an animal-model and results cannot be directly extrapolated to humans without further research. However, his results may explain the findings that serum catecholamine levels rise in response to

caffeine. Robertson (1978) reported an increased catecholamine release in response to caffeine via adrenal or sympathetic nervous system stimulation. Acute caffeine consumption raised both norepinephrine and epinephrine serum levels: epinephrine increased significantly within 15 minutes and norepinephrine was elevated 30 minutes after caffeine consumption (Robertson, 1981). Both catecholamines peaked around three hours after caffeine. After chronic ingestion of caffeine, both plasma norepinephrine and epinephrine failed to rise significantly. Plasma renin activity (PRA) was significantly increased after acute administration of caffeine, however, after three days of caffeine administration, no significant increase in PRA was noted. The reduced uptake and/or metabolism of catecholamines in non-neuronal tissue does not explain the tolerance that develops to caffeine.

Caffeine and Heart Rate and Blood Pressure

The inverse relationship between heart rate and blood pressure has been documented in studies on the effects of caffeine. Seven recent studies will be reviewed: two involve chronic caffeine consumption and five involve subjects who were withdrawn from caffeine at least 24 hours before testing.

In a double-blind randomized crossover protocol, Robertson (1978) administered 250 mg of caffeine to nine caffeine-naive subjects. Caffeine-naive is defined as subjects who have no detectable serum caffeine levels and do not consume caffeine on a regular basis. The subjects reported they did not habitually consume coffee and had abstained completely from caffeine 21 days before the study. The heart rate showed two distinct phases in response to caffeine: (1) an initial small maximal decrease in heart rate at 45 minutes that persisted approximately one hour and corresponded roughly to the period of greatest blood pressure elevation, and (2) a phase in which pulse was mildly increased over baseline that lasted the remaining two and a quarter hours the subjects were studied. The increased heart rate occurred even though B/P was still slightly raised. A statistically significant increase in blood pressure was noted at 30

minutes and was maximal (14 mm Hg systolic and 10 mm Hg diastolic) 60 minutes after caffeine.

In a single-blind crossover protocol, Charney (1984) studied nine subjects who reported to be modest caffeine users (less than 200 mg/day) and one subject who consumed approximately 400 mg of caffeine daily. The volunteers abstained from caffeine for 14 days prior to the study. After administration of 10 milligrams per kilogram (mg/kg) of caffeine, a consistent decrease in heart rate (HR) for three hours was noted (-8 beats per minute [bpm] plus or minus 3 at 60 minutes and -7 bpm $\pm$ 2 at 90 minutes). Blood pressure and heart rate were measured at 20, 40, 60, 90, 120, 180, 240, and 300 minutes. A small increase in systolic and diastolic pressure was noted: sitting, the systolic pressure was elevated 5 mm Hg $\pm$ 5 and diastolic pressure elevated 3 mm Hg $\pm$ 3; standing, the systolic pressure increased 7$\pm$4 and diastolic pressure increased 6 mm Hg $\pm$2 ($p<.05$).

Pincomb (1985) used a placebo-controlled, double-blind crossover design to administer 3.3 mg/kg of caffeine to 15 male subjects with varied caffeine consumption habits (35 to 400 mg/kg/day) who had abstained from caffeine for 30 hours. He found that over a 45-minute period after ingestion, systolic and diastolic blood pressure increased; mean systolic

increase was 5.1 mm Hg and mean diastolic increase was 8.4 mm Hg at 40 minutes. Using impedance-derived measurements, it was determined that the blood pressure increase was the result of increased systemic vascular resistance and resulted in greater stroke work. A biphasic HR response was noted. Heart rate was significantly increased ($p < .05$) at 30 minutes after caffeine, after an initial decrease at 10 and 20 minutes, and then decreased significantly again 40 minutes after caffeine ingestion. Stroke work and left ventricular ejection time were also significantly increased, while heart rate and systemic ejection acceleration decreased. No significant changes were seen in stroke volume, cardiac output, pre-ejection period, or minute work in response to caffeine.

Whitsett (1984) in an unblinded, randomized, crossover evaluation, administered a 2.2 mg/kg dose of caffeine to 54 subjects with caffeine consumption habits ranging from intolerant to caffeine to heavy coffee drinkers. The subjects experienced a 24-hour withdrawal from caffeine and an overnight fast before administration of an equivalent 2.2 mg/kg dose of caffeine as coffee and caffeine in tablet to each subject. No significant differences were found between classification categories when blood pressure and HR responses were compared. Blood pressure increased an

average of 9 to 10 mm Hg over four hours, with greatest increases noted by 90 minutes. A maximal 10 mm Hg increase in diastolic pressure correlated with a maximal decrease in HR of 15 bpm in six subjects. A maximal decrease in HR of 10 bpm was also observed over a 4-hour period. The overall cardiovascular changes in this study were essentially the same as in naive subjects, which may be the result of the 24-hour withdrawal period from caffeine before testing.

Sutherland (1985) studied HR response in two groups with varied caffeine consumption habits. Blood pressure was not monitored in this study. After a 48-hour abstinence period, two 24-hour Holter monitoring periods were conducted over a six-day time span on both groups of subjects. The first Holter was obtained after 48 hours of abstinence from caffeine and before the ingestion of 1 mg/kg of caffeine. After the ingestion of the 1 mg/kg of caffeine, the plasma half-life of caffeine was determined for each subject. Then on day five, the subjects received 1 mg/kg of caffeine at each plasma half-life of caffeine for that person over the next 24 awake hours. During that time a continuous 24-hour Holter monitor recording was taken. There were no significant differences in sinus rates between control and test periods. The mean HR for the non-ectopy group, mean age 32 years, was 77 $\pm$

10 bpm before caffeine and 73 ± 9 bpm during caffeine ingestion. The non-ectopy group averaged less than one ventricular ectopic beat per hour. The ectopy group, whose mean age was 39 years, had an average sinus rate during the caffeine-free period of 76 ± 11 bpm and 76 ± 10 bpm during the caffeine period. The ectopy group averaged 207 ± 350 ventricular ectopic beats per hour.

In a double-blind 14-day study of 18 caffeine-habituated subjects, Robertson (1981) concluded after the chronic ingestion of caffeine for seven days that little or no effect on heart rate or blood pressure was seen in response to caffeine and no subsequent fall in blood pressure was noted when caffeine was withdrawn. The subjects were randomly assigned to two groups, a placebo group and an experimental group. The placebo group received placebo the entire 14 days of the study. After a three-day washout period, the test subjects were given 250 mg of caffeine with each meal for seven days. Initially, a maximal increase in systolic pressure of 11.2 (± 2.5 mm Hg) was noted two hours after administration of the first dose of caffeine. By the fourth day of caffeine administration, blood pressure returned to baseline values and remained at baseline the remainder of the caffeine period and after caffeine was withdrawn and placebo reintroduced. Robertson (1981) measured a mean heart rate increase in

the placebo group of 6 (±4 bpm) after meals and a 7 bpm (±4 bpm) increase in the caffeine group after meals.

Robertson (1981) also collected HR and blood pressure data on 16 additional subjects who habitually consumed caffeine. After a 24-hour abstinence period, plasma caffeine levels were measured. All subjects were not completely free from caffeine. The subjects were divided according to the plasma concentration levels into two groups: those with plasma caffeine levels equal to or greater than 1 microgram per milliliter (mcg/ml) of caffeine and those with less than 1 mcg/ml of plasma caffeine. Heart rate and blood pressure measurements were taken after administration of a single 250-mg dose of caffeine. The subjects with plasma levels equal to or greater than 1 mcg/ml of plasma caffeine were found to have a lesser blood pressure response to caffeine than the subjects with a plasma level less than 1 mcg/ml. Robertson (1981) speculated that the acute pressor response was a result of increased cardiac contractility due to the direct effect of methylxanthines on myocardial contractility rather than to increased vascular resistance. Robertson observed that plasma renin activity, initially increased in response to caffeine, was attenuated at the end of the subsequent 7-day caffeine administration period. Acute consumption initially

raised both norepinephrine and epinephrine plasma levels, but after seven days of consuming 250 mg caffeine three times per day, both norepinephrine and epinephrine failed to rise significantly; in fact, norepinephrine declined.

