Cardiovascular Responses to Psychological Stress and Caffeine

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Abstract

While considerable information exists regarding the independent effects of caffeine and psychological stress on cardiovascular activity, there is relatively little information on their combined effects. Since caffeine may enhance cardiovascular responsivity to psychological stress, research on hemodynamic responses to caffeine-stress combinations may help elucidate mechanisms of hypertension development. In a series of studies, regular consumers of caffeine were exposed to laboratory and naturalistic stressors with and without prior caffeine intake. Among the findings were 1) caffeine and stress produced additive increases in blood pressure, 2) caffeine appears to potentiate beta-adrenergic responsivity to active coping, but not passive coping, stressors, 3) caffeine enhanced emotional responses to stress, and 4) cardiovascular responses to caffeine and stress in a naturalistic setting were similar to those observed in the laboratory. These results indicate that caffeine may enhance cardiovascular and psychological responses to stress, and that these responses may contribute to risk for essential hypertension.

Résumé

Quoiqu'il existe beaucoup d'information sur les effets indépendants de la caféine et du stress psychologique sur l'activité cardiovasculaire, il existe très peu d'information quant à leurs effets combines. Etant donne que la caféine pourrait augmenter la réponse cardiovasculaire au stress psychologique, la recherche sur les réactions hémodynamiques aux combinaisons caféine-stress pourrait aider à dévoiler les méchanismes du développement de l'hypertension. Une série d'études a été entreprise dans laquelle des sujets qui consomment de la caféine régulièrement ont été exposés à des stresseurs créés en laboratoire et en milieu naturel et ce, avec ou sans avoir consommé de caféine à priori. Les résultats des recherches ont révélé, entre autres, que: 1) la caféine et le stress produisent un effect additif qui a pour résultat de faire augmenter la pression artérielle, 2) il semble que la caféine intensifie la réaction beta-adrénergique durant l'adaptation active aux stresseurs, mais non durant l'adaptation passive, 3) la caféine augmente les réactions émotionnelles au stress, 4) les réactions cardiovasculaires à la caféine et au stress en milieu naturel sont similaires à celles observées en laboratoire. Ces résultats indiquent que la caféine pourrait augmenter les réactions cardiovasculaires et psychologiques au stress, et que ces réactions pourraient contribuer au développement de l'hypertension essentielle.

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Statement of Authorship

The following is a statement regarding the contributions of myself and Dr. Ditto to each of the three papers included in this thesis.

The three papers included in this thesis were co-authored by myself and Dr. Ditto. For each of these studies Dr. Ditto served in an advisory capacity, helping me to develop, clarify, and translate my ideas into viable research projects, as well as to guide my writing of the final reports.

Statement of Original Contributions

The research presented in this thesis provides an original contribution to knowledge in the area of caffeine effects on physiological and psychological responses to laboratory and naturalistic stressors. Previous research on the independent effects of caffeine and psychological stress indicated that each of these stimuli produce significant changes in cardiovascular activity, suggesting that repeated or chronic exposure may lead to increased risk for cardiovascular disease. Within the last few years researchers have begun to explore the combined effects of caffeine and psychological stress in determining cardiovascular activity. These investigations have been motivated in part by the possibility that caffeine and psychological stress may stimulate cardiovascular activity through similar physiological pathways, hence caffeine consumption may potentiate both level of reactivity and risk for disease. Further, because of the prevalence of both caffeine and psychological stress in day-to-day life, the potential health consequences of simultaneous exposure to caffeine and stress is a significant concern for much of the population.

While information on the independent effects of caffeine and psychological stress on cardiovascular activity has been available for many years, it is only within the last decade that researchers have begun to examine the joint

effects of these stimuli. Presently, the literature has a number of important limitations, including 1) the narrow range of stressors examined, 2) a tendency to restrict measurement of cardiovascular activity to the more common indices of blood pressure and heart rate, 3) a paucity of information on psychological responses to the combination of stress and caffeine, and 4) little information on the generalizability of laboratory findings to naturalistic settings. The present thesis comprises a series of studies which have attempted to address these limitations. By focusing on an expanded range of physiological and psychological measures, a diversity of stressors, and both laboratory and naturalistic settings, the investigations included in this thesis provide several distinct contributions to the literature. Specifically, assessment of the effects of multiple stressors using a variety of cardiovascular measures provides insight into the physiological effects of caffeine on cardiovascular responsivity to active versus passive coping stressors, as well as the potentially distinct mechanisms responsible for the observed cardiovascular responses. The results suggest that, despite consistent additive effects of stress and caffeine on blood pressure across stressors, the mechanisms of these joint elevations of blood pressure may differ depending on the stressor. Caffeine and passive coping stressors may elevate blood pressure primarily through their effects on vascular resistance which combine in an additive

fashion. In contrast, caffeine may potentiate some underlying physiological responses to active coping stressors (e.g., cardiac output), and as such may be implicated in the development of hypertension and cardiovascular disease. Further, the effects of caffeine on cardiovascular responses to stress can be observed in regular caffeine consumers tested under naturalistic circumstances, indicating that laboratory findings may generalize to the everyday lives of many caffeine consumers. Finally, evidence of caffeine-induced enhancement of negative emotional responses following psychological stress (e.g., increased anger and anxiety) provides suggestive evidence that caffeine may influence not only present physiological and emotional responsivity but also subsequent coping behavior.

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Table of Contents

Introduction

Since early in the twentieth century, a steady increase in deaths due to cardiovascular disease has led to the current status of cardiovascular disease, in all forms, as the leading cause of death in the industrialized world (Page, 1983). Hypertension, or chronically elevated blood pressure, is a major risk factor for a number of cardiovascular diseases, including coronary heart disease, cerebrovascular disease, intermittent claudication, and congestive heart failure (Kannel & Sorlie, 1975). While hypertensive status is typically presented as a discrete categorical distinction based on agreed upon cutting points of hypertensive versus normotensive levels of blood pressure, the relationship between blood pressure and risk for cardiovascular disease is a continuous function. That is, from the lowest to highest blood pressure levels, each 10 mmHg rise in blood pressure is associated with a 30% increase in risk for cardiovascular disease in both men and women (Page, 1983). This point was dramatically emphasized by Kannel and Sorlie (1975) in their statement that it is not hypertension that kills, but blood pressure.

A recent survey (Hypertension prevalence, 1985) estimated that 33% of adult males and 27% of adult females have blood pressure levels in the hypertensive range (i.e., above 140/90 mmHg). Approximately 15% of all diagnosed cases

of hypertension are secondary to known pathologies such as chronic renal disease, renovascular disease, coarctation of the aorta, primary aldosteronism, and pheochromocytoma. For the remaining 85% of all diagnosed cases, referred to as Primary or Essential Hypertension, specific etiological factors remain to be elucidated (Julius, 1977). Based on findings from diverse experimental and epidemiological investigations, a number of authors have endorsed biopsychosocial or multifactorial models of essential hypertension (Page, 1977; Shapiro, 1983). Such models assert that the development of essential hypertension is attributable to a complex interaction among many biological, psychological, and social factors. In the subsequent review, evidence relating select biological, social, and psychological factors to essential hypertension will be presented. This will be followed by a more extensive review of the literature on the possible interaction between two specific factors, psychological stress and dietary caffeine intake.

Biological Factors and Essential Hypertension:

While a number of biological factors have been proposed to account for the pathogenic process of hypertension, perhaps none has received as much attention as dietary sodium intake. Epidemiological studies of various cultural groups have revealed that dietary sodium intake is significantly related to blood pressure level, with extremes

of very high and very low sodium intake related to high and low blood pressure levels respectively (Page, 1980; Page, Damon, & Moellering, 1974). Experimental treatment regimes involving dietary sodium restriction have revealed a positive relationship between sodium intake and blood pressure level. Systolic and diastolic blood pressure reductions on the order of 5 to 10 mmHg have been observed following significant sodium-intake restriction, and persist at two-year follow-up (Morgan et al., 1978; Parijs, Joossens, Van der Linden, Verstreken, & Amery, 1973). Conversely, healthy subjects placed on a high sodium diet have experienced significant increases in blood pressure (Luft, Bloch, Weyman, Murray, & Weinberger, 1978). While these findings are consistent with a relationship between dietary sodium intake and blood pressure levels, they tend to mask individual differences in dietary sodium sensitivity. Both human and animal studies support the notion of an interaction between sodium intake and genetic risk for hypertension, such that genetic differences in salt-sensitivity moderate risk for high blood pressure levels under conditions of high sodium intake (Kawasaki, Delea, Bartter, & Smith, 1978; Louis, Tabei, & Spector, 1971).

Whatever the mechanism of transmission, there are a number of lines of evidence which suggest that hereditary factors play a significant role in determining blood

pressure levels. First, the correlations for resting blood pressure levels are approximately twice as high for monozygotic twins as compared to dizygotic twins (Feinleib, 1979). As well, studies of families with natural and adopted children have revealed significant correlations in blood pressure between parents and their biological offspring, but not with their adopted children (Biron, Mongeau, & Bertrand, 1976). Finally, a positive family history of hypertension is a significant predictor for the development of hypertension (Feinleib, 1979). While these data support the notion of a genetic component in hypertension, it has been hypothesized that genetic factors serve mainly to predispose individuals to hypertension development given specific environmental circumstances (Page, 1983). This point is illustrated above by the literature on genetic differences in sodium sensitivity and will be reiterated below in relation to genetic differences in cardiovascular responsivity to psychological stress.

Social Factors and Essential Hypertension:

Social factors which have been shown to be significant in predicting blood pressure levels include sociocultural change, socioeconomic status, and social crowding. In order to assess the effect of Westernized acculturation on blood pressure levels in members of pre-industrialized societies, Cassel (1975) compared Polynesian, Melanesian, and Zulu groups who were living with or without significant outside

cultural contact. It was concluded that exposure to cultural change was associated with increases in blood pressure across these diverse groups. A more in-depth analysis of this process is provided by a study of the migration of residents of Tokelau Island. Following a devastating typhoon, Tokelauans were resettled in New Zealand and as a result were exposed to significant cultural changes. Significant increases in blood pressure were observed in migrants versus non-migrants as well as in those migrants who interacted more with New Zealand white society (Beaglehole, Salmond, Hooper, & Prior, 1977). Even though the social interaction effects remained significant after controlling for body weight, age, and duration of stay, differences in social interaction accounted for only 2.1% of the variance in blood pressure levels in males and 1.4% in females. Factors related to dietary changes, including changes in body mass, salt intake, and carbohydrate intake accounted for a significantly larger portion of the variance in blood pressure levels (Prior, Stanhope, Evans, & Salmond, 1974). A comparison of males of Japanese descent living in Japan, Hawaii, and California confirmed the importance of dietary influences on blood pressure levels (Marmot, Kagan, & Koto, 1980). While Japanese men living in the U.S. were heavier, had higher serum cholesterol levels, and significantly higher blood pressure, there was no relationship between blood pressure levels and cultural

traditionalism (Marmot et al., 1980).

Variables such as low socioeconomic status and social instability (e.g., marital instability; living in a high density, high crime area) have also been related to higher blood pressure levels (Harburg et al., 1973). Harburg and colleagues compared blood pressure levels of Detroit residents living in high- versus low-stress areas as defined by socioeconomic status and social instability levels in a given area. After adjusting for age and weight, it was observed that residents in the high-stress areas had a significantly higher likelihood of being hypertensive. Similar naturalistic analyses of the role of social density on blood pressure levels have been carried out using prison inmates housed under varying degrees of cell crowding. D'Atri (1975) observed that prisoners housed in dormitories had significantly higher blood pressure levels than prisoners housed in single cells. Similarly, comparisons of blood pressure levels of prisoners housed in two, three, or six person cells revealed that inmates had significantly higher systolic blood pressure levels under the more crowded conditions (Paulus, McCain, & Cox, 1978). Similar results have been obtained in animal analog studies, with social crowding leading to elevated risk for hypertension (Henry & Stephens, 1977). It is clear from this brief review of social influences on blood pressure status that it is difficult, if not impossible, to disentangle the

contribution of social and psychological factors in the development of hypertension. In many respects cultural adaptation, economic poverty, and social crowding represent environmental challenges which can be construed as psychosocial stressors. As such, these psychosocial stressors lend support to the notion that psychological factors may influence the process of hypertension development.