Using a single-blind crossover protocol, Smits (1985) studied eight young (mean age 23.4 years) normotensive subjects whose average estimated coffee use ranged from 4 to 9 cups per day. To control for tobacco and oral contraceptive use, each subject's individual half-life was established. The subjects abstained from all caffeine-containing products for 4.5 half-lives (ranging from 2 to 8.5 hours) prior to testing. Each subject was required to take 200 mg caffeine at his or her particular 4.5 half-life time to assure that abstinence from caffeine was not longer than 4.5 half-lives. The subjects then submitted themselves to five tests, in a randomly determined order, each requiring the subject to consume 300 ml of regular coffee, strong coffee, decaffeinated coffee, no coffee (300 ml of hot water), and no intervention. The findings show that the caffeinated beverages (regular coffee and strong coffee) resulted in an increase in blood pressure after abstinence of 4.5 half-lives. Regular coffee increased systolic blood pressure 4 $\pm$ 1 mm Hg and diastolic blood pressure was increased 8 $\pm$ 1

mm Hg. There was also a significant difference in the blood pressure increase in response to strong coffee over regular coffee. After strong coffee the systolic blood pressure increased 5 $\pm$ 2 mm Hg and diastolic pressure increased 9 $\pm$ 1 mm Hg. The maximal increase in blood pressure was noted in the second hour of monitoring.

In summary, subjects who are withdrawn from caffeine experience blood pressure stimulant effects after acute ingestion of caffeine. In one study, chronic ingestion resulted in tolerance to the blood pressure pressor effects (Robertson, 1981). However, Smits (1985) studied the effect of chronic caffeine on blood pressure at 4.5 half-lives for each individual and observed a pressor effect from a single dose of caffeine. The use of 4.5 plasma caffeine half-lives (2 to 8.5 hours) or abstinence before measurement of cardiovascular response allows for the normal time a chronic caffeine user may allow between cups of coffee. Thus, the test simulates actual caffeine-induced cardiovascular responses in the general public. Except for one study in caffeine-habituated subjects (Robertson, 1981), blood pressure has been demonstrated to increase in response to caffeine.

In all studies, heart rate has shown an initial decrease in response to a single caffeine dose.

However, two studies demonstrated a biphasic response (Robertson, 1978; Pincomb, 1985). The effect of caffeine on heart rate appears to be an initial decrease; in some studies this has been followed by an increase in heart rate.

Caffeine and Heart Rhythm

Three studies of the effect of caffeine on heart rhythm under monitored conditions will be reviewed here. In two studies subjects were Holter monitored and in the third the subjects experienced intermittent electrocardiographic (EKG) monitoring after caffeine dosaging to assess arrhythmia production.

Newberg (1982) studied 25 women between the ages of 21 and 35 years whose regular daily caffeine consumption ranged from zero to 1883.4 mg/day. Subjects received 150 ml of electric percolator coffee (approximately 100 mg. caffeine) after a 12-hour fast. No significant increase in supraventricular ectopy or ventricular ectopy was noted following administration of caffeine.

Sutherland (1985) investigated the effect of caffeine on rate, rhythm, and ventricular repolarization. Two groups of 18 subjects each were studied. Group one, the non-ectopy group, averaged

less than one premature ventricular contraction (PVC) per hour at baseline and an estimated mean caffeine intake of 336 ± 190 mg/day. Group two was composed of subjects who had an estimated average caffeine intake of 550 ± 450 mg/day. Their average baseline PVC's were 207 ± 350 beats per hour. Both groups abstained from caffeine and caffeine products for 48 hours before testing and negative plasma caffeine levels were obtained before the study was started. Continuous Holter monitoring was done to quantitate baseline and test ectopy and rate. After quantitation of baseline arrhythmias, a single dose of 1 mg/kg of caffeine was administered and blood was drawn to determine the plasma caffeine half-life for each subject. Following a 40-hour abstinence period, subjects in both groups were thus given 1 mg/kg caffeine during waking hours at each half-life period for that individual. Continuous Holter monitoring was conducted during this caffeine administration period. The number of ventricular ectopic beats in group two increased from 207 ± 350 to 307 ± 414 PVC's per hour ($p < .01$). Group one did not experience a statistically significant increase in PVC's or supraventricular ectopy (SVE) during the test period. The results suggest that caffeine may increase quantity of ventricular ectopy in those people with pre-existing electroconduction defects.

Sutherland (1985) reports three possible limitations of his study. A possible beta error may have affected group one, resulting in the change in supraventricular beats not being significant. Second, natural temporal variability may have been operating. Arrhythmic occurrence can vary greatly from day to day.

Robertson (1981) used continuous electrocardiographic recording (Holter monitors) to monitor heart rhythm in five caffeine-habituated subjects after a 2-day washout period and another 24-hour Holter recording during a period of caffeine administration of 250 mg of caffeine three times a day with meals. No significant increase of supraventricular ectopy or ventricular ectopy was noted in this small sample.

Dobmeyer (1983) performed electrophysiologic studies on two groups of subjects: a healthy control group of subjects and a group of 12 subjects with known cardiac disease. All subjects normally drank an average of three to five cups of coffee per day and abstained from caffeine 48 hours prior to being electrophysiologically studied (EPS). Testing showed caffeine caused no changes in sinoatrial, interatrial, intra-atrial, atrioventricular-node, HIS-Purkinje conduction intervals, or sinus-node recovery times. Caffeine did significantly shorten the effective

refractory period of the high and low right atrium, the atrioventricular node, and the right ventricle. Simultaneously, caffeine increased the effective refractory period of the left atrium. There were no differences between the healthy group and the subjects with cardiac disease in regard to the above changes. Dysrhythmogenesis before and after caffeine was also studied. After programmed ventricular stimulation, two "patients" developed unsustained ventricular tachycardia. Three control subjects developed sustained atrial flutter in response to atrial extrastimuli after coffee; however, control subject No. 1 had 50 seconds of atrial flutter before caffeine and 20 minutes of atrial flutter after caffeine after atrial stimuli, and control subject No. 2 had sustained atrial flutter before and unsustained atrial flutter after caffeine on atrial stimulation. Of the "patients," one patient had pre-study atrial arrhythmias and six had sustained atrial fibrillation/flutter after caffeine. Caffeine reduced the effective refractory period of the fast atrioventricular nodal pathway by 30 milliseconds (Dobmeyer, 1983). Reasons for the cardiovascular electrophysiological changes are unknown. Dobmeyer (1983) speculates that there may be two possibilities: (1) caffeine's demonstrated ability to increase serum

concentrations of epinephrine and norepinephrine (Robertson, 1978); (2) intracellular levels of cyclic-AMP are increased directly by stimulation of adenylcyclase (Rall, 1980) or indirectly by inhibition of phosphodiesterases.

McMillan and Meyers (1985) gave 300 mg of caffeine to patients with myocardial infarction and subsequently monitored heart rhythm for four hours. He found no increase in ventricular arrhythmias in response to caffeine while the patients were monitored. The findings on the arrhythmogenic properties of caffeine indicate that in healthy young subjects (37 or younger), no increased supraventricular or ventricular activity is generated in response to caffeine.

HYPOTHESIS

1. Caffeine-habituated subjects who receive 200 mg caffeine dose will have a significantly greater decrease in HR than subjects who do not receive caffeine.

2. There is no significant difference in the number of supraventricular ectopics between healthy subjects who receive 200 mg caffeine and healthy subjects receiving decaffeinated coffee.

3. There is no significant difference in the number of ventricular ectopics between healthy subjects who receive caffeine and those receiving decaffeinated coffee.

4. There is no significant increase in BP in caffeine habituated subjects who receive 200 mg after having abstained from caffeine for 12 hours.

OPERATIONAL DEFINITIONS

The operational definitions are as follows:

Caffeine Dose: 200 mg caffeine tablet in a 240-ml cup of decaffeinated coffee.

Average Daily Caffeine Intake: Usual amount of caffeine consumed per day as estimated by the Daily Caffeine Intake Questionnaire.

Blood Pressure: Indirect measurement of the force exerted by the blood against the arterial vessel wall when heart contracts and relaxes; quantified by systolic and diastolic pressure measured with a calibrated mercury sphygmomanometer while listening with a stethoscope over the brachial artery.

Heart Rate: The number of QRS complexes in a 1-minute Lead II electrocardiogram; determined by averaging the number of QRS complexes in a 2-minute electrocardiogram (Newberg, 1982).

Heart Rhythm: The pattern of QRS complexes and their relationship to P-waves. A normal rhythm is one in which every QRS is preceded by a P-wave, every P-wave

is followed by a QRS, the P-P and R-R intervals are regular, and the P-R intervals are consistent from one beat to the next. Rhythmic alterations in the R-R and P-P intervals coinciding with respiration (sinus arrhythmia) are considered normal providing the pattern does not emerge after ingestion of the control or experimental beverage (Andreoli et al., 1979; Newberg, 1982).

Supraventricular Ectopy: Supraventricular ectopics are composed of premature QRS complexes of less than 0.10 seconds in duration. These complexes may be preceded by a premature P-wave of a different configuration than the normal P-wave and are followed by a noncompensatory pause. A premature P-wave not followed by a QRS (blocked PAC) is also considered supraventricular ectopy (Andreoli et al., 1979; Newberg, 1982.)

Ventricular Ectopy: Ventricular ectopics are composed of premature QRS complexes of 0.10 seconds or longer in duration. Ventricular ectopics are followed by fully compensatory pauses and are not preceded by premature P-waves (Andreoli et al., 1979). Any beat, or group of beats, occurring prematurely (at a shortened R-R) but not meeting all the criteria for

ventricular ectopy, will be considered supraventricular ectopy (Newberg, 1982).

SUMMARY

Three possible mechanisms for caffeine action are discussed. Arrhythmia production and blood pressure regulation are reviewed. The literature was reviewed to construct a framework for the predicted effect of a single dose of caffeine on blood pressure, heart rate, and cardiac rhythm. It was hypothesized that heart rate decreases and blood pressure remains unchanged in response to caffeine and no stimulation of ventricular or supraventricular ectopics occurs in healthy young subjects.

CHAPTER 3

METHODOLOGY

As in Newberg's study, the effect of caffeine on heart rate and rhythm was measured. The need to investigate the effect of caffeine on blood pressure was an implication for further research by Newberg (1982). Study design and setting are discussed. The sample criteria, data collection protocol, and plan for data analysis are also described.

Design

An experimental design was implemented in which subjects were recruited to participate in a double-blind crossover study. In a double-blind study the investigator and the subjects are unaware of the dispensing sequence of caffeine and placebo. The crossover design allowed each subject to take the placebo and the test medicine, caffeine, on different testing days.

Setting

The study was conducted in the Nursing Biological Studies Laboratory of a southwestern college of nursing. Subjects sat in a recliner chair in a small room away from the central area for testing to decrease external stimuli. Only the principal investigator will be present during the testing.

Sample

Ten volunteers were recruited. The criteria for inclusion were:

1. Female
2. Age 18-38
3. Able to speak and read English
4. No history of chronic or acute physical or psychiatric illness
5. No history of significant weight loss (20 pounds) within the past six months
6. Not more than 30 percent over ideal body weight
7. No habitual use of any medication
8. No known hypersensitivity to caffeine
9. Consumption of the equivalent of at least one cup of caffeinated coffee daily (approximately 80 mg caffeine).

No studies have shown a significant difference in caffeine metabolism between males and females. However, a convenience sample of women were recruited to participate. The women had to be between 18 and 38 years of age. Age has been shown to affect an individual's cardiovascular sensitivity to caffeine. Prineas (1980) found that there is a "significant" relationship between prevalence of ventricular premature beats for age and the average daily number of cups of coffee and tea consumed in a study of men between 37 and 57 years of age. It has also been demonstrated that age accentuates the cardiovascular effects of oral caffeine (Izzo, 1983).

Subjects had to be able to read and speak English to complete the Daily Caffeine Intake Questionnaire and follow verbal instructions. The subjects must not have had a history of chronic or acute physical or mental illness which would interfere with ability to perceive or report symptoms. A mental or physical illness may have required the subject to take a prescribed medication that would alter the metabolic action of caffeine.

A reduced response of the resting metabolic rate to caffeine has been observed in post-obese women of normal weight (Jung, 1981). Therefore, no one who had lost 20 pounds or more within the previous six months

was included. Caffeine is also distributed in the body in direct proportion to body weight and the elimination half-life tends to be greater in obese subjects (Abernethy, 1985a). Therefore, women who were 30 percent or more over ideal body weight were not included. The larger distribution of caffeine into the body compartments may result in lower concentrations of caffeine at the same dose, thus affecting the cardiovascular responses related to caffeine.

Tobacco users were not eligible to participate. Cigarette smokers have been found to excrete caffeine more rapidly than nonsmokers (Parsons & Neims, 1978; Abernethy, 1985). Hypertensive patients experienced a highly significant and sustained rise in blood pressure when drinking coffee and smoking simultaneously (Ramsay, 1985). Caffeine also increased puffing rate of smokers (Chait, 1983). Assuming that the changes observed in relation to caffeine are related to nicotine, subjects also had to abstain from smokeless tobacco.

Other medications can also affect the way the body responds to caffeine. For example, oral contraceptives increased the residence time of caffeine in nine young women by a factor of 2 (Rietveld, 1985), and the elimination half-life of caffeine was markedly

prolonged in oral contraceptive users as compared to controls (Abernethy, 1985).

Subjects who reported that they were sensitive to caffeine were not included. The study protocol required that volunteers report an average daily consumption of at least the equivalent of one cup of coffee a day; thus, those who limited their caffeine use because of intolerance to the drug were omitted.

This study examined the possibility of tolerance to the cardiovascular responses elicited by caffeine. Therefore, only subjects who consumed at least one cup of caffeinated coffee per day were recruited. There is evidence that moderate prior caffeine use attenuates the cardiovascular effects of oral caffeine (Izzo, 1983). It has also been found that the pressor response disappears after four days of caffeine administration (Robertson, 1981).

Protection of Human Subjects

Approval from the Human Subjects Committee was obtained before subjects were recruited (see Appendix A). The subjects read the consent explaining the purpose and procedures of the study (Appendix B). Subjects were allowed time to ask questions during orientation to the setting and before data collection.

Subjects were told they could withdraw any time without incurring any ill will.

The subjects were given code numbers and their identities were known only to the principal investigator to ensure anonymity. All data collected were labeled only with the subject's code number.

Data Collection Procedure

The subjects were asked to report to the College of Nursing Biological Studies Laboratory on three different occasions. The first visit was to familiarize the subjects with the environment and allow the subjects to ask any questions to decrease the effects of unknown external stimuli on blood pressure. After the subjects had read and signed the consent (see Appendix B), the subjects' height, weight, and date of birth were recorded and the Daily Caffeine Intake Questionnaire was completed. The subject also received a 100 mg dose of caffeine that was to be taken 12 hours before reporting to the lab for the first testing. Partial or complete tolerance to caffeine can be lost within 24 hours after the last caffeine dose (Robertson, 1981; Whitsett, 1984). To assure subjects were in the habituated state and abstinence from caffeine was no greater than 12 hours, subjects were

instructed to take a 100-mg tablet 12 hours before each test period. Preferably, the second visit was to be the day following orientation, but no more than four days after the orientation visit, visit one. All visits were to be completed within a 10-day time period; however, the time from the first to the last visit was extended from 10 to 15 days when the first three subjects had trouble returning for visit three in the 10-day time limit. In view of the fact that the subjects were a homogeneous group of health-related professionals, the time extension was not considered a problem.

Prior to the second and third visits, subjects were asked to fast eight hours, except for water, prior to reporting to the laboratory. The procedure for the second and third visits was the same except the subjects received either placebo or 200 mg caffeine in decaffeinated coffee. No difference in cardiovascular response has been found after administration of caffeine tablets or caffeinated coffee (Smits, 1985; Whitsett, 1984). This indicates that the changes observed are related to the caffeine in the coffee and not the coffee itself or other components found in coffee.