Psychological Factors and Essential Hypertension:

In an attempt to understand the role of psychological factors in the development of hypertension, researchers have focused on psychological characteristics of both the individual and the environment as potential mediators of risk for cardiovascular disease. Hypertension has long been associated with emotional difficulties, especially subdued anger and hostility (Alexander, 1939). Problems with anger expression have been related to an increased risk for hypertension (Diamond, 1982; Harburg et al., 1973) and increases in blood pressure reactivity (Johnson, Schork, & Spielberger, 1987; Johnson, Spielberger, Worden, & Jacobs, 1987). Similarly, the Type A behavior pattern, which encompasses a number of characteristic responses to environmental challenge, including a sense of time urgency, competitive achievement striving, and hostility, has been associated with risk for heightened sympatnetic responsivity to stress and coronary heart disease (Glass, 1977; Rosenman

et al., 1975). Consistent with earlier personality theories, recent evidence suggests that the anger-in and hostility components of the Type A behavior pattern may be the critical aspects in predicting both cardiovascular responsivity and risk for coronary heart disease (Dembroski, MacDougall, Williams, Haney, & Blumenthal, 1985; Glass et al., 1980; Matthews, Glass, Rosenman, & Bortner, 1977).

The role of environmental stressors as potential contributors to cardiovascular disease has received extensive consideration. Early investigations of dramatic real-life stressors revealed that exposure to such extreme situations as desert warfare (Graham, 1945) and chemical explosion (Ruskin, Beard, & Schaffer, 1948) was capable of producing transient increases in blood pressure lasting several days. Subsequent investigations of more common stressful experiences, such as chronic exposure to stressful occupational environments, revealed a significant relationship between psychological stressors, blood pressure elevations, and risk for cardiovascular disease. Cobb and Rose (1973) observed a significantly higher incidence of hypertension among air traffic controllers as compared to a control group of second-class airmen. Moreover, within the air traffic controller group the highest rates of hypertension were observed among controllers who worked at the busiest airports. Prolonged exposure to high occupational noise levels has also been related to both

acute blood pressure elevations (Andren, Hansson, Bjorkman, & Jonsson, 1980) and a higher prevalence of hypertension (Parvizpoor, 1976). Finally, high levels of job strain, due to such factors as high work demands combined with low opportunity to control the job situation, predict cardiovascular disease and mortality levels (Karasek, Theorell, Schwartz, Pieper, & Alfredsson, 1982). These and similar findings have stimulated and supported the stress-reactivity model of hypertension.

The stress-reactivity model of hypertension asserts that exaggerated cardiovascular responsivity to stressful environmental stimuli may predict the development of essential hypertension. Evidence for this position has been obtained from longitudinal investigations wherein the development of hypertension has been predicted by exaggerated blood pressure responses to such stressors as the cold-pressor test (Menkes et al., 1989; Wood, Sheps, Elveback, & Schirger, 1984), physical exercise (Dlin, Hanne, Silverberg, & Bar-Or, 1983; Jackson, Squires, Grimes, & Beard, 1983; Wilson & Mayer, 1981), and a psychological stressor (Falkner, Kushner, Onesti, & Angelakos, 1981). While there have also been a number of failed attempts to predict blood pressure elevations using the cold pressor test (Armstrong & Rafferty, 1950; Eich & Jacobsen, 1967; Harlan, Osborn, & Graybiel, 1964), these studies have been criticized on the grounds of insufficient follow-up (Manuck

& Krantz, 1986). In addition, as will be illustrated below, stressors such as the cold pressor test may not serve as the best predictors of stress-related hypertension.

Obrist (1981) hypothesized that repeated exposure to acute psychological stressors may promote a gradual shift from transient increases in blood pressure, mediated by neurogenic mechanisms, to a more established hypertension, wherein high blood pressure levels are maintained primarily through elevated peripheral resistance. Obrist and colleagues observed that stressors which allow effortful control over the environment, known as active coping, tend to elicit greater increases in beta-adrenergic sympathetic activity (Langer et al., 1985; Sherwood, Allen, Obrist, & Langer, 1986). In contrast, stressors which require passive coping due to minimal environmental control (e.g., cold pressor, aversive film) tend to elicit primarily alpha-adrenergic sympathetic nervous system activity (Buhler, Bulli, Hulthen, Amann, & Kiowski, 1983; Obrist et al., 1978; Obrist, Light, McCubbin, Hutcheson, & Hoffer, 1979). More importantly, active coping stressors tend to elicit metabolically-exaggerated cardiac adjustments (Sherwood et al., 1986; Turner & Carroll, 1985), meaning that they elicit increases in the flow of oxygenated blood to body tissues in excess of metabolic demands. Obrist (1981) hypothesized that such metabolically-inappropriate increases in cardiac activity could elicit physiological adjustments resulting in

sustained elevations in blood pressure.

Physiological mechanisms which have been proposed to account for a transition from repeated, exaggerated cardiac activity to sustained elevations in vascular resistance, and hence blood pressure, include autoregulation theory (Guyton & Coleman, 1969) and structural adaptation (Folkow, Grimby, & Thulesius, 1958; Folkow, Hallback, Lundgren, Sivertsson, & Weiss, 1973). Autoregulation theory refers to a process whereby local tissues act intrinsically to promote vascular dilation or constriction in order to regulate blood flow. Since local autoregulatory responses in most tissues appear to be closely related to cellular delivery and utilization of oxygen (Carrier, Walker, & Guyton, 1964), tissue overperfusion following active coping stressors would be expected to elicit a vasoconstrictive response and subsequent increases in blood pressure. It is as yet unclear how, or if, repeated autoregulatory responses would lead to the more permanent vasoconstrictive responses which would promote a sustained elevation in blood pressure. A second mechanism which has been proposed to account for a transition from elevated cardiac output to elevated peripheral resistance is structural adaptation (Folkow et al., 1958; 1973). This theory proposes that repeated and prolonged increases in cardiac output and blood pressure produce a hypertrophic response in the vascular smooth muscles of the arterioles, leading to a narrowing of the

vessel diameter and an elevation of peripheral resistance. Once again, a permanent increase in peripheral resistance would result in sustained blood pressure elevations. It must be noted that these mechanisms may be operating in concert to influence the hypertensive process. Autoregulation may represent a more acute response to increased cardiac output while structural adaptation may result from a more chronic exposure to metabolically-exaggerated cardiac activity.

Under the assumption that enhanced cardiovascular responsivity may contribute to the development of sustained elevations in blood pressure, the stress-reactivity model of hypertension would predict that some hypertensive-prone individuals would show enhanced cardiovascular responsivity to stress. Consistent with this hypothesis, compared to normotensive offspring of normotensive parents, normotensive offspring of hypertensive parents have revealed significantly greater cardiovascular responses to mental arithmetic (Ditto, 1986; Falkner, Onesti, Angelakos, Fernandes, & Langman, 1979; Jorgensen & Houston, 1981; Manuck & Proietti, 1982; Manuck, Proietti, Rader, & Polefront, 1985), reaction-time tasks (Gintner, Hollandsworth, & Intrieri, 1986; Hastrup, Light, & Obrist, 1982), shock avoidance (Jorgensen & Houston, 1981), the Stroop word-color interference test (Ditto, 1986; Jorgensen & Houston, 1981; Shapiro, 1961), and a concept formation task (Manuck & Proietti, 1982). While significant

differences have also been observed for the cold pressor test (Shapiro, 1961), these differences were not replicated in subsequent studies (Hastrup et al., 1982). Interestingly, both within and across studies, there is a tendency to observe group differences on active but not passive coping stressors, which is consistent with Obrist's (1981) theory that risk for hypertension is related to exaggerated cardiac responsivity to active coping stressors.

In sum, while it is as yet unclear whether cardiovascular responses to stress play a causative or correlative role in the pathogenic process of hypertension, both longitudinal investigations and studies of at-risk populations support the notion that psychological stressors are, in some individuals, related to the hypertensive disease process. Further, the preceding review clearly illustrates the interactive nature of biological, psychological, and social factors in the pathogenesis of hypertension. Therefore, an ultimate understanding of the relationship between psychological stressors and risk for essential hypertension will require a consideration of other biological, psychological, and social factors that may modulate the stress-reactivity relationship.

The remainder of this introduction will focus on one factor which has received increasing attention as a potential modulator of risk for cardiovascular disease -- caffeine consumption. Information will be presented on the

relationship between dietary caffeine intake and risk for cardiovascular disease, followed by a more specific consideration of the notion that caffeine may moderate risk for hypertension, and hence cardiovascular disease, via its influence on cardiovascular responses to psychological stressors.

Caffeine Use in North America:

Caffeine is a common constituent in the diet of North Americans, present in a wide range of products including coffee, tea, cocoa, chocolate, many soft drinks, and a variety of prescription and non-prescription medications. The results of a survey of United States adults indicated that 80% of respondents over 20 years of age drink coffee on a regular basis (Bonham & Leaverton, 1979). Canadian surveys reveal similar statistics, with one survey in the province of Ontario reporting that more than 90% of adults drink a caffeine-containing beverage each day (Gilbert, Marshman, Schwieder, & Berg, 1976). The popularity of caffeine-containing beverages is usually accredited to the belief that caffeine has stimulant properties which elevate mood, decrease fatigue, and increase capacity for work. While there is evidence to support claims for the beneficial effects of caffeine (Goldstein, Kaizer, & Warren, 1965; Goldstein, Kaizer, & Whitby, 1969), there is also evidence to suggest that these beneficial effects may come at some cost to both physical and psychological well-being (Curatolo

& Robertson, 1983). As a stimulant of both the central and peripheral nervous systems (Curatolo & Robertson, 1983), caffeine may be associated with a variety of undesirable psychological and physiological effects. For example, caffeine has been shown to increase levels of anxiety and exacerbate the symptoms of anxiety disorders (Charney, Heninger, & Jatlow, 1985). It has also been suggested that caffeine may enhance levels of aggression, as observed in one study in which mice given caffeinated water on a chronic basis exhibited increased levels of aggressive behavior (Henry & Stephens, 1980). Although speculative at this point, these results merit further attention given the increasing evidence of the relationship between emotional responses such as anger and hostility and risk for cardiovascular disease (Diamond, 1982). While caffeine has been implicated in a variety of physiological disorders (Curatolo & Robertson, 1983), the present discussion will focus on the potential pathogenic role of caffeine in the development of cardiovascular disease. A number of lines of evidence support the notion of a relationship between caffeine consumption and risk for cardiovascular disease, including 1) the results of animal experimentation, 2) human epidemiological evidence, 3) the association between caffeine and stimulation of cardiovascular activity, and, most recently, 4) evidence of a possible potentiation of cardiovascular responses to psychological stress by

caffeine.

Before proceeding with a presentation of the evidence concerning a relationship between caffeine and cardiovascular disease, a brief literature review will be presented on the putative mechanisms of caffeine's effects on cardiovascular activity.

Pharmacological Effects of Caffeine:

Oral administration of caffeine leads to a rapid and virtually complete absorption of caffeine into the bloodstream. Greater than 99% of ingested caffeine is absorbed into the bloodstream, and peak plasma levels are typically reached in 15 to 45 minutes (Bonati et al., 1982; Neims & von Borstel, 1983). Once absorbed into the bloodstream, caffeine continues to exert its effects for several hours. The elimination half-life of caffeine can range from three to eight hours (Curatolo & Robertson, 1983). Individual differences in caffeine metabolism may be related to environmental factors such as smoking, which significantly reduces caffeine elimination half-life (Parsons & Neims, 1978; Whitsett, Manion, & Christensen, 1984), oral contraceptive use, which significantly increases elimination half-life (Patwardham, Desmond, Johnson, & Schenker, 1980), as well as genetic factors (Grant, Tang, & Kalow, 1983).