A standard drip grind decaffeinated coffee was brewed according to package directions and 240 ml was

administered to the subjects between 50 and 60 degrees Centigrade to be ingested over no more than a 5-minute period. No-Doz tablets (Registered Trademark, active ingredient: 100% caffeine) were crushed and packaged in gelatin capsules to look identical to the placebo. The caffeine/placebo administration was randomly determined and double-blinded. Another investigator coded the caffeine so that the principal investigator was not able to identify the capsules. The powdered form of both substances enhances solubility and the 240-ml volume allows for decreased concentration in the fluid and masks the taste of the caffeine. This method allows for ready absorption from the stomach and lessens individual variation of the absorption of gelatin capsules.

The caffeine content of the brand of coffee used in this study was 3-5 mg per six ounce cup (General Foods, 1986). The 240 ml. cup of coffee, therefore, contained approximately 12 mg of caffeine (using 4 mg per six ounce cup. This amount was added to the total amount of caffeine consumed by the subjects when computing the milligrams per kilogram of caffeine consumed on the caffeine administration visit. The coffee was served without cream or sugar.

All visits were conducted between 8:00 a.m. and 7:00 p.m. Two of the subjects were tested in the

morning on their first visit and returned in the afternoon after 5;00 p.m. for the second test visit.

On the second and third visits, 20 minutes was allowed for the subjects to accommodate to the setting after arrival in the laboratory. Any questions were also answered during this time period. Baseline heart rate, rhythm, and blood pressure was measured 10 minutes after arrival. Twenty minutes after arrival, the subjects consumed, over no more than a 5-minute period, 240 ml of decaffeinated coffee between 50-60 degrees centigrade with either placebo or 200 mg caffeine added. Subjects remained in the reclining position during the entire testing period and were not permitted to read magazines or books during the test period. Blood pressure and 2-minute rhythm strips were obtained at 10, 20, 30, 40, 50, and 60 minutes after consuming the beverage. At the end of the first test visit only, the subjects were given another 100-mg dose of caffeine to take 12 hours before the second testing visit.

Assumptions

Cardiovascular changes are assumed to be related to caffeine and not to other substances contained in coffee (Smits, 1985; Whitsett, 1984). Self-report

measures of caffeine consumption are also assumed to reflect habitual caffeine use (Lelo, 1986).

Study Instruments

Daily Caffeine Intake Questionnaire

The Daily Caffeine Intake Questionnaire (DCIQ) was designed by Newberg (1982) to measure the subjects' reported average daily caffeine intake (Appendix C). Content validity for the DCIQ was obtained through review of the literature (Newberg, 1982). Newberg pilot-tested the questionnaire on five subjects to establish test-retest reliability over a one-week time period. Two sources of inherent bias in Newberg's DCIQ were identified: (1) differences in caffeine content of different food and beverages are reported in the literature and (2) self-report bias. After further review of the literature on caffeine content of coffee, an error in one of the references was identified. The reference used by Newberg for the content of caffeine in coffee was Bunker and Hill (1979). However, subsequent to her research, it has been noted that the disclosure statement of Bunker and Hill's brewing technique revealed that twice as much coffee grounds were used than was instructed on the package directions

(Grossman, 1984). The caffeine content of coffee section of the table was revised using caffeine content of coffee from Lelo (1986). Coffee brewing techniques follow a trend and change over the years (Burg, 1975). Therefore, the analysis of caffeine content of substances prepared by consumers and determined by Lelo (1986) was averaged for caffeine content per ounce of coffee and used in this study to determine usual daily caffeine intake in coffee. Lelo (1986) also pointed out that the average size of brewed coffee as consumed is 240 ml. and that it is very difficult to determine the caffeine content of beverages as consumed and the amount of fluid consumed is not an indication of the amount of caffeine consumed. Lelo (1986) found that the questionnaire accurately assessed the usual caffeine intake (amount and number of drinks) of subjects measured over 24 hours. Otherwise, the table remained unchanged (see Table 1 for caffeine content of commonly used substances). The possible reporting discrepancy bias of subjects recognized by Newberg may have been less in this study because of the recruitment criteria requiring a minimum caffeine consumption. Subjects may not have felt a stigma was attached to caffeine consumption and may have reported use more accurately. As suggested by Newberg (1982), a "NONE" response column was added to the questionnaire to

Table 1. Caffeine Content of Common Beverages.

Substance	Mean Caffeine Content in Milligrams per Ounce
Coffee, One Ounce:	
Brewed Regular (Caffeinated)	10.0 mg./oz.
Instant Regular (Caffeinated)	8.6 mg./oz.
Decaffeinated, instant and brewed	0.5 mg./oz.
Tea, One Ounce:	
Tea prepared with one tea bag and five ounces hot or boiling water:	
-One minute brew*	4.2 mg./oz.
-Three minute brew	7.0 mg./oz.
-Five minute brew	8.0 mg./oz.
Tea prepared with one teaspoon loose tea leaves and five ounces hot or boiling water:	
-One minute brew	4.2 mg./oz.
-Three minute brew	5.4 mg./oz.
-Five minute brew	5.6 mg./oz.
Instant tea with lemon and/or sugar	1.6 mg./oz.
Instant Tea, unflavored	4.8 mg./oz.
Soft Drinks, One Ounce:	
Diet Rite	2.6 mg./oz.
Diet RC	2.8 mg./oz.
RC Cola	2.8 mg./oz.
Pepsi Cola	3.6 mg./oz.
Tab	4.1 mg./oz.
Diet Dr. Pepper	4.5 mg./oz.
Mountain Dew	4.6 mg./oz.
Dr. Pepper	5.0 mg./oz.
Coca Cola	5.4 mg./oz.
Diet Coke	3.8 mg./oz.
Chocolate, One Ounce:	
Milk Chocolate	1.2 mg./oz.
Hot Chocolate or Cocoa	1.7 mg./oz.

*Tea values are an average of green and black tea rounded to the nearest one-tenth ounce. Brew time refers to the length of time the tea bag or leaves remain in the hot water before consumption.

Data From: Bunker & McWilliams, 1979; Clark et al., 1982; Graham, 1978; Lelo, 1986; Coca Cola USA, 1985.

eliminate doubt as to whether there is no consumption of a certain beverage or the question was not answered by the subject.

Blood Pressure

Blood pressure is defined as the force exerted by the blood against any unit area of the vessel wall (Guyton, 1986). This pressure is created in the vessels as the heart contracts and relaxes. The flow through the vessel can be calculated by Ohm's Law (Guyton, 1986), with blood flow (Q) equal to the difference in pressure between the two ends of the vessel (P) divided by the resistance (R). Blood pressure is regulated by three mechanisms: (1) local control of blood flow, (2) nervous control, and (3) humoral control (hormones, ions, and other chemicals) (Guyton, 1986).

In local control the blood is supplied to an area of the body based on that body area's need for an increased supply of blood. The nervous system B/P response is controlled by the autonomic nervous system (ANS), which is composed of the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is the most important part of the ANS for regulation, primarily acting to increase blood pressure (Guyton, 1986). Humoral regulation of

circulation is mediated by hormones, ions, or other chemicals such as that produced and released by body organs and systems and circulated to target organs via the blood stream. Factors that can activate one of these three mechanisms to affect blood pressure acutely are exercise, fluid volume, excitement, and stress (Harlan, 1962; Brod, 1962).

Arterial blood pressure is indirectly measured with a sphygmomanometer to quantitate Korotkoff sounds. Korotkoff sounds are caused by the turbulence created by the laminar flow of blood in the arteries (Malasanos, 1981) and are noted in five stages. The first stage is the onset of the Korotkoff sounds, the systolic pressure. In stage two the sounds have a swishing or murmurlike quality; in stage three the sounds become crisper and increase in intensity and become muffled in stage four to become soft and blowing. Systolic pressure is generated by ventricular contraction determined by left ventricular stroke volume, peak rate of ejection, and distensibility of the aortic walls (Malasanos, 1981).

Selection of proper cuff size and technique for application was done according to the American Heart Association (AHA) guidelines (1980). The cuff width was to be 40 percent of the circumference of the midpoint of the limb on which it is used (AHA, 1980).

A Littman stethoscope diaphragm head was used to measure the first and last Korotkoff sounds. A mercury sphygmomanometer that was calibrated before data collection was used for B/P measurement. The face of the manometer was placed so that it was viewed at eye level. Care was taken to assure that the cuff bladder was applied directly over the artery, approximately 2-1/2 cm above the antecubital space. The subject remained in a semi-recumbent position with arm at heart level during measurement. The B/P was measured while the two-minute EKG rhythm strip was being obtained. Baseline B/P was obtained on both arms at baseline as part of the physical exam screening. If the differences in the systolic and diastolic measurements between the two arms was greater than 10 mm Hg, the subject would not continue in the study and was to be referred for investigation of the difference. The arm most convenient to the investigator was then used for the remaining measurements at 10, 20, 30, 40, 50, and 60 minutes after the test beverages were administered.

Electrocardiogram

With the subject in the semi-recumbent position, electrodes were applied to the anterior chest to record two-minute Lead II rhythm strips. The negative electrode was applied in the right shoulder area just

below the clavicle at the mid-clavicular line; the positive electrode was applied over the fifth intercostal space at mid-clavicular line; and a ground electrode was placed in the left shoulder area just below the clavicle at the mid-clavicular line. The two-minute rhythm strips was be obtained at baseline and at 10, 20, 30, 40, 50, and 60 minutes after the test beverages were administered.

The three-second EKG paper markers were used to quantify the two-minute period. The EKG machine was calibrated prior to its use. The two-minute heart rates were averaged together for heart rate determination at each increment specified.

Demographic data were collected at the time the subject presented for orientation to the setting. Age, weight, and a statement of the subject's general good health was obtained at that time and recorded on the data collection sheet (Appendix D). Blood pressure, EKG findings, and HR were also recorded on data collection sheets.

Data Analysis Plan

Demographic data were analyzed with descriptive statistics. Frequencies, means, and standard deviations were used. The following hypotheses were tested.

Hypothesis One

Analysis of covariance for repeated measures (ANCOVA) was used to assess whether a significant difference (decrease) in HR occurred when the subjects received decaffeinated coffee without caffeine added and when they received decaffeinated coffee with 200 mg of caffeine added. The values for each subject when taking caffeine and when taking decaffeinated coffee were compared at baseline, 10, 20, 30, 40, 50, and 60 minutes.

Hypotheses Two and Three

Analysis of covariance for repeated measures was also employed to determine if a significant difference in the number of supraventricular and ventricular ectopics occurred when a group received decaffeinated coffee with placebo as opposed to decaffeinated coffee with 200 mg caffeine. The results of the data obtained

during the two test periods at baseline, 10, 20, 30, 40, 50, and 60 minutes were compared.

Hypothesis Four

Analysis of covariance for repeated measures were also applied to determine if there was a significant difference in the systolic and diastolic B/P response when healthy subjects received decaffeinated coffee with a placebo as opposed to decaffeinated coffee with 200 mg caffeine. The results of the data obtained during the two test periods at baseline, 10, 20, 30, 40, 50, and 60 minutes were compared.

Summary

This methodology section describes the study design, setting, sample demographics, data collection procedure, and planned data analysis. A double-blind crossover design was employed. Heart rate, B/P, and cardiac rhythm data were also collected from ten subjects at two different sessions. Revisions in the DCIQ and caffeine table are discussed.

CHAPTER 4

RESULTS OF DATA ANALYSIS

Introduction

The results of data analysis are presented in this chapter. A description of the sample characteristics, daily caffeine intake and patterns of heart rate, rhythm and blood pressure findings are reported. The analysis of differences in heart rate and blood pressure between the placebo administration visit and the caffeine administration visit is detailed.

Description of the Sample

Ten females were randomly assigned alternately to either caffeine or placebo on two different test visits. Data were collected over a six week time period. The average age of all subjects was 30.7 ±5.59. The ages of subjects ranged from 22 to 38 years. The average weight of all subjects was 58.55 ±10.1 kg. Weights of subjects ranged from 47 to 78 kg. All subjects were within 30 percent ideal body weight

using tables from Metropolitan Life Statistical Bulletin (Anon, 1959). All subjects reported compliance to the 12-hour pre-study 100 mg. caffeine dosaging. The subjects were all either registered nurses or students in a baccalaureate nursing program. The two test visits (visits number two and three) were both at least 24-hours apart.

Daily Caffeine Intake

Caffeine intake was calculated for each subject based on the results of the Daily Caffeine Intake Questionnaire (DCIQ). The DCIQ was pilot-tested by Newberg (1982) to determine the clarity and stability of the instrument. In this study a "NONE" response column was added. In the tea and beverage categories it was specified "Beverages Not Labeled Caffeine-Free" be reported to remind subjects to report caffeine consumption and make them aware that there are many caffeine-free products currently on the market at this time that previously contained caffeine. Otherwise the DCIQ remained unchanged.

Average daily caffeine intake for subjects in the study was 226.3 $\pm$107 mg, with a range of 85 mg to 480 mg per day and 1.5 to 10.2 mg/kg/day. No subject reported consumption of electric percolator coffee or usual daily consumption of decaffeinated coffee on the

DCIQ. The heart rate, rhythm and blood pressure responses were analyzed for the entire group of subjects (n=20), and analyzed between two groups (10 subjects each) based on the usual daily amount of caffeine consumed per kilogram per day per subject as reported on the DCIQ. The subjects were divided into two groups. All subjects who received more caffeine per milligram in the study than they usually consumed on an average daily basis were labeled the "low consumption" group. This group also had the lowest consumption of caffeine in milligrams per day and in milligrams per kilogram per day.

Conversely, the subjects who usually consumed more caffeine or the same amount per day as the amount administered in milligrams per kilogram in the study were placed into the "high consumption" group. This group also had the highest consumption of caffeine in milligrams per day and in milligrams per kilogram per day. The milligrams per kilogram in the "low consumption" group ranged from 3.2 to 4.4 in the study and 1.5 to 3.3 mg/kg/day on a usual daily basis. The caffeine consumption of the subjects in the "high caffeine" consumption group ranged from 2.7 mg/kg to 4.6 mg/kg in the study and 2.6 to 10.2 mg/kg/day on a usual daily basis. The caffeine consumption of the

highest and lowest subjects was verified by phone call after their visits.

Heart Rhythm and Rate

Six subjects demonstrated sinus arrhythmias which were considered a normal respiratory variant. All test strips were compared to a single two minute baseline rhythm strip obtained on either test visit; test visit one or two. Subject #101 demonstrated a prolonged P-R interval (.22 millimeters). However she was extremely athletic and muscular, and so the conduction pattern was considered normal and not pathological in nature.

Heart rate was obtained between 10 and 20 minutes after the subject arrived in the laboratory. Heart rate was determined either by averaging together the rate of three heart beats on the rhythm strip after 30 seconds of recording in subjects with a normal sinus rhythm or by counting each heart beat for two minutes in subjects who demonstrated a sinus arrhythmia (normal respiratory variant). Heart rate measurements by both methods were spot-checked and found to be accurate. The rhythm strip and HR measurement at 60 minutes for subject #104 on the caffeine administration day is missing as it was recorded at 76 minutes. The 76

minute recording was not included in the analysis of data.

Blood Pressure

A standard-sized blood pressure cuff was used for all subjects. The bladder width on the cuff was 5 inches, and all arm circumferences were within 40 per cent of this range based on the American Heart Association (AHA) guidelines (Kirkendall, 1980). The mercury manometer was placed at eye level. Blood pressure readings were taken on both arms on test days before the test beverage was administered and the readings averaged together to get the baseline value for that day. If the first blood pressure reading obtained was questionable, the investigator repeated the BP measurement after 30 seconds. Both readings were recorded on the data collection worksheet and averaged together for that time period. Blood pressure measurement on subject 104 at 60 minutes is missing as it was recorded at 76 minutes. The 76 minute reading is not included in the analysis of data.