A number of mechanisms have been posited to account for the cardiovascular effects of caffeine. One direct

peripheral mechanism which has been put forward suggests that caffeine inhibits the breakdown of cyclic adenosine monophosphate (cAMP) by the enzyme cAMP phosphodiesterase (Beavo, Rogers, & Crofford, 1970). Because cAMP appears to mediate the actions of many neurotransmitters and hormones in the nervous system, it was believed that caffeine could enhance this activity by inhibiting its degradation. However, it has been observed that even high doses of caffeine fail to influence tissue cAMP levels in animals (Burg & Warner, 1975), leading to the conclusion that levels of caffeine required to significantly increase cAMP levels in vitro would be toxic or lethal to animals.

A second direct peripheral mechanism which has been hypothesized to account for the cardiovascular effects of caffeine is antagonism of endogenous adenosine activity. Adenosine receptors are widely distributed in neural, cardiovascular, respiratory, and other tissues. Endogenous adenosine is know to have a variety of effects on various tissues, including 1) modifying release of neurotransmitters or hormones, 2) altering the actions of neurotransmitters, drugs, or hormones, and 3) acting directly upon tissues (von Borstel & Wurtman, 1984). In the cardiovascular system, adenosine has been shown to decrease the rate and force of contractions of the heart and to produce widespread vasodilation of the vasculature (Drury, 1936). Rall (1980) reported that plasma caffeine levels obtained following

consumption of one to three cups of coffee are sufficient to competitively antagonize the actions of endogenous adenosine. Although adenosine antagonism may explain such cardiovascular responses to caffeine as increases in blood pressure, caffeine and adenosine share some common effects, such as bradycardia (von Borstel & Wurtman, 1984), suggesting that a simple adenosine antagonism model may not account for all of the cardiovascular effects of caffeine.

Indirect peripheral mechanisms proposed to explain the effects of caffeine on cardiovascular activity include enhancement of catecholamine release and/or increase in plasma renin activity. Robertson and colleagues (1978) observed plasma epinephrine increases of 207% and norepinephrine increases of 75% following consumption of 250 mg of caffeine in non-coffee drinkers. Subsequent studies of regular caffeine consumers have generally confirmed these findings, consistently demonstrating significant increases in plasma epinephrine with smaller increases, or no significant change, in plasma norepinephrine following caffeine consumption (Izzo, Ghosal, Kwong, Freeman, & Jaenike, 1983; Smits, Hoffmann, Thien, Houben, & van't Laar, 1983; Smits, Pieters, & Thien, 1986; Smits, Thien, & van't Laar, 1985a; Smits, Thien, & van't Laar, 1985b). However, there is convincing evidence that increases in plasma catecholamines following caffeine consumption cannot account for observed pressor responses. Onrot and colleagues (1985)

examined the effects of caffeine on a group of patients with autonomic failure. Although there were no significant changes in plasma epinephrine or norepinephrine levels in these patients following caffeine consumption, significant increases in blood pressure were observed. Similarly, Smits et al. (1986) observed significant increases in blood pressure in response to caffeine in a group of adrenalectomized patients who showed no significant increases in plasma catecholamine levels. Interestingly, increased plasma catecholamine levels following caffeine consumption may also be attributable to blockade of adenosine receptors, given that adenosine can inhibit epinephrine and norepinephrine release (Neims & von Borstel, 1983).

An initial report of significant increases in plasma renin activity following caffeine consumption (Robertson et al., 1978) supported the hypothesis that caffeine may produce its pressor effects through stimulation of plasma renin activity. However, subsequent studies have revealed either no significant increases, or even decreases, in plasma renin activity following caffeine consumption (Izzo et al., 1983; Smits et al., 1983; 1985a; 1985b; 1986). Further, no significant increases in plasma renin activity were observed in patients with impaired adrenomedullary activity (Smits et al., 1986; Onrot et al., 1985), despite significant increases in blood pressure.

Caffeine readily crosses the blood-brain barrier to stimulate central nervous system activity (Hirsch, 1984), and therefore caffeine may exert some of its cardiovascular effects through stimulation of vagal and vasomotor centers in the brain. Once again, it is possible that any central effects of caffeine may be attributable to adenosine antagonism given the presence of adenosine receptors in the central nervous system (Snyder, 1984).

In sum, caffeine appears to exert some of its cardiovascular effects through inhibition of endogenous adenosine activity. Since caffeine may antagonize adenosine inhibition of sympathetic nervous system (SNS) activity at rest, it has been proposed that combining caffeine with another SNS stimulant (e.g., psychological stress) may lead to a potentiation of SNS activity (Shapiro, Lane, & Henry, 1986). In this manner caffeine consumption during exposure to stress might exacerbate the effects of stress on cardiovascular activity.

Tolerance to Caffeine Effects: One issue which has received much attention in relation to the cardiovascular effects of caffeine is the presence or absence of tolerance. This issue is of particular importance since the development of tolerance to the cardiovascular effects of caffeine would argue against caffeine as a significant risk factor in cardiovascular disease. The earliest studies on caffeine effects on cardiovascular activity at rest supported the

notion that individuals did not show tolerance to chronic caffeine consumption, given that observed pressor effects were produced in individuals who were regular caffeine consumers (Horst, Willson, & Smith, 1936), and that these effects could be reproduced despite repeated caffeine consumption over a period of several weeks (Horst, Buxton, & Robinson, 1934). More recently, investigators have reported evidence of tolerance to the cardiovascular effects of caffeine. Colton, Gosselin, and Smith (1968) reported that regular coffee drinkers were significantly less likely to show bradycardia following consumption of 150 mg of caffeine as compared to non-drinkers. Robertson, Wade, Workman, Woosley, and Oates (1981) investigated cardiovascular responses to caffeine in regular coffee drinkers over a period of two weeks. For the first three and last four days of the study subjects received a placebo drink. On days four through ten, subjects received a drink containing 250 mg of caffeine, three times per day, with each meal. The results indicated that significant increases in blood pressure were observed on only the first two caffeine days, with a return to baseline pressure levels on subsequent days. While these findings indicate that tolerance to caffeine's effects on cardiovascular activity may be observed under some conditions, interpretation of these findings must remain guarded given the limited sample size (n = 9), the use of particularly large daily doses of caffeine (equivalent to

approximately eight cups of coffee), and the analysis of average daily blood pressure levels rather than response to each caffeine administration. This final point is particularly important, given that a large number of recent studies indicate that smaller doses of caffeine (e.g., equivalent of two to three cups of coffee per day) can produce significant blood pressure and heart rate changes in regular caffeine consumers after periods of caffeine abstinence as short as twelve hours (Greenberg & Shapiro, 1987; Lane & Williams, 1987; Pincomb, Lovallo, Passey, Brackett, & Wilson, 1987; Pincomb, Lovallo, Passey, & Wilson, 1988). In order to better understand the issue of tolerance to the cardiovascular effects of caffeine, it is necessary to know that a strong correlation exists between basal plasma caffeine concentration and blood pressure response to caffeine consumption (Smits et al., 1985b). Since pressor responses are related to plasma caffeine levels, significant changes in blood pressure following caffeine consumption may only be observed when abstinence from caffeine is of sufficient duration to allow plasma caffeine levels to drop below an unspecified level. Overnight abstinence would allow for a significant elimination of caffeine from the bloodstream in most caffeine users, given that the average elimination half-life for caffeine in regular caffeine consumers is approximately 4 hours (Smits et al., 1985b; Whitsett et al., 1984). In

addition, differences in basal plasma caffeine level are not determined exclusively by length of abstinence from caffeine. Individual differences in caffeine metabolism may be related to environmental factors such as smoking, which significantly reduces caffeine elimination half-life (Parsons & Neims, 1978; Whitsett et al., 1984), as well as genetic factors (Grant et al., 1983). Therefore, caffeine consumption may produce cardiovascular effects in daily life to varying extents depending on both patterns of consumption and individual difference factors related to rate of caffeine clearance. Most importantly, significant cardiovascular adjustments to caffeine are likely to emerge under typical patterns of usage and therefore caffeine may indeed be a significant risk factor in cardiovascular disease.

Caffeine and Cardiovascular Disease:

Several retrospective and prospective epidemiological studies have investigated the relationship between caffeine consumption and heart disease. One of the first reports of a positive association between coffee consumption and ischemic heart disease in a prospective study concerned the outcome of 1,951 men employed at Western Electric in Chicago (Paul et al., 1963). Although this early investigation reported a significant correlation between coffee consumption and ischemic heart disease, a subsequent report indicated that this relationship could be accounted for by tobacco use

(Paul, MacMillan, McKean, & Park, 1968).

The Boston Collaborative Drug Surveillance Program (1972) surveyed 24 hospitals in an attempt to investigate the relationship between use of various drugs and the development of disease. Caffeine intake was surveyed for 276 patients with myocardial infarction as compared to 1,104 control patients who were hospitalized with other chronic diseases. It was observed that patients with myocardial infarction drank significantly greater amounts of coffee prior to hospitalization. In a related investigation, data from 440 patients diagnosed as having had a myocardial infarction were examined from among records accumulated from 12,759 hospitalized patients (Jick et al., 1973). After controlling for a variety of potentially confounding factors, including age, sex, past ischemic disease, hypertension, and smoking, these investigators concluded that the risk of myocardial infarction was related to coffee consumption. Individuals who drank one to five cups of coffee per day had approximately 1.6 times the expected rate of infarction, while consumption of six or more cups per day was associated with a risk which was 2.2 times the expected rate. A more recent retrospective investigation compared coffee consumption in 487 women hospitalized for a first myocardial infarction against 980 controls who were admitted to hospital for acute emergencies. (Rosenberg et al., 1980). This study concluded that coffee drinking was associated, at

most, with a modest increase in risk for myocardial infarction in young women. Specifically, after controlling for factors such as age and smoking, women who drank five or more cups of coffee per day had a relative risk of infarction 1.2 times that of non-drinkers. In an attempt to reconcile their more modest findings with those of the Boston Collaborative Drug Surveillance Program (1972), the authors suggest that the use of patients with chronic diseases as controls may lead to an overestimation of the association between coffee consumption and risk for infarction since chronic patients may tend to give up caffeine.

A number of prospective investigations have failed to support the notion of a significant relationship between coffee consumption and risk for heart disease. Data from the Framingham study, a prospective study of coronary heart disease begun by the National Heart and Lung Institute in 1949, was analyzed to provide information on the relationship between coffee drinking and total coronary heart disease, angina pectoris, myocardial infarction, sudden death, and death from all causes (Dawber, Kannel, & Gordon, 1974). The only significant relationship observed was for an increased risk of death from all causes in men drinking more than four cups of coffee per day. Based on a subsequent analysis controlling for the effects of smoking behavior, it was concluded that the relation of overall

mortality to coffee consumption was based on the association between coffee drinking and cigarette smoking. Similarly, prospective studies of various populations, including Swedish males (Tibblin, Wilhemsen, & Werko, 1975), Japanese men living in Hawaii (Yano, Rhoads, & Kagan, 1977), and residents of Evans county, Georgia (Heyden, Tyroler, Heiss, Hames, & Bartel, 1978), have failed to find a significant relationship between coffee consumption and various cardiovascular diseases. In contrast, a more recent prospective study of 1,130 male medical students reported a strong, positive, dose-dependent relationship between coffee consumption and risk for coronary heart disease, even after controlling for such risk factors as age, smoking, hypertension, and serum cholesterol (LaCroix, Mead, Liang, Thomas, & Pearson, 1986). Consumption of one to two, three to four, and more than four cups of coffee per day was associated with a 1.3, 1.9, and 2.5 times increase in risk of coronary heart disease, respectively. Interestingly, data collected from participants at five year intervals, allowing assessment of changes in personal habits, revealed that the association between coffee consumption and risk for coronary heart disease was strongest when the most recent consumption figures prior to the coronary event were used. This suggests that current coffee consumption is a much better predictor of heart disease, and may explain the failure to observe a significant relationship in some of the previous prospective

investigations.