Hypothesis Testing

The results presented in this section do not provide information on repeated measures for the same subjects. The statistics are unable to account for the cross-over, rather the data were analyzed as if there were 20 different people presenting to the laboratory for testing. Repeated measures for the measurement of the same dependent variables over time compared to the baseline (covariate) readings are presented. The information on the heart rate and systolic and diastolic BP measurements are be presented in three different groups. The first group presented are the results of analysis of variance on all 20 subjects for treatment (caffeine verses placebo), repeated measures in time of both the placebo and the caffeine groups together, and the interaction between caffeine and placebo and time. Reports on the second and third groups, comprised of 10 subjects each, describe the same analysis as conducted in group one above, but give the results of analysis on HR and blood pressure in the "low caffeine consumption" and the "high caffeine consumption" groups. The second and third groups also include both caffeine and placebo groups. The sphericity test for symmetry of orthognal components was used to test for the assumption of equal

correlations and equal variances across measurements. Violation of this assumption uincreases the likelihood of making a Type 1 error (Monro, 1986).

Hypothesis One

The first null hypothesis tested was: there is no significant difference in HR in healthy subjects who receive decaffeinated coffee without caffeine added and subjects who receive decaffeinated coffee with 200 mg caffeine added. When the results from all 20 subjects were analyzed together (see Table 2.) the analysis of covariance for repeated measures indicated a trend toward significance (p=.07) over time. The mean values for heart rate in the caffeine treatment group showed a decrease over time from 67.77 $\pm$ 12.28 at baseline to 62.22 $\pm$9.22. The placebo group decreased also, but not as much, from 67.10 $\pm$9.76 at baseline to 64.20 $\pm$12.67 at 60 minutes. However, there was no significant difference in the caffeine verses placebo treatment analysis or the interaction between the treatment (caffeine and placebo) and time. Thus, the first hypothesis could not be rejected. The sphericity test for symmetry of orthognal components was not significant (p=.61); therefore, the data met the assumption.

Table 2. Comparison of Caffeine and Placebo Treatments on Heart Rate: ANCOVA For Repeated Measures, N=20.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	68.13	1	68.14	.81	.38
Covariate (baseline heart rate)	2179.39	1	2179.39	24.58	.00*
Within Subjects					
Time	101.04	5	20.21	2.15	.07
Time x Treatment	53.25	5	10.65	1.13	.35

(*Significant at p=.05.

Hypothesis one was then tested separately for both the "low caffeine" and the "high caffeine" consumption groups. In the "low caffeine" consumption group, there was no significant effect of treatment (caffeine vs. placebo), time or interaction between caffeine or placebo treatment and time. The mean heart rate in the caffeine group did decrease from 72.75 $\pm$10.56 at baseline to 64.75 $\pm$5.32 at 60 minutes. This is a mean decrease of 8 beats per minute. The heart rate in the placebo group decreased from 69.0 $\pm$6.44 at baseline to 65.8 $\pm$10.61 at 60 minutes. This is a mean decrease of 3.2 beats per minute. The mean heart rate measurements

in both the placebo and the caffeine groups were less after the test beverages than at baseline. Thus hypothesis one could not be rejected for the "low caffeine" consumption group (Table 3). The sphericity test for orthognal components to test for assumption is not significant at p=.87.

There was no significant effect of either treatment or the interaction between the caffeine and placebo treatments and time on HR analysis in the "high caffeine" consumption groups. There was a significant effect (p=.03) of time on HR. The mean values show that mean HR in the caffeine treatment group decreased from 63.80 ±13.16 at baseline to 60.2 ±11.71 over time at 60 minutes. The heart rates in the placebo group decreased from 65.2 ±12.79 at baseline to 62.60 ±15.57 at 60 minutes (Table 4). The sphericity test for orthognal components was not significant (p=.32). Thus the first hypothesis could not be rejected for the "high caffeine" group.

Table 3. Comparison of Caffeine and Placebo Treatments in "Low Caffeine" Group on HR: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	19.28	1	19.28	.24	.64
Covariate (baseline heart rate)	1047.75	1	1047.75	13.21	.01*
Within Subjects					
Time	47.26	5	9.45	.65	.66
Time x Treatment	69.49	5	13.90	.96	.46

*Significant at p=.05.

Table 4. Comparison of Caffeine and Placebo Treatments in "High Caffeine" Group on HR: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	13.83	1	13.83	.28	.61
Covariate (baseline heart rate)	8140.09	1	8140.09	164.09	.00*
Within Subjects					
Time	77.88	5	15.58	2.69	.03*
Time x Treatment	21.48	5	4.30	.74	.60

*Significant at p=.05.

Hypothesis Two

The second null hypothesis states that there is no difference in the number of supraventricular ectopics between healthy subjects who receive 200 mg of caffeine and healthy subjects receiving only decaffeinated coffee. In this study no supraventricular ectopics were noted at baseline or after administration of either the beverage with 200 mg caffeine or with placebo. The null hypothesis, therefore, was not tested statisticaly.

Hypothesis Three

The third null hypothesis states that there is no significant difference in the number of ventricular ectopics between healthy subjects who receive caffeine and those receiving decaffeinated coffee. None of the subjects in this study experienced ventricular ectopy at baseline or during the two test periods. Therefore, the null hypothesis was not tested statistically.

Hypothesis Four

The fourth null hypothesis states that there is no significant increase in systolic (SBP) and diastolic blood pressure (DBP) in healthy subjects who receive decaffeinated coffee with 200 mg of caffeine and

healthy subjects who received decaffeinated coffee with a placebo. When data on all 20 subjects were analyzed together for systolic and diastolic blood pressure, without regard to amount of average daily caffeine consumption, there was no significant effect of treatment (caffeine verses placebo), time or interaction between the treatment (caffeine and placebo) and time. Thus null hypothesis four could not be rejected (Table 5). The sphericity test for symmetry of orthognal components was not significant (p=.19).

Table 5. Comparison of Caffeine and Placebo Treatments on SBP: ANCOVA for Repeated Measures, N= 20.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo).	10.99	1	10.99	.04	.84
Covariate (baseline heart rate)	6109.85	1	6109.85	23.51	.00*
Within Subjects					
Time	72.60	5	14.52	.62	.68
Time x Treatment	151.97	5	30.40	1.30	.27

*Significant at p=.05.

Comparison of the diastolic blood pressure analyasis of covariance did not show any significant

differences when treatment, time and interaction of treatment (caffeine/placebo) and time were analyzed on all 20 patients (Table 6). The sphericity test for symmetry of orthognal components to test for assumption was not significant (p=.61).

Table 6. Comparison of Caffeine and Placebo Treatments in All Subjects on DBP: ANCOVA For Repeated Measures, N=20.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	257.83	1	257.83	2.91	.11
Covariate (baseline heart rate)	2179.39	1	2179.39	24.58	.00*
Within Subjects					
Time	109.52	5	21.90	1.25	.29
Time x Treatment	1494.02	5	3.01	.17	.97

*Significant at p=.05.

The fourth hypothesis was then tested separately for the "low caffeine" consumers and the "high caffeine" consumers. There were no significant findings in the "low caffeine" consumption group when SBP analysis was conducted for treatment, repeated measures of time and interaction between placebo/caffeine groups and time. Thus this hypothesis could not be rejected (Table 7). The sphericity test

was not significant at p=.70, therefore the data have met this assumption.

The SBP interaction of treatment (caffeine/placebo) over time in the "high caffeine" consumption group was significant at p=.02. The mean SBP readings showed a greater increase over time in the placebo group. Mean SBP was 97.2 ±3.77 at baseline and increased to 102.0 ±4.47 at 60 minutes; the mean SBP readings in the caffeine treatment group were 99.0 ±6.04 at baseline 99.0 ±8.25 at 60 minutes. There were no significant differences for treatment or time. The sphericity test to test for assumption is not significant (p=.12). Thus, the null hypothesis could only be rejected for the interaction.

Table 7. Comparison of Caffeine and Placebo Treatments in the "Low Caffeine" Group on SBP: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo).	.03	1	.03	.00	.99*
Covariate (baseline heart rate)	5941.39	1	5941.39	16.10	.01*
Within Subjects					
Time.....	60.43	5	12.09	.46	.80
Time x Treatment..	1.76	5	.35	.01	1.00

*Significant at p=.05.

Table 8. Comparison of Caffeine and Placebo Treatments in "High Caffeine" Group on SBP: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo).	2.81	1	2.81	.09	.77
Covariate (baseline heart rate)	179.85	1	179.85	5.82	.05*
Within Subjects					
Time	112.93	5	22.59	1.11	.37
Time x Treatment	312.33	5	62.47	3.07	.02*

*Significant at p=.05.

There was no significant effect on the DBP when treatment, time or interaction between treatment (caffeine vs. placebo) and time were analyzed in the "low caffeine" consumers. Thus, the null hypothesis could not be rejected (Table 9). The regression coefficient was .87 (p=.06). The standard deviation for the baseline DBP (covariate) in the caffeine group was over twice the standard deviation for the placebo group. The sphericity test for orthognal components was not significant (p=.21).

There was a trend toward significance (p=.08) in the treatment (caffeine vs. placebo) DBP analysis for the "high caffeine" consumption group. (See Table 10.) The DBP in the placebo group ranged from 63.4 $\pm$9.4 to 68.4$\pm$8.88 and in the caffeine administration group from 66.2 $\pm$5.36 to 72.4 $\pm$3.29. The values in both groups remained elevated over baseline throughout both test periods. The interaction of treatment (caffeine vs. placebo) and time and time alone were not significant. Thus the hypothesis could be rejected for treatment in this group.

Table 9. Comparison of Caffeine and Placebo Treatments in the "Low Caffeine" Group for DBP: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	154.37	1	154.37	.96	.37
Covariate (baseline heart rate)	827.37	1	827.37	5.13	.06
Within Subjects					
Time	158.87	5	31.77	1.99	.11
Time x Treatment.	67.76	5	13.55	.85	.53

Table 10. Comparison of Caffeine and Placebo Treatments in the "High Caffeine" Group on DBP: ANCOVA For Repeated Measures, N=10.

SOURCE	SS	df	MS	F	P
Between Subjects					
Treatment (caffeine vs. placebo)	174.77	1	174.77	4.15	.08
Covariate (baseline heart rate)	859.57	1	859.57	20.41	.00*
Within Subjects					
Time	45.75	5	9.15	.49	.78
Time x Treatment.	31.88	5	6.38	.34	.88

*Significant at p=.05.

SUMMARY

No significant changes were noted when data on all 20 subjects were analyzed together. However, there was a trend toward significance (p=.07) for HR analysis with time. Mean HR values showed a decrease in both the placebo and the caffeine groups from baseline to 60 minutes. However, a greater decrease in the caffeine treatment group was noted, starting at 20 minutes.

When subjects were controlled for average daily caffeine intake in relation to the amount administered in this study, significant changes were noted in the "high caffeine" consumption group in three different areas. Significant differences were observed (p=.03) for HR in relation to time in the "high caffeine" consumption group. Cell mean values were observed to decrease over time. Results were significant (p=.02) in the "high caffeine" consumption group for the interaction of treatment (placebo vs. caffeine) in relation to time on the SBP. The mean systolic blood pressure readings in the caffeine treatment group were relatively the same at baseline and at 60-minutes. The mean systolic blood pressure readings in the placebo group increased a mean of 4.8 mm Hg from baseline to 60 minutes. Last, a trend toward significance (p=.08) in the DBP analysis for the "high caffeine" consumption group in treatment (placebo vs. caffeine) was noted.

The sphericity test for symmetry of orthognal components was not significant in all nine analyses; thus, the data met this assumption.

CHAPTER FIVE

DISCUSSION AND INTERPRETATION OF RESULTS

Introduction

Conclusions drawn from the data analysis results are discussed in the final chapter. Implications for nursing practice are also addressed.

Heart Rate Response to Treatment

As theorized, there was a trend toward a decrease in HR when all 20 subjects were analyzed together and a significant difference in HR in interaction with time in the "high caffeine" consumption group. This finding is consistent with the literature. The significant difference noted in the high caffeine consumption group and the decrease in the mean heart rate values over time is of interest as Newberg (1982) proposed that there may be an attenuation of the heart rate response in caffeine-habituated subjects. Such was not the case in the findings of this study.

Response of Heart Rhythm to Treatment

No supraventricular or ventricular ectopy was observed in any of the subjects either at baseline or during the test periods. This heart rhythm response in healthy subjects is consistent with the previous findings reported earlier in Chapter Two and with Newberg (1982). One subject reported previously documented arrhythmias in response to caffeine. However, she did not demonstrate either supraventricular or ventricular arrhythmias during the study.

Blood Pressure Response to Treatment

Consumers of caffeine do not usually report blood pressure changes due to caffeine consumption in most instances because they have no way of perceiving a slight or moderate blood pressure change, unlike palpitations. Therefore, data on blood pressure response can only be obtained under controlled experimental conditions. When all 20 subjects were analyzed together there were no significant changes in systolic or diastolic blood pressure in response to treatment. When the subjects were grouped according to usual daily caffeine consumption, significant differences were noted in the "high caffeine", consumption group. The analysis of the interaction of

caffeine verses placebo with time was significant (p=.Ø2). The mean values demonstrated almost no change in SBP over the 6Ø-minute time period after caffeine administration, but an average increase of 4.8 mm Hg from baseline to 6Ø-minutes in the placebo group. The "high caffeine" consumption group also showed a trend toward significance (p=.Ø8) in the DBP analysis by treatment (caffeine verses placebo). The mean diastolic blood pressure values showed an increase in both the placebo and the caffeine groups. The mean diastolic blood pressure at baseline in the placebo group was 63.4Ø ±9.4Ø and was the highest at 4Ø minutes at 68.4 ±8.88, but remained elevated at 6Ø minutes at 66.2Ø ±8.84. The mean diastolic blood pressure at baseline in the caffeine group was 66.2 ±5.36 and was 72.2Ø ±4.6 at 4Ø minutes and 72.4Ø ±3.29 6Ø minutes.

Effect of Data Collection Protocol on Findings

Decaffeinated coffee was brewed using an automatic dripolator following package directions. Two subjects complained of either an upset stomach or nausea after drinking the coffee when the caffeine was added. The coffee was also reported by some subjects to have a "minty" taste when the caffeine was added to the coffee. However, subjects did not know if the taste was due to the caffeine or the placebo. Caffeine is

odorless and soluble in water (Graham, 1978). A telephone call to Bristol-Myers about No-Doz (Registered Trademark) revealed that the product contains 100 mg caffeine per tablet, flavorings peppermint and menthol, mannitol sucrose, and microcrystalline cellulose (Sterbenz, 1986). The quantity of each additive present was unknown to the investigator. Also, the effect of the additives on cardiovascular response was also unknown. It is interesting to note that the No-Doz (Registered Trademark) package is labeled only "100 mg caffeine" per tablet. The additives were not considered to influence the responses of the subjects in believing they were receiving caffeine. The investigator made an effort to disregard the comments about the minty taste during data collection after consumption of the test beverage by the subjects.

Implications for Nursing Practice

Individual sensitivity to caffeine varies greatly and it is important for nurses to tell patients to listen to their bodies and to avoid caffeine if they experience palpitations or adverse effects from its use. In the acute cardiovascular setting, nurses often care for patients with caffeine restrictions. Most patients readily switch to decaffeinated coffee, others feel they function better when they have had a cup of coffee. Increased alertness (Goldstein, 1965) and improved behavioral routine and speed (Battig, 1984) are attributed to caffeine at therapeutic levels. Caffeine is a benefit to people who depend on the side-effects.

This study did not find any significant deleterious effects on the cardiovascular system in young healthy female subjects. However, more studies are needed in patients with cardiovascular disease to determine whether caffeine needs to be restricted in patients who do not experience palpitations or irregular heart beats from its use. The findings in the study need to be kept in perspective with other areas of caffeine research, such as increase in all serum free fatty acid (FFA) and serum cholesterol levels response to caffeine (Patwardhan, 1980; Thelle,

1983). Increased cholesterol levels and increased FFA in response to caffeine may contribute to coronary artery disease. It is also possible blood pressure is reset upward slightly with prolonged caffeine use (Miner, 1985) and that blood pressure increases more during exercise after caffeine consumption than in subjects who have not had caffeine (Toner, 1985). There is still a question as to whether regular caffeine consumption contributes to heart disease and mortality (Heyden, 1978, LaCroix, 1986). LaCroix (1986) found that heavy coffee drinkers are nearly two-and-one-half times as likely as non-users to have heart disease.