In attempt to better understand the relationship between caffeine intake and increased risk of cardiovascular disease, epidemiological studies have also examined the relationship between caffeine consumption and cardiovascular disease risk factors such as blood pressure level and blood cholesterol level. Studies of blood pressure levels in caffeine consumers have typically revealed a modest, positive association between these variables, usually on the order of a 1 or 2 mmHg difference between coffee drinkers and non-coffee drinkers (Birkett & Logan, 1988; Lang, Bureau, Degoulet, Salah, & Benattar, 1983a; Lang et al., 1983b). In an epidemiological study of 5147 Australians, caffeine consumption was found to be associated with significantly higher mean systolic and diastolic blood pressure (Shirlow, Berry, & Stokes, 1988). However, this association disappeared after controlling for time since caffeine consumption. These findings support the notion that caffeine can produce modest elevations in blood pressure levels on a time-limited basis, even in habitual caffeine consumers. These findings also suggest that chronic caffeine use does not necessarily lead to sustained blood pressure elevations, rather higher blood pressure levels in caffeine consumers appear directly related to continued exposure to caffeine. It is important to note that while caffeine may not lead to sustained blood pressure elevations, the

repeated acute blood pressure rises produced by caffeine may have detrimental physiological effects.

As well, based on evidence of the relationship between serum cholesterol levels and heart disease (Marx, 1976), a number of epidemiological studies have investigated the potential relationship between caffeine consumption and cholesterol level. These studies have revealed that coffee consumption is significantly related to higher levels of total cholesterol and low-density lipoprotein cholesterol, even after controlling for potentially confounding factors such as age, body mass index, smoking, and alcohol use (Forde, Knutsen, Arnesen, & Thelle, 1985; Haffner et al., 1985; Heyden et al., 1979; Pietinen, Geboers, & Kesteloot, 1988; Thelle, Arnesen, & Forde, 1983; Williams et al., 1985).

In sum, while caffeine consumption may be related to several risk factors for cardiovascular disease (e.g., blood pressure and cholesterol levels), there have been conflicting results regarding the direct relationship between caffeine consumption and risk for cardiovascular disease. These discrepancies may be largely attributable to experiment-specific methodological issues such as measurement of caffeine intake, as well as general methodological problems inherent in attempts to statistically control for associated risk factors. In a recent article, Schreiber, Maffeo, Robins, Masters, and Bond

(1988) argue that some of the failures to link caffeine intake to cardiovascular disease may be due to imprecise measurement strategies. For example, the majority of studies have focused exclusively on reported levels of coffee consumption, despite the wide range of dietary sources of caffeine. Therefore, estimates of the relationship between caffeine intake and development of disease will be inaccurate for both experimental and control samples. Moreover, because there is a good deal of variability in individual habits of caffeine consumption, prospective studies may be confounded by a failure to ascertain caffeine consumption patterns at regular intervals to detect potentially important fluctuations. This point has empirical support in the findings of LaCroix et al. (1986), in which the more recent assessment of caffeine consumption was a better predictor of risk for heart disease. As well, other problems cloud the interpretation of previous results. Statistical control of associated risk factors, typically using regression procedures, is carried out in epidemiological studies in order to tease apart the relative contributions to disease of various health-related variables. While such procedures are widely accepted, a decision to statistically remove the effects of one independent variable on the dependent variable before assessing the effects of another requires the assumption that the two independent variables are not operating via the

same causal pathway. In the case of smoking, it is possible that both caffeine and smoking are operating via a common causal pathway to influence risk for heart disease, such as sympathetic adrenal-medullary stimulation. Therefore, it is possible that caffeine consumption and smoking interact synergistically, and it would thus be inappropriate to control for one factor or the other. Rather, it would be necessary to consider the joint effects of these factors on risk for cardiovascular disease.

The epidemiological studies provide suggestive evidence that caffeine may be an important risk factor for cardiovascular disease. Perhaps more importantly, these studies provide the impetus for additional research strategies that will supplement epidemiological findings. Specifically, there is a need to examine both the acute and long-term effects of caffeine in conjunction with other naturally-occurring risk factors, such as stress and nicotine, in laboratory and field settings.

Caffeine and Cardiovascular Activity:

Information on the effects of caffeine on resting cardiovascular activity in humans has been available for over fifty years (Grollman, 1930; Horst, Buxton, & Robinson, 1934; Horst, Robinson, Jenkins, & Bao, 1934; Horst, Willson, & Smith, 1936). In general, these early studies indicated that caffeine produced a combination of slight decreases in heart rate (approx. 5 bpm) and slight increases in blood

pressure (approx. 5-10 mmHg). Since these initial investigations, a large number of studies have confirmed these findings using both regular consumers and non-consumers of caffeine (Greenberg & Shapiro, 1987; Izzo et al., 1983; Lane, 1983; Lane & Williams, 1985; 1987; Pincomb et al., 1985; 1987; 1988; Robertson et al., 1978; Smits et al., 1983; 1985a; 1985b; 1986; Whitsett et al., 1984). While the more recent studies have tended to yield a greater variability in heart rate and blood pressure responses to caffeine, this variability is largely attributable to differences in experimental protocol including dose of caffeine administered, length of abstinence from caffeine, previous experience with caffeine, and length of time after consumption that measures were obtained. While the ability of caffeine to produce small blood pressure elevations may not be sufficient reason for concern for individuals without borderline or established hypertension, combined with other sources of cardiovascular stimulation, such as psychological stress, caffeine may prove a significant risk factor for a larger segment of the population.

Caffeine and Psychological Stress:

Increasingly, research on the etiology of cardiovascular disease has focused on multiple risk factor models of causation which assert that a variety of environmental and genetic factors combine to determine risk for cardiovascular disease. In line with this approach,

studies on the interaction between two potential risk factors for cardiovascular disease, caffeine and psychological stress, began to appear in the literature in the 1980s. There are several reasons to believe that caffeine and psychological stress could combine to increase risk for cardiovascular disease, including 1) both stimuli have been independently linked to risk for cardiovascular disease in epidemiological studies, 2) both stimuli are known to affect cardiovascular activity, including acute and possibly chronic increases in blood pressure, and 3) both stimuli are omnipresent in the day-to-day lives of many North Americans, making their simultaneous exposure a common occurrence. In fact, there is evidence that caffeine consumption may actually increase during times of stress (Conway, Vickers, Ward, & Rahe, 1981). Because caffeine and psychological stress may act through similar physiological mechanisms to stimulate cardiovascular activity (e.g., enhanced sympathetic nervous system activity), it is possible that the combination of these stimuli may lead to more than a cumulative relationship in which the effects of caffeine add to the effects of stress. Caffeine may potentiate cardiovascular responses to a psychological stressor and in so doing may further enhance risk for cardiovascular disease.

Some of the strongest initial evidence for the potential interaction between caffeine and stress was

reported by Henry and Stephens (1980). In this study, mice were reared in a competitive social environment and received either regular drinking water or water with added caffeine. Over a period of months, the mice who received caffeine exhibited greater stress-induced increases in blood pressure, plasma corticosterone, plasma renin, and adrenal weight. Further, morbidity and mortality rates were significantly higher in mice receiving caffeinated drinking water as compared to normal drinking water.

In one of the first published reports concerning the effects of caffeine on cardiovascular responses to stress in humans, Lane (1983) observed that caffeine elevated systolic and diastolic blood pressure during a mental arithmetic task in ten male college students who were not regular caffeine consumers. The pressor effects of caffeine were cumulative, such that blood pressure increases produced by caffeine combined in an additive fashion with the increases produced by stress. Measures of heart rate revealed no significant effects of caffeine. This initial study was followed by a larger study in which the cardiovascular responses of 33 college students, who also did not normally consume caffeine, were assessed at rest and during a mental arithmetic task (Lane & Williams, 1985). Once again, the increases in blood pressure produced by caffeine at rest were observed to combine in an additive fashion with the increases produced by the stressor, and there were no

significant effects of caffeine on heart rate. In addition to measures of heart rate and blood pressure, forearm blood flow and forearm vascular resistance responses were assessed. While caffeine had no significant effect on either measure at rest, caffeine potentiated the forearm blood flow responses to the stressor. This observed potentiation was important in that it suggested a possible mechanism whereby acute exposure to the combination of caffeine and stress could lead to the pathological effects in mice following chronic exposure (Henry & Stephens, 1980). Specifically, in line with existing models of hypertension development (Folkow, 1987; Obrist, 1981), it was hypothesized that caffeine's ability to enhance stress-related increases in blood flow could lead to increases in vascular resistance as part of an autoregulatory process. Further, with repeated exposure to these stimuli the increases in resistance could become permanent due to structural changes in the vasculature, leading to sustained elevations in blood pressure. These hypotheses were highly speculative since the effects of caffeine and stress had been tested only on non-regular consumers of caffeine. The possibility remained that regular caffeine consumers would exhibit some form of tolerance to the cardiovascular effects of stress and caffeine, and therefore would not reveal similar cardiovascular adjustments. As a result, Lane and Williams (1987) replicated their earlier study using a group of

regular coffee drinkers. Consistent with the previous findings, caffeine produced additive increases in blood pressure, no effects on heart rate, and a potentiation of forearm blood flow responses to a mental arithmetic stressor. In contrast to the previous study, caffeine also potentiated forearm vascular resistance responses to the stressor.

Pincomb and colleagues (1987; 1988) have also examined cardiovascular responses to stress and caffeine in regular caffeine consumers. In 1987, Pincomb et al. published a study on cardiovascular responses to the combination of caffeine and a naturalistic stressor. Male medical students were tested for the effects of caffeine on cardiovascular activity during a period of low stress (a week with no exams) and high stress (final exam week). The results indicated that caffeine produced significant increases in systolic and diastolic blood pressure and significant decreases in heart rate. The exams produced increases in systolic blood pressure and heart rate and these effects combined in an additive fashion with the effects produced by caffeine alone. In a subsequent laboratory study (Pincomb et al., 1988), cardiovascular responses to the combination of caffeine and a reaction-time task were assessed in regular caffeine consumers. In this study impedance cardiography techniques were used to collect a variety of cardiovascular indices beyond the more common measures of blood pressure

and heart rate. Blood samples were also obtained in order to assess norepinephrine and cortisol activity in response to stress and caffeine. At rest, caffeine produced significant increases in systolic blood pressure, diastolic blood pressure, and plasma norepinephrine, and significant decreases in heart rate. During performance of the reaction-time task, caffeine produced additive increases in blood pressure, potentiated increases in cardiac output and plasma cortisol, and potentiated decreases in vascular resistance. This pattern of results indicated that at rest caffeine increased blood pressure primarily through increases in vascular resistance, but during stress caffeine's pressor effects were related to elevations in cardiac output.

Consistent with a view of multiple risk factors for cardiovascular disease, a number of researchers have looked at cardiovascular responses to caffeine and psychological stress in combination with other potential risk factors such as a family or personal history of hypertension (Goldstein & Shapiro, 1987; Greenberg & Shapiro, 1987; Greenstadt, Yang, & Shapiro, 1988; Lane & Williams, 1987; Lovallo et al., 1989; MacDougall, Musante, Castillo, & Acevedo, 1988), race (Strickland, Myers, & Lahey, 1989), smoking (MacDougall et al., 1988), and the Type A behavior pattern (Greenstadt et al., 1988; Lane & Williams, 1985; 1987).

A number of researchers have examined cardiovascular responses to the combination of stress and caffeine in

offspring of hypertensives. Lane & Williams (1987) reported no differences between individuals with and without a parental history of hypertension in terms of blood pressure responses, however offspring of hypertensives did show enhanced forearm blood flow and forearm vascular resistance responses to stress following caffeine consumption. Greenberg and Shapiro (1987) assessed systolic blood pressure and heart rate responses to the combination of a mental arithmetic stressor and caffeine in regular caffeine consumers with and without a parental history of hypertension. Although the offspring of hypertensives showed a greater systolic blood pressure response to the stressor, both groups revealed additive increases in blood pressure to the combination of stress and caffeine. No significant caffeine effects were observed for heart rate. This study was subsequently replicated using a population of Chinese males (Greenstadt et al., 1988). Consistent with the first study, in both groups caffeine and stress produced additive increases in blood pressure and caffeine had no significant effect on heart rate. Interestingly, the offspring of hypertensives showed significantly higher systolic blood pressure levels at rest following caffeine consumption, in large part due to an absence of a pressor response to caffeine in the offspring of normotensives group. Most recently, Lovallo and colleagues (1989) reported equivalent additive increases in blood pressure in response to the

combination of caffeine and a reaction-time stressor in offspring of hypertensives and normotensives. However, while the offspring of normotensives had similar cortisol increases in response to the stressor on both caffeine and placebo days, offspring of hypertensives revealed significantly greater increases in plasma cortisol in response to the combination of stress and caffeine. In sum, these studies indicate that potentiation of cardiovascular or neuroendocrine responses to the combination of stress and caffeine may be more pronounced when these stimuli are assessed in conjunction with other risk factors for cardiovascular disease. Comparatively little information is available on the interaction between stress and caffeine and other cardiovascular disease risk factors. Goldstein and Shapiro (1987) examined the effects of caffeine on 18 male hypertensives who were taking diuretic medication. Results revealed that caffeine produced blood pressure increases at rest, but there were no significant differences in blood pressure levels during a mental arithmetic task on the caffeine versus placebo day. However, as noted by the authors, given the large pressor responses to mental arithmetic observed in these hypertensive individuals (who, by definition, already have elevated baseline blood pressure levels), it is possible that the failure to observe additive effects of caffeine and stress may have been due to a ceiling effect. In support of this position, very high

average blood pressures levels were observed during stress on the caffeine day (163/100 mmHg).

In a recent study of cardiovascular reactivity to caffeine and stress in black and white normotensive females (Strickland, Myers, & Lahey, 1989), it was revealed that there were no significant racial differences in response to caffeine or stress. While these female subjects did not show significant systolic blood pressure responses to caffeine, diastolic blood pressure responses were consistent with previous investigations in that the pressor effects of caffeine and stress combined in an additive fashion. Finally, consistent with a number of the aforementioned studies, this study revealed no significant differences in pressor responses to caffeine or stress as a function of parental history of hypertension.

The joint effects of cigarette smoking and caffeine consumption on blood pressure and heart rate responses to mental arithmetic and video games stressors was examined in male and female college students who smoked and consumed caffeine on a regular basis (MacDougall et al., 1988). MacDougall and colleagues observed a potentiation of both systolic blood pressure and heart rate responses to the mental arithmetic stressor in the caffeine group versus a placebo control group. While a potentiation of blood pressure reactivity is inconsistent with previous findings, this discrepancy may be due to the use of a between-subject

design. That is, subjects in the control condition may have been less reactive to the stressor resulting in an apparent caffeine-induced potentiation effect when comparing the caffeine and placebo groups. While it is also possible that within-subject designs fail to observe potentiation due to an attenuation of cardiovascular reactivity with repeated exposure to the stressors, this possibility is less likely given the failure to observe significant order effects in previous investigations. While smoking combined with stress to produce additive increases on all cardiovascular measures obtained, the combined effects of smoking and caffeine on cardiovascular responses to stress were no different from the effects of either smoking alone or caffeine alone. Finally, in general there were no sex differences in response to smoking, caffeine, and stress. While this study suggests that the combination of caffeine and smoking does not elicit significantly greater reactivity to psychological stress than either stimulus alone, the results also suggest that the findings must be interpreted with caution given the use of between-subject comparisons. A final verdict on the joint effects of these stimuli awaits a replication using a within-subjects design.

Investigations of the relationship between the Type A behavior pattern and cardiovascular responses to stress and caffeine have revealed mixed results. While Type A scores derived from the Jenkins Activity Survey have not been

significantly related to cardiovascular responses to stress and caffeine (Greenstadt et al., 1988; Lane & Williams, 1985; 1987), a significant relationship has been observed using the structured interview (Lane & Williams, 1987). Lane and Williams (1987) observed that caffeine significantly enhanced forearm blood flow and forearm vascular resistance responses to stress in Type Bs but not Type As. Further analyses revealed that this effect was restricted to individuals with a positive family history of hypertension, although these results should be interpreted with caution since they are based on an extremely limited sample of positive family history Type Bs (n=5).

The review presented here suggests that caffeine, stress, and other cardiovascular disease risk factors may combine to exacerbate cardiovascular reactivity. Nonetheless, information about the potential pathogenic consequences of the combination of stress and caffeine continues to be limited by several factors, including 1) the narrow range of stressors which have been examined, 2) a tendency to restrict measurement of cardiovascular activity to the more common indices of blood pressure and heart rate, and 3) a lack of information concerning the degree to which existing findings are applicable to the day-to-day experiences of regular caffeine consumers.

Existing studies of caffeine-stress interactions have focused almost exclusively on active coping stressors.

Active coping stressors can be differentiated from passive coping stressors on the basis of the degree of control the individual may exert during an unpleasant event. In a series of investigations, Obrist (1981) observed that stressors which differ on the active-passive coping dimension tended to elicit different patterns of cardiovascular activity. Responses to active coping stressors (tasks where the participant can exert some degree of control over outcome, e.g., shock-avoidance reaction-time tasks) resulted in primarily beta-adrenergic sympathetic activity, with consequent cardiac stimulation and increases in systolic blood pressure. In contrast, passive coping stressors (tasks where the participant has no control over outcome, e.g., uncontrolled electric shock) resulted in primarily alpha-adrenergic sympathetic activity. Under these circumstances, cardiovascular responses included increases in peripheral resistance and relatively larger increases in diastolic blood pressure. Since different stressors may elicit different patterns of cardiovascular activity, an ultimate understanding of caffeine-stress interactions will require a consideration of a variety of different types of stressors.

A second limitation of the existing literature on caffeine-stress interactions is the tendency to restrict measurement of cardiovascular activity to blood pressure and heart rate responses. Consequently, information on the potential mechanism(s) which account for observed blood

pressure and heart rate changes is limited. This is particularly important given that studies which have explored other physiological responses have observed potentiation effects as compared to the purely cumulative effects typically observed for blood pressure responses. Moreover, since different stressors may elicit cardiovascular adjustments through different mechanisms, combining multiple indices of physiological responsivity with multiple stressors may provide information on potentially divergent underlying mechanisms of cardiovascular effects.

Finally, despite the fact that caffeine has been shown in a number of studies to exacerbate cardiovascular responses to laboratory stressors in regular caffeine consumers, the extent to which these findings are generalizable to the day-to-day experiences of regular caffeine consumers remains to be determined. While psychological responses to laboratory stressors are often assumed to mimic responses in real-life circumstances, this assumption remains largely untested. Pincomb and colleagues (1987) examined cardiovascular responses to caffeine and the naturalistic stressor of exam stress in medical students. However, measurement of cardiovascular activity was not obtained concomitant with performance of the stressful task but during periods when the students were studying quietly. Thus the degree to which these results are comparable to

responses observed during stressful tasks, as assessed in previous laboratory studies, is unclear.

The studies to be presented address the previously mentioned issues. The first two papers, "Caffeine effects on several indices of cardiovascular activity at rest and during stress" (France & Ditto, 1988) and "Cardiovascular responses to the combination of caffeine and active coping, passive coping, and exercise stressors" (France & Ditto, 1990), address the issue of multiple indices of cardiovascular activity. In these studies measures of blood pressure and heart rate are supplemented by additional indices of cardiovascular activity in an attempt to provide additional information as to the mechanism(s) responsible for caffeine-stress interactions. The second paper also addresses the issue of caffeine effects on different types of stressors by comparing cardiovascular responses to an active coping stressor (mental arithmetic), passive coping stressor (cold pressor), and exercise stressor (isometric leg exercise). Finally, the third paper presented, "Cardiovascular responses to occupational stress and caffeine in telemarketing employees" (France & Ditto, 1989), examines cardiovascular responses to caffeine during performance of a challenging occupational activity (telemarketing sales). By examining regular caffeine consumers in their normal working environments this paper provided one of the first "real-world" assessments of

cardiovascular responses to caffeine and stress.

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Caffeine Effects on Several Indices of Cardiovascular Activity at Rest and During Stress

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The effects of caffeine on cardiovascular responses to a mental arithmetic task were assessed using a between-subjects, double-blind design Thirty-six male undergraduates were randomly assigned to either a placebo group or a group which received 250mg of caffeine. Repeated measurements of systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), digital blood volume pulse (DBVP), and finger pulse transit time (FPTT) were obtained during a predrug baseline, a postdrug resting period, and a mental arithmetic task Significant Period (i.e , stress) effects were observed on all measures, except DBVP which revealed a marginally significant Period effect Significant main effects of Drug were observed on DBP and DBVP There were no significant Drug × Period interactions These results indicate that the increases in DBP and the decreases in DBVP produced by caffeine were additive with effects produced by stress

KEY WORDS: caffeine, stress, cardiovascular activity

INTRODUCTION

Recently, researchers have begun to focus on the possibility of additive and/or synergistic effects of psychological stress and caffeine These efforts have been motivated, in part, by the possibility that caffeine may

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exacerbate the potential pathogenic effects of stress in the development of disorders such as hypertension and heart disease.

When administered to a subject at rest, caffeine has consistently been shown to produce increases in systolic and diastolic blood pressure (Lane, 1983; Pincomb *et al*, 1985, Sawyer *et al.*, 1982; Smits *et al*, 1986; Whitsett *et al.*, 1984) and often a significant decrease in heart rate (Pincomb *et al*, 1985, Smits *et al*, 1986, Whitsett *et al*, 1984). Based on additional evidence of no significant increase in cardiac contractility or, in general, cardiac output, caffeine's pressor effect has been attributed to an increase in systemic vascular resistance (Pincomb *et al*, 1985, 1986).

Relative to the number of studies available on the effects of caffeine at rest, there exists a paucity of research on the combined influences of caffeine and psychological stress The results of early research in this area, which was conducted with individuals who were not regular caffeine users, suggested that the elevations in blood pressure produced by caffeine and psychological stress combine in an additive fashion (Lane, 1983; Lane and Williams, 1985). Presently, reports of only a few studies on the effects of caffeine and stress on cardiovascular activity in regular users of caffeine have been published While this research has been consistent in finding cumulative pressor responses to stress and caffeine, few of the reports provide information beyond blood pressure and heart-rate results. Consequently, information on the potential mechanism(s) of these cardiovascular adjustments is lacking In one of the few studies to include measures other than blood pressure and heart rate, Pincomb *et al.* (1986) found that caffeine potentiated the increases in heart rate, cardiac index, and ejection acceleration produced by a signaled reaction-time task The pattern of results obtained by these researchers suggests that cardiac effects are important in mediating the effects of caffeine during stress

In sum, caffeine has been shown to produce increases in blood pressure at rest and during stress. However, while the pressor effect of caffeine at rest appears to be related to changes in vascular activity, its ability to increase stress-induced blood-pressure elevations appears to be related to changes in cardiac activity. One possible explanation for these apparently contradictory actions is that caffeine differentially influences vascular and cardiac activity It is possible that the effect of caffeine on vascular activity is somewhat more pronounced, allowing its appearance at rest However, active coping stressors (e g , mental arithmetic) elicit increases in cardiac activity (Obrist, 1981), perhaps allowing the observation of caffeine's actions on this system

The present study was conducted to evaluate the possibility that caffeine's influences on cardiovascular activity are limited primarily to changes in vascular function while the subject is at rest but are visible in measures reflecting both cardiac and vascular function while the subject is exposed to an active coping stressor Therefore, an index of cardiovascular activity

which reflects predominantly vascular changes (blood volume pulse) and an additional index of cardiac activity (pulse transit time) were added to the more common measures of blood pressure and heart rate.

METHOD

Subjects

Thirty-six healthy male undergraduates were randomly assigned in equal numbers to either a placebo or a caffeine condition. There was no significant group difference in reported daily caffeine consumption between the placebo ($\bar{X}$ = 158.6 ± 140.1 mg) and the caffeine ($\bar{X}$ = 161 1 ± 149.8 mg) groups. Each subject received $6.00 for participating in the study.

Apparatus

Measurements of systolic (SBP) and diastolic (DBP) blood pressure were obtained at 2-min intervals throughtout the experiment using a Critikon Dinamap 845XT automatic blood-pressure monitor The blood-pressure cuff was placed on the subject's nondominant arm. Other physiological measures were obtained using various transducers and electrodes, a Grass Model 7D polygraph, a set of Med Associates signal processing modules, and an IBM Personal Computer Heart rate (HR) was derived from an electrocardiogram obtained using small Beckman electrodes. Finger pulse transit time (FPTT) was obtained by measuring the time between the occurrence of the electrocardiogram R-wave and the upswing of the finger pulse wave as detected by a Grass Model PTTL-6 photoplethysmograph attached to the second finger of the subject's dominant hand. Digital blood-volume pulse (DBVP) was obtained from the same photoplethysmograph.

Arithmetic problems were presented on audiotape using a Sony Walkman, Model WM-14. The subject was given a foot response box to be used in responding to the arithmetic problems. The response box consisted of an inclined platform on which to rest the foot, with two buttons labeled "true" and "false" at either side of the foot The response box was designed to permit the subject to answer the arithmetic problems without the use of speech and with a minimum of movement of the foot

Procedure

All subjects were tested in the morning in order to enhance adherence to the dietary restrictions. Dietary restrictions involved fasting from the previous evening and avoiding caffeinated beverages during this same interval

Upon arrival at the laboratory, the subject was seated in a quiet, carpeted room. The experimental procedures were discussed and informed consent was obtained. Once the blood-pressure cuff, electrodes, and transducers were attached, two casual blood-pressure readings were obtained. The physiological recording equipment was housed in a room adjacent to the subject room. An average resting SBP of 140 mm Hg or greater and/or DBP of 90 mm Hg or greater was considered grounds for discontinuation. However, no subject exhibited such a resting blood-pressure level.

The subject was then asked to put on his headphones so that the remainder of the experimental protocol could be governed by taped instruction. For the first 2 min the subject was instructed on the use of the response box and was encouraged to ask the experimenter if he had any remaining questions. This was followed by instructions to sit quietly and relax for 10 min while baseline measurements were taken. Following the relaxation period, the subject received 100 ml of orange-flavored water containing either the placebo (5 mg of quinidine) or caffeine (250 mg) plus the placebo. Administration was double-blind. Since caffeine was administered in a between-subjects manner, the order of presentation of the drink was randomly determined for the 36 subjects prior to commencement of the study. Before recording continued, the subject rested for 30 min to allow for absorption of caffeine into the bloodstream.

After this period, physiological recording resumed and the subject was asked to continue to rest for 10 min. This was followed by a mental arithmetic task which included a set of arithmetic problems developed and used by Carroll *et al.* (1986). The arithmetic problems were presented in four 4-min blocks, with 2-min rest periods between each block. In all, the task comprised 96 discrete, 10-sec problem trials. Each problem trial involved a 6-sec problem delivery, followed 2 sec later by an answer, which was delivered in 1 sec and finally, 1 sec in which to respond as to the correctness of the given answer. The subject was promised a monetary reward for correct problem solutions. Before each block of problems, the subject was informed as to the amount of incentive to be received for correct solutions during that block. On half of the blocks the subject was given $0.25 for every two problems correct, and on the other half he received $0.01 for every two problems correct. The arithmetic problems were divided into three levels of difficulty: easy, difficult, and impossible. Subjects in both the caffeine and the placebo groups were randomly assigned in equal numbers to either the easy, the difficult, or the impossible problems condition. This division was carried out as part of a separate investigation, and the results for each difficulty level are not presented due to insufficient sample sizes. During each 2-min rest period between problem sets, subjects rated levels of arousal, effort, and perceived problem difficulty for the previous set using visual ana-

log scales. The total protocol lasted 74 min, excluding explanation of the procedures, etc

Physiological Data Reduction

Physiological data collected during the 74-min sessions were reduced in the following manner The recorded values of SBP and DBP were averaged to obtain mean levels (mm Hg) for each of the following periods 10-min predrug baseline, 10-min postdrug resting, and stress (excluding between-block rest periods) HR, FPTT, and DBVP values were analyzed on-line by the computer and averaged within 1-min periods. These values were subsequently reduced in the same manner as the blood-pressure values in order to obtain mean levels for each of the three periods

RESULTS

The experimental design for the analysis of the combined effects of stress and caffeine included the between-subject factor of drug with two levels (caffeine, placebo) and the within-subject factor of period with three levels (predrug baseline, postdrug resting, stress). The effects of caffeine at rest were evaluated by a series of 2 Drug Condition (caffeine, placebo) × 2 Period (predrug baseline, postdrug resting) ANOVAs The combined effects of caffeine and stress were tested in a series of 2 Drug Condition (caffeine, placebo) × 2 Period (postdrug resting, stress) ANOVAs of change scores corrected for predrug baseline values. The mean values for each of the three periods are presented in Table I

Caffeine Effects on Cardiovascular Activity at Rest

The results of the 2 (caffeine, placebo) × 2 (predrug baseline, postdrug resting) ANOVAs are presented in Table II

As can be seen by the significant interactions, only DBP and DBVP exhibited significant effects of caffeine at rest DBP increased 5 mm Hg in the caffeine group, compared to 0 mm Hg in the placebo group Similarly, DBVP decreased approximately 12%, compared to a 1% increase in the placebo group In addition, consistent with previous research, HR showed a marginally significant ($p < .10$) decrease of 2 bpm in the caffeine group relative to the placebo group The significant Period effect for HR reflected a reduction in both groups (6 bpm for caffeine, 4 bpm for placebo) following the 30-min rest between the baseline and the postdrug resting periods

Table I. Means and Standard Deviations of Cardiovascular Variables at Different Points in the Study

Phase	Measure				
	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	FPTT (msec)[a]	DBVP (units)[a]
	Caffeine group (N = 18)				
Predrug baseline	120 (10)	71 (7)	78 (10)	245 (15)	2691 (590)
Postdrug resting	122 (9)	76 (7)	72 (10)	248 (12)	2365 (463)
Stress	128 (11)	79 (7)	78 (12)	244 (17)	2131 (518)
	Placebo group (N = 18)				
Predrug baseline	123 (7)	75 (7)	76 (12)	246 (12)	2386 (508)
Postdrug resting	123 (6)	75 (7)	72 (10)	250 (13)	2405 (605)
Stress	126 (8)	78 (8)	77 (13)	240 (19)	2370 (564)

[a]Low values are associated with high arousal

Table II Effects of Caffeine on Cardiovascular Activity at Rest Results of Predrug Baseline, Postdrug Resting Analyses

Source	$F(1, 34)$[a]				
	SBP	DBP	HR	FPTT	DBVP
Drug	56	79	05	17	67
Period	53	11 64***	29 25***	4 23**	3 68*
Drug × Period	1 12	9 99***	2 96*	64	4 64**

[a]df of some analyses were lower due to missing data

*p < 10
**p < 05
***p < 01

Caffeine Effects on Cardiovascular Response to Stress

The results of the analyses of caffeine effects on cardiovascular response to stress are presented in Table III.

Consistent with the previous analysis, DBP showed a significant Drug main effect The SBP ANOVA also revealed a marginally significant main effect of Drug. Interestingly, post hoc tests revealed that while there was no significant effect of Drug on resting SBP, individuals who received caffeine exhibited marginally greater SBP responses to stress than individuals who received placebo [$t(1,34) = -1\ 99$, $p < 06$, two tailed] Given the absence of a significant ANOVA interaction, this finding should be interpreted with caution However, it suggests that caffeine may potentiate SBP responsivity to stress, as opposed to adding to the DBP response to stress This finding is consistent with the experimental hypothesis in that the ratio of vascular

to cardiac influences on DBP is higher than on SBP. Both DBP and SBP revealed significant Period effects, related to increases during stress.

Analysis of the HR data revealed a significant Period effect but no significant Drug effect of Drug × Period interaction. The increase in HR in response to the mental arithmetic task averaged 5.5 bpm for both groups. As with HR, FPTT showed a significant response to stress but did not reveal a significant Drug effect or Drug × Period interaction.

Finally, DBVP showed a significant Drug effect and a marginally significant ($p < .07$) Period effect. Once again, there was no significant Drug × Period interaction. It would appear that DBVP behaved much in the same manner as DBP. In fact, the correlation between change in DBP from the predrug baseline to the stress period was significantly correlated with change in DBVP from the predrug baseline to the stres period ($r = -.50$). The significant decreases in DBVP produced by caffeine appear to have combined in an additive fashion with the decreases produced by stress.

Caffeine Effects on Subjective Ratings and Performance

There were no observed effects of caffeine on any of the subjective rating scales or on the actual performance of the mental arithmetic task. According to a series of one-way ANOVAs, subjective ratings of arousal, effort, and task difficulty showed no significant differences between groups. A similar analysis of number of correct responses to the math problems revealed no significant difference between the caffeine ($\bar{X}$ = 79.0% correct) and the placebo ($\bar{X}$ = 76.0% correct) groups.

DISCUSSION

The cumulative increase in DBP produced by the combination of stress and caffeine is consistent with the results of recent research using regular

Table III. Effects of Caffeine on Cardiovascular Responses to Stress: Results of ANOVAs of Postdrug Resting and Stress Change Scores

	$F(1, 34)^a$				
Source	SBP	DBP	HR	FPTT	DBVP
Drug	3.02*	8.98**	1.51	1.10	7.64**
Period	21.31**	22.59**	33.05**	9.62**	3.73*
Drug × Period	2.10	0.42	0.15	0.79	2.06

[a]df on some analyses were lower due to missing data.
*$p < .10$
**$p < .01$

caffeine users (Lane and Williams, 1987; Pincomb *et al.*, 1987). However, the failure to obtain a significant increase in resting SBP in response to caffeine is a rare finding in this literature It is possible that a significant SBP response was not observed due to the fact that postcaffeine baseline measures were taken just 30 min after caffeine ingestion, thereby minimizing the opportunity to absorb caffeine into the bloodstream Although this interval has proven sufficient to produce SBP effects in the past (Greenberg and Shapiro, 1987), there is considerable individual variability in the rate of caffeine absorption (Robertson *et al* , 1978). Consistent with evidence of considerable individual variability in caffeine absorption rates, the between-subjects design used in the present study would tend to mitigate against finding an effect of caffeine on SBP

To the authors' knowledge, the present report represents the first information on the response of pulse transit time and blood-volume pulse measures to caffeine The inclusion of these variables proved informative in at least two respects The observed effects of caffeine on blood-volume pulse but not pulse transit time during the postdrug resting period support the notion that caffeine influences predominantly vascular activity under resting conditions Therefore, the present results are consistent with previous reports of no significant cardiac stimulation by caffeine under resting conditions (Pincomb *et al* , 1985, Smits *et al* , 1983) and provide original evidence of change in vascular activity Moreover, on the basis of the significant Drug effect and marginally significant Period effect observed on blood-volume pulse during stress, it appears that caffeine and stress combine to produce additive changes in vascular function The DBP results are consistent with this belief.

Given the equivocal nature of the SBP results, the present study failed to provide much evidence of a caffeine-induced enhancement of cardiac activity during stress. Although both pulse transit time and heart rate revealed significant responses to the stressor, suggesting an increase in cardiac activity, it is possible that a caffeine-induced enhancement of this activity was not observed because the mental arithmetic task was insufficiently demanding In fact, the different levels of difficulty of arithmetic problems used in the present study have been shown to produce differing levels of cardiac activity (Carroll *et al* , 1986) Specifically, the inclusion of easy and impossible mental arithmetic problems may have attenuated the involvement of these subjects in the task, thereby decreasing the cardiac response and the strength of the Drug × Period interactions This explanation is supported by the relatively modest increases in blood pressure and heart rate observed Although firm conclusions cannot be drawn from the present results, the hypothesis that caffeine differentially affects the vasculature and the heart is physiologically plausible in several respects. First, while caffeine does not appear to influence cardiovascular activity by directly stimulating adrenergic recep-

tors, there is evidence that it reduces the uptake and/or metabolism of norepinephrine in nonneural tissues. Kalsner and colleagues (1971, 1975) found that caffeine enhanced the effects of norepinephrine at both cardiovascular alpha- and cardiovascular beta-adrenergic receptors Therefore, the present pattern of results may be related to the fact that, in contrast to the vasculature, parasympathetic control of the heart at rest is much greater than sympathetic control (Ganong, 1985) Stressors which elicit active coping behavior tend to elicit increases in cardiac sympathetic activity (Obrist, 1981), increasing the likelihood of observing an effect of caffeine on this response system Alternatively, it is possible that the present pattern of results may correspond in some manner to differences in the nature of the adrenergic receptor sites in the vasculature (primarily alpha) and the heart (primarily beta) It is possible that caffeine influences preferentially activity at alpha-adrenergic receptor sites, permitting the observation of an effect on vascular resistance at rest

In conclusion, the results of the present study are clearly consistent with the notion that caffeine enhances vascular activity at rest and during stress Given the mounting evidence that caffeine and stress combine to produce changes in cardiovascular activity, increased efforts are required in order to elucidate more fully the mechanisms of these interactions.

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The study described in "Caffeine effects on several indices of cardiovascular activity at rest and during stress" proved informative in demonstrating the role of vascular activity in mediating blood pressure responses to caffeine. The results suggested that caffeine enhanced vascular activity, but not cardiac activity, at rest and during a moderately challenging mental arithmetic task. The following study "Cardiovascular responses to the combination of caffeine and active coping, passive coping, and exercise stressors" addressed a number of limitations of the earlier study. First, the earlier study used a mental arithmetic task that may not have elicited maximal task involvement in all subjects, possibly attenuating observed levels of cardiac stimulation. Thus the following study used a set of uniformly challenging mental arithmetic problems combined with a potentially greater monetary incentive for successful performance. In addition, subjects were exposed to several different types of stressors, known to elicit varying degrees of cardiac or vascular activity, in order to test the hypothesis that caffeine effects on cardiovascular responses to stress are dependent on the prevailing stimulus conditions. As well, measurements of cutaneous vascular resistance responses were supplemented by assessment of vascular responses in the forearm skeletal muscles. Because vascular beds in the forearm skeletal muscles are innervated by neurons having sympathetic beta-adrenergic receptors,

forearm blood flow and forearm vascular resistance responses allow for a differentiation of active versus passive coping stressor effects on vascular activity. Finally, the potential correlations between physiological and psychological responses to stress and caffeine were assessed using a set of standardized psychological questionnaires.

Cardiovascular Responses to the Combination of Caffeine and Active Coping, Passive Coping, and Exercise Stressors

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Running Head: CAFFEINE AND STRESS

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Abstract

The present study examined cardiovascular responses to the combination of caffeine (250mg) and active coping, passive coping, and exercise stressors in 48 healthy males. Subjects were tested in a within-subject, placebo-controlled, double-blind design. Repeated measurements of systolic, diastolic, and mean arterial blood pressure (SBP, DBP, MAP), heart rate (HR), finger temperature (TEMP), respiratory sinus arrhythmia (RSA), and forearm blood flow (FBF) were obtained during a pre-drug resting baseline, a post-drug resting baseline, the three stressor tasks, and a recovery baseline. The primary analyses were 2 (drug) x 5 (period) x 6 (stress order) MANCOVAs using pre-drug baseline values as covariates. Significant period main effects were observed for all measures. Significant drug main effects were observed for SBP, DBP, MAP, TEMP, RSA, and FBF. The significant changes in blood pressure and finger temperature produced by caffeine combined in an additive fashion with the effects produced by the stressors. Significantly greater increases in FBF and HR during mental arithmetic on the caffeine day suggested a potentiation of sympathetic, beta-adrenergic activity. Questionnaires administered during baseline periods to assess psychological responses to stress and caffeine revealed a potentiation of anxiety and anger responses to stress on the caffeine day.

Cardiovascular Responses to the Combination of Caffeine and Active Coping, Passive Coping, and Exercise Stressors

Although information on caffeine's effects on cardiovascular activity at rest has been available for many years (Grollmann, 1930; Sollman & Pilcher, 1911), it is only in the last decade that researchers began to examine caffeine's effects on cardiovascular responses to stressful stimuli. This information has become important with emerging evidence that lifestyle factors, such as caffeine consumption, may interact with life stress to contribute to risk for pervasive and chronic disorders such as hypertension and heart disease.

One of the first studies of the interaction between caffeine and psychological stress found that mice reared in a competitive social environment exhibited greater stress-induced increases in blood pressure, plasma corticosterone, plasma renin, and adrenal weight when caffeine was added to their drinking water (Henry & Stephens, 1980). As well, morbidity and mortality rates were significantly higher in mice receiving caffeinated water as compared to normal drinking water. In humans, caffeine and acute stress combine to produce additive increases in systolic and diastolic blood pressure (France & Ditto, 1988; Greenberg & Shapiro, 1987; Lane, 1983; Lane & Williams, 1985; 1987; Pincomb,

Lovallo, Passey, & Wilson, 1988). That is, the increases in blood pressure produced by caffeine combine in a cumulative fashion with the increases produced by stress. Moreover, it has been observed in humans that caffeine may interact in a synergistic fashion with stress, potentiating such physiological responses as heart rate, stroke volume, and, hence, cardiac output (Pincomb et al., 1988), forearm blood flow (Lane & Williams, 1985; 1987), and plasma cortisol levels (Lovallo et al., 1989; Pincomb et al., 1988).

Published reports on the effects of caffeine on cardiovascular responses to stress have included a variety of psychological stressors such as mental arithmetic, reaction-time tasks, and the naturalistic stressors of exam (Pincomb et al., 1987) and occupational stress (France & Ditto, 1989). In general, these studies have been largely consistent in finding additive blood pressure increases in response to the combination of stress and caffeine. However, this consistency may be related to the fact that the stressors sampled to date have been predominantly examples of active coping stressors. Active coping stressors can be differentiated from passive coping stressors on the basis of the degree of control the individual may exert during an unpleasant task. Obrist (1981) conducted a number of studies which indicated that opportunity for control (active coping) resulted in primarily beta-adrenergic sympathetic activity,

with consequent increases in cardiac activity and systolic blood pressure. In contrast, when opportunity for control was minimal or non-existent (passive coping) alpha-adrenergic sympathetic activity predominated. Under these circumstances, cardiovascular responses included increases in peripheral resistance and relatively larger increases in diastolic blood pressure. Since stressors which differ on the active-passive coping dimension tend to produce different patterns of cardiovascular activity, an ultimate understanding of caffeine-stress interactions will require a consideration of both active and passive coping stressors.

Consistent with a broader focus on the effects of caffeine on cardiovascular responses to stress, it is important to consider the potential effects of caffeine on psychological reactions to stress. As with the physiological caffeine literature, there is a long tradition of investigations of caffeine's effects on one's psychological state (Hollingworth, 1912). Once again, however, there has been relatively little information on psychological responses to stress following caffeine consumption. This information may prove important given the hypothesized role of emotional factors such as anger in mediating risk for both hypertension and heart disease (Diamond, 1982; Siegel, 1984). Henry and Stephens (1980) provided an anecdotal report of caffeine's effects on psychological responses to

stress, indicating that caffeine increased aggressive behavior in mice living under stressful conditions. In humans, Lane and Williams (1985) used visual analog scales to assess subjective reports of effort, importance, task difficulty, and relaxation to a mental arithmetic task on both placebo and caffeine days. Although the task produced significant decreases in reported "relaxation", there were no significant effects of caffeine or caffeine-stress interactions. In a subsequent study (Lane & Williams, 1987), subjects were asked to provide ratings on eleven affective dimensions, once again using visual analog scales, in response to a mental arithmetic task on both a caffeine and a placebo day. Caffeine and stress each produced independent increases in ratings of "alertness" and decreases in ratings of "relaxation". Moreover, a caffeine-stress interaction was observed for the subjective dimension of fear such that ratings of "afraid" were significantly higher following the stressor on the caffeine versus the placebo day. In sum, the limited information which exists on psychological responses to stress following caffeine consumption suggests that further studies are warranted.

In the present study, subjects were exposed to three different types of stressors (mental arithmetic, cold pressor, isometric leg exercise), and were required to complete standardized mood questionnaires in an attempt to

address both the need for a diversity of stressful stimuli and for additional information on psychological responses to stress following caffeine consumption. A variety of physiological measures were obtained to investigate the joint effects of caffeine and stress on blood pressure and blood pressure control mechanisms, and their relationships to subjective mood.

Method

Subjects

Forty-eight healthy young males aged 16 to 36 were recruited for the study. Descriptive characteristics of the subjects are shown in Table 1. Subjects received $7.50/hr for participating in the study.

Apparatus

Measurements of systolic blood pressure (SBP, in mmHg), diastolic blood pressure (DBP, in mmHg), and mean arterial pressure (MAP, in mmHg) were obtained at 2-min intervals throughout the experiment using a Critikon Dinamap 845XT automatic blood pressure monitor. The blood pressure cuff was placed on the subject's right arm. Other physiological measures were obtained using various transducers and electrodes, a Grass Model 7D polygraph, a set of Med Associates signal processing modules, and an IBM XT personal computer. Heart rate was derived from an electrocardiogram

recorded using two disposable Medi-Trace electrodes placed in a bipolar configuration on opposite sides of the rib cage. The signal was amplified and a continuous record of heart rate (HR, in bpm) was obtained using a Grass Model 7P4 tachograph and the computer. Finger temperature (TEMP, in degrees Celsius) was obtained from the ring finger of the subject's right hand using a Thought Technology Model 200T temperature module connected to the computer. Respiration was recorded using a Grass Model TCT1R thermistor, and amplified using a Grass Model 7P5 amplifier. As in previous studies conducted in this laboratory (e.g., Ditto & Miller, 1989), forearm blood flow (FBF, in ml/min/dl of forearm volume) measures were obtained according to the classic procedure described by Whitney (1953). This procedure relies on mercury-in-Silastic strain gauge plethysmography with intermittent occlusion in the left arm by a blood pressure cuff concurrent with isolation of the wrist and hand circulation by a second cuff. Measurements were obtained during minutes 2 and 3 of every 4-minute block during the baseline and stressor tasks and averaged by computer. Forearm vascular resistance (FVR) was calculated for each period by dividing the average MAP by the average FBF. Respiratory sinus arrhythmia (RSA, in msec) was obtained according to the method described by Grossman and Svebak (1987).

Procedure

All subjects were tested on two consecutive mornings. Testing began between 8:00 and 10:00 a.m. in order to enhance adherence to the dietary restrictions. Dietary restrictions included fasting from the previous evening and avoiding caffeinated beverages, alcohol, nicotine, and non-prescription drugs during this same interval.

On each morning, upon arrival at the laboratory, the subject was seated in a quiet, carpeted room. The experimental procedures were discussed and informed consent was obtained. Once the blood pressure cuffs, electrodes, and transducers were attached, two casual blood pressure readings were taken. The physiological recording equipment was housed in a room adjacent to the subject room. An average resting SBP of 140 mmHg or greater and/or DBP of 90 mmHg or greater was considered grounds for discontinuation. However, no subject exhibited such a resting blood pressure level.

For the first 10 min the subject was asked to sit quietly and relax while pre-drug baseline measurements were obtained. Following the relaxation period, the subject received grapefruit juice that either contained or did not contain 250 mg of caffeine. The caffeine was administered in a double-blind fashion, with order of presentation counterbalanced across subjects. Grapefruit juice was chosen

based on previous evidence that it masks the somewhat bitter taste of caffeine (Pincomb et al., 1985). Before recording continued, 42 min were allowed for absorption of caffeine into the bloodstream. At the beginning of this rest period the subject completed the Profile of Mood States questionnaire (POMS; McNair, Lorr, & Droppleman, 1971) and the Spielberger State Anxiety questionnaire (STAI; Spielberger, Gorsuch, & Lushene, 1970). On the first day the subject also completed questionnaires concerning personal and family health history, daily caffeine intake, and the Jenkins Activity Survey (JAS; Jenkins, Zyzanski, & Rosenman, 1979). During the remainder of this period the subject read quietly. Immediately prior to the post-drug baseline period, the subject once again completed the POMS and STAI questionnaires.

Following the caffeine absorption period, physiological recording resumed and the subject was asked to rest for a 10 min post-drug baseline. This was followed by the presentation of alternating 3 min task and 5 min rest periods. Three stressor tasks were presented. Order of stressor presentation was consistent across days for each subject, but was counterbalanced across subjects. The stressor tasks included (1) mental arithmetic, (2) cold pressor, and (3) isometric leg exercise. The mental arithmetic task involved the addition and subtraction of two

and three digit numbers presented on flashcards. Each of the 36 problems was presented for 5 s. At the end of 5 s the subject was required to report his answer aloud. The experimenter responded either "correct" or "incorrect" to each answer, and recorded the total number correct at the end of the task. Prior to the task the subject was informed that the person with the highest total score for both days would win $50.00. The cold pressor task involved the immersion of the subject's left foot in 4 degree Celsius water for 2.5 min. The isometric leg exercise task, which lasted 3 min, involved a horizontal extension of the right leg to a height of 38cm while seated. Immediately following each stressor the subject was asked to rate the previous task in terms of subjective "arousal", "difficulty", and "stressfulness" using visual analog scales. Following the third stressor, the subject was once again asked to rest quietly during a 10 min recovery baseline. Finally, the subject completed a third set of POMS and STAI questionnaires.

Data Reduction and Analyses

Repeated measures of cardiovascular activity were averaged for the following periods: pre-drug resting baseline, post-drug resting baseline, mental arithmetic, cold pressor, isometric leg exercise, and recovery baseline. A regression analysis to predict RSA using respiration rate

was conducted. The z-score residual values (ZRSA), corrected for respiration rate, were used in subsequent analyses as recommended by Grossman, Stemmler, Karemaker, and Wieling (1988). Analyses of the effects of caffeine on cardiovascular activity at rest were conducted using 2 Drug (caffeine, placebo) x 2 Period (pre-drug resting, post-drug resting) x 2 Drug Order (caffeine day 1/placebo day 2, placebo day 1/caffeine day 2) repeated measures analyses of variance (ANOVAs). These analyses were conducted to determine whether caffeine exerted significant effects on cardiovascular activity prior to the stress session. Analyses of the effects of caffeine on cardiovascular responses to stress were conducted using 2 Drug (caffeine, placebo) x 5 Period (post-drug resting, mental arithmetic, cold pressor, isometric leg exercise, recovery) x 6 Stress Order repeated measures MANCOVAs using pre-drug resting values as covariates. Previous studies have reported significantly greater increases in HR (MacDougall, Musante, Castillo, & Acevedo, 1988; Pincomb et al., 1988; Strickland, Myers, & Lahey, 1989) and FBF (Lane & Williams, 1985; 1987), and significantly greater decreases in FVR (Lane & Williams, 1987) in response to active coping stressors following caffeine consumption. Therefore, in the present study, planned comparisons of change in HR, FBF, and FVR responses to stress on caffeine versus placebo days were conducted in

order to determine whether enhancement of these responses is consistent across different types of stressors. Planned comparisons were conducted using the modified Bonferroni test (Keppel, 1982).

Results

The Effects of Caffeine on Cardiovascular Activity at Rest

A 2 Drug (caffeine, placebo) x 2 Period (pre-drug resting, post-drug resting) x 2 Drug Order (caffeine day 1/placebo day 2, placebo day 1/caffeine day 2) MANOVA was conducted using the eight physiological dependent variables (SBP, DBP, MAP, HR, TEMP, FBF, FVR, ZRSA). Significant main effects of drug condition (Wilks' lambda=.41, $F(8,28)=4.98$, $p<.01$) and period (Wilks' lambda=.30, $F(8,28)=8.35$, $p<.01$) were observed. The interaction effects of drug x period (Wilks' lambda=.25, $F(8,28)=10.67$, $p.<01$) and drug order x drug (Wilks' lambda=.59, $F(8,28)=2.44$, $p<.05$) were also significant. No other significant effects were observed. Given these results, the drug, period, drug x period, and drug order x drug effects of the comparable univariate ANOVAs were examined. The means and standard errors for the physiological dependent measures are displayed in Table 2.

There were no significant drug order x drug interactions observed in the univariate ANOVAs. A significant drug x period interaction indicates a significant effect of caffeine on resting cardiovascular

activity. Significant drug x period interactions were observed for SBP, DBP, MAP, and TEMP ($F(1,46)=24.21$, 91.24, 49.14, and 8.78, respectively, all $p<.01$). The significant effects on blood pressure reflected post-drug resting blood pressure levels approximately 6 mmHg higher on the caffeine day as compared to the placebo day. The significant finger temperature effect reflected a greater decrease in finger temperature during the post-drug resting baseline on the caffeine versus the placebo day. The observed significant effect of caffeine on TEMP, a measure of peripheral resistance, but not on any indices of cardiac output, suggests that the increases in blood pressure observed at rest may be attributable to increases in peripheral resistance. This finding is consistent with other studies in which measures of peripheral resistance were obtained at rest following caffeine administration (France & Ditto, 1988; Pincomb et al., 1985, 1988).

The Effects of Caffeine on Cardiovascular Response to Stress

A 2 Drug x 5 Period (pre-drug resting, post-drug resting, mental arithmetic, cold pressor, leg exercise, recovery) x 2 Drug Order x 6 Stress Order MANCOVA using pre-drug baseline values as covariates was conducted using the eight dependent variables. Significant effects of drug condition (Wilks' lambda=.15, $F(8,9)=6.34$, $p<.01$), period

(Wilks' lambda=.11, $F(32,330)=8.48$, $p<.01$), and stress order x period (Wilks' lambda=.15, $F(160,679)=1.22$, $p<.05$) were observed. No other significant effects were observed. Given these results, the drug and period main effects and stress order x period interaction effects from a series of repeated measures MANCOVAs were examined. Means and standard errors are displayed in Table 2.

Blood Pressure. Significant drug and period effects were observed for SBP, DBP, and MAP (Table 3). As illustrated in Figure 1, these significant effects indicate that the increases in blood pressure produced by caffeine at rest combined in an additive fashion with the increases in blood pressure produced by the stressors. These findings provide original evidence of caffeine's ability to produce additive increases in blood pressure to a variety of different types of stressors.

Heart Rate. As indicated in Table 3, the heart rate analysis revealed a significant period effect and a marginally significant drug effect. Planned comparisons were conducted to compare change in heart rate (stressor task - post-drug resting baseline) on each day. As can be seen in Figure 2, these analyses revealed a significantly greater response to mental arithmetic on the caffeine versus the placebo day ($t(47)=2.31$), but not to the cold pressor ($t(47)=0.36$) or leg exercise ($t(47)=0.40$) tasks. These

results are consistent with previous evidence of enhancement of HR responsivity during an active coping stressor (MacDougall et al., 1988; Pincomb et al.,1988; Strickland et al., 1989), and suggest that such enhancement may not occur during passive coping or exercise stressors.

Finger Temperature. As indicated in Table 3, significant drug, period, and stress order x period effects were observed for finger temperature. The observed significant stress order x period effect suggests caution is required in attributing finger temperature changes to specific stressors. Visual inspection of finger temperature curves within stress order suggested that the stress order x period interaction was due to a tendency of finger temperature to increase following the cold pressor task, regardless of the subsequent stressor. That is, previous exposure to the vasoconstrictive cold pressor stimulus appears to have resulted in rebound vasodilation. Nonetheless, the significant drug and period main effects suggest that the significant decreases in finger temperature produced by caffeine at rest combined in an additive fashion with the decreases produced by the stressors. These results are consistent with previous evidence of additive decreases in digital blood volume pulse to the combination of stress and caffeine (France and Ditto, 1988), since both of these measures respond to changes in digital vascular resistance.

Moreover, the present findings provide original evidence of caffeine's ability to produce additive decreases in finger temperature to a variety of different types of stressors.

Forearm Blood Flow. Analyses of forearm blood flow responses revealed significant drug and period effects. Planned comparisons were conducted to compare change in forearm blood flow (stressor task - post-drug resting baseline) on each day. As can be seen in Figure 3, these analyses revealed significantly greater increases in FBF on the caffeine versus the placebo day during the mental arithmetic task ($t(45)=2.81$) and the cold pressor ($t(44)=2.16$) task, but not during the leg exercise task ($t(44)=1.54$). These results are consistent with previous evidence of caffeine-induced enhancement of FBF responsivity during stress (Lane & Williams, 1985; 1987).

Forearm Vascular Resistance. As indicated in Table 3, analyses of forearm vascular resistance responses revealed a significant period effect, but no significant drug effect. Visual inspection of Figure 3 suggests that the period effect is attributable to decreases in FVR during the mental arithmetic task and either no change or increases in FVR during the cold pressor and leg exercise tasks. Planned comparisons were conducted to compare change in forearm vascular resistance (stressor task - post-drug resting baseline) on each day. These analyses revealed no

significant differences in FVR responses on the caffeine versus placebo day during each stressor. Previous reports of FVR responses to the combination of stress and caffeine present contradictory findings. Lane and Williams (1985) reported that caffeine had no significant effect on FVR responses to a mental arithmetic stressor, although the mental arithmetic task produced significant decreases in FVR. A subsequent report (Lane & Williams, 1987) indicated that caffeine and mental arithmetic stress combined to produce synergistic decreases in FVR. The present findings are consistent with the earlier report (Lane & Williams, 1985), and extend the negative findings to a variety of different stressors.

Respiratory Sinus Arrhythmia. As indicated in Table 3, analyses of residualized respiratory sinus arrhythmia scores revealed both significant drug and period effects. Although the increases in ZRSA observed at rest following caffeine consumption were not significant, the significant drug main effect observed during the stressors reflects the fact that caffeine produced significantly higher ZRSA levels across the different stressors. This finding suggests that caffeine consumption results in an increase in tonic vagal activity, which may explain existing evidence of caffeine's ability to produce significant decreases in resting heart rate (Pincomb et al., 1985; Smits, Pieters, & Thien, 1986; Whitsett,

Manion, & Christensen, 1984).

The Effects of Caffeine on Psychological Responses

As with the analyses of caffeine effects on physiological activity at rest, analyses of caffeine effects on resting psychological state began with a 2 Drug x 2 Period x 2 Drug Order MANOVA of seven dependent measures (state anxiety, and the POMS subscales of anxiety, depression, anger, vigor, fatigue, and confusion). The drug x period interaction effect was not significant, indicating that caffeine did not have a significant effect on these measures at rest.

Analyses of caffeine effects on psychological responses to the stressors began with a 2 Drug x 2 Period (post-drug resting, recovery) x 2 Drug Order x 6 Stress Order MANCOVA using pre-drug resting values as covariates of the seven dependent measures. A significant drug x period effect (Wilks' lambda=.58, $F(7,29)=3.04$, $p<.05$) was the only significant effect observed. Given these results, the drug x period effects of the comparable univariate ANOVAs were examined. These analyses revealed significant drug x period effects for state anxiety ($F(1,47)=4.91$, $p<.05$), the Anger subscale of the POMS ($F(1,46)=7.24$, $p<.01$), and the Fatigue subscale of the POMS ($F(1,46)=5.50$, $p<.03$). The Anxiety subscale of the POMS revealed a marginally significant drug

x period effect ($F(1,46)=3.01$, $p<.09$). As can be seen in Figure 4, these results indicate that the subjects reported significantly higher levels of anger and anxiety following the stressors on the caffeine versus the placebo day. The significant interaction effect observed for the Fatigue subscale reflects a significantly lower reported fatigue level following the stressors on the caffeine day versus placebo day. There were no significant correlations between POMS Anger, POMS Anxiety, or STAI and cardiovascular responses of SBP, DBP, or HR on either the caffeine or placebo day. The fact that psychological