Implications for Future Research

Several recommendations for future research, nursing and medical, are indicated as a result of the study and review of the literature. Recommendations from Newberg's (1982) study are also taken into account. The implications are as follows:

1. Increase sample size (Newberg, 1982).
2. Study patients with known cardiovascular disease (Newberg, 1982).
3. Robertson (1985) indicated more research is needed in the clinical pharmacology of adenosine,

inter-individual variation in response to caffeine in hypersensitive individuals, hypersensitive individuals and selective effects in specific vascular beds. Even though all of these implications are not nursing related, they are an indication of where science currently is in regard to caffeine research.

4. Repeat the study using caffeine-naive subjects.

5. Repeat the study in healthy subjects under exercise conditions.

SUMMARY

A homogeneous group of females who consumed at least the caffeine equivalent of one cup of coffee per day were sampled. The results demonstrate that the decreased heart rate effects of caffeine do persist in habitual caffeine users. When the data on all 20 subjects were analyzed together, no significant effects on blood pressure were noted. Interestingly, the "high caffeine" consumption groups demonstrated blood pressure changes. Mean SBP values in the "high caffeine" consumption group after caffeine administration did not increase, while mean SBP values in the placebo group did increase slightly. Conversely, the DBP mean values in the "high caffeine" administration group did increase after caffeine

administration and remained relatively the same after administration of a placebo. This resulted in a net decrease in pulse pressure in response to caffeine. None of the subjects experienced arrhythmias at baseline or after test beverages.

Implications for nursing research and recommendations for nursing practice were discussed. Nurses need to become aware of the controversy surrounding caffeine restrictions and monitor their cardiac patients on an individual basis. It is important for nurses to teach patients to respond to their body's reaction to the stimulant. Based on the study results, young healthy females may consume moderate amounts of caffeinated beverages without untoward cardiovascular effects.

APPENDIX A

The University of Arizona

Human Subjects Committee
1609 N. Warren (Building 220), Room 112
Tucson, Arizona 85724
(602) 626-6721 or 626-7575

25 September 1986

Jerene Maune, R.N.
College of Nursing
Arizona Health Sciences Center

Dear Ms. Maune:

We are in receipt of your project, "Effect of a Single Dose of Caffeine on Heart Rate, Rhythm, and Blood Pressure", which was submitted to this Committee for review. The procedures to be followed in this study pose no more than minimal risk to the participating subjects and the drug to be studied is FDA-approved. Regulations issued by the U.S. Department of Health and Human Services [45 CFR Part 46.110(b)] authorize approval of this type project through the expedited review procedures, with the condition(s) that substances are administered at approved doses and that subjects' anonymity be maintained. Although full Committee review is not required, a brief summary of the project procedures is submitted to the Committee for their endorsement and/or comment, if any, after administrative approval is granted. This project is approved effective 25 September 1986.

Approval is granted with the understanding that no changes or additions will be made either to the procedures followed or to the consent form(s) used (copies of which we have on file) without the knowledge and approval of the Human Subjects Committee and your College or Departmental Review Committee. Any research-related 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

Milan Novak, M.D., Ph.D.
Chairman
Human Subjects Committee

MN/jm

cc: College Review Committee

APPENDIX B

SUBJECT CONSENT FORM

THE EFFECTS OF A SINGLE CAFFEINE DOSE ON HEART RATE, RHYTHM AND BLOOD PRESSURE

To the Participant,

I, Jerene Maune, am conducting a study entitled, "The Effects of a Single Caffeine Dose on Heart Rate, Rhythm and Blood Pressure". The purpose and objective of this study is to determine the effects of a single 200 milligram (mg.) dose of caffeine on the heart rate, rhythm and blood pressure of normal subjects. Participants in the study are females, age 18-35, who have no known history of chronic or acute illness, hypersensitivity to caffeine or recent significant (twenty pounds or more) weight loss. In addition, participants are non-smokers who do not use medications on a regular basis.

If you choose to participate, you will be asked to report to the College of Nursing Biological Sciences Laboratory on three occasions. You will be oriented to the setting, weighed and a questionnaire describing your usual daily caffeine consumption will be completed on the first 20-30 minute visit. You will also receive a 100 mg. dose of caffeine at the first visit that is to be taken 12 hours before returning for visit two, which will be scheduled within four days of orientation. All three visits are to be completed within a ten day period. When you return for visits two and three you will be requested to drink 240 milliliters (ml.) of decaffeinated coffee with or without 200 mg. of caffeine. Seven two-minute electrocardiograms and blood pressures will be recorded - before consumption of the coffee, and then again at 10-20-30-40-50 and 60 minutes after consumption of the test beverage. Approximately three to three-and-one-half hours will be required to complete all three visits; 20 to 30 minutes for the first visit and one-and-one half to one hour and forty-five minutes for visits two and three.

There will be no cost or known risk incurred by you as a result of your participation. You will be asked not to eat or drink anything except water for eight hours prior to your appointment at the biological studies laboratory. A continental breakfast will be provided after the completion of the testing.

Subject Consent
Caffeine
Page Two.

Your name will be known only to the primary investigator. All information will be kept confidential and reported using only an identification number. Data may be used for future publication.

I have read the above "Subject's Consent". The nature, demands, and risks, and benefits of the project have been explained to me. I understand that I may ask questions and that I am free to withdraw from the project at any time without incurring ill will. I also 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 particular department. A copy of this consent form will be given to me.

Subject's Signature_____ Date_____,1986.

APPENDIX C

SUBJECT I.D. NUMBER:_____

DAILY CAFFEINE INTAKE QUESTIONNAIRE

This questionnaire is intended to estimate the amount of caffeine you use on a daily basis. Please state the number of ounces of each substance you consume on an average day. If you DO NOT consume a substance on an average day, check the box marked "NONE".

Coffee:	Number of ounces/day (Average serving is 5 oz.)	NONE
Automatic Dripolator		
Non-Automatic Dripolator		
Electric Percolated Coffee		
Non-Electric Percolated		
Instant Coffee		
Decaffeinated Brewed Coffee, Dripolator or Percolated		
Decaffeinated, Instant		

Instant Tea (Not Labeled "Caffeine-Free"):	# OZ/DAY (Avg. serv. 12 oz.)	NONE
Prepared according to package directions		
Flavored with lemon and/or sugar		
Unflavored		
Tea (Not Labeled "Caffeine-Free"):	**# OZ/DAY (Avg. serv. 5 oz.)**	
Tea prepared with 1 tea bag and five ounces hot or boiling water.		
1 minute brew*		
3 minute brew		
5 minute brew		

(*The brew time indicates the amount of time the tea bag or leaves are left in the hot water before drinking the tea.)

SUBJECT I.D. NUMBER:_____
Page Two.
DCIQ

Tea (Not Labeled "Caffeine-Free"):	# CZ/DAY (Avg. serv. 5 oz.)	NONE
Tea prepared with 1 teaspoon loose tea leaves and five ounces hot or boiling water.		
1 minute brew		
2 minute brew		
3 minute brew		

Soft drinks (Not labeled "Caffeine-Free"):	# OZ/DAY (Avg. Serv. 12 CZ.)	NONE
Coca Cola		
Pepsi Cola		
RC Cola		
Dr. Pepper		
Diet Dr. Pepper		
Diet RC-------		
Diet Rite		
Tab		
Mountain Dew		
Other		

Chocolate:	
Hot chocolate or Cocoa (Avg. serv. 5 oz.)	
Milk chocolate (Number of one-ounce bars/day)	

APPENDIX D

DATA COLLECTION SHEET

SUBJECT IDENTIFICATION #_____

AGE_____ WEIGHT_____

TIME	HEART RATE		BLOOD PRESSURE		ECTOPY			
					SV		VENTRICULAR	
	DAY ONE	DAY TWO	DAY ONE	DAY TWO	DAY 1	DAY2	DAY One	DAY 2
BASELINE			RT._____ LT._____	RT._____ LT._____				
1o								
20								
30								
40								
50								
60								

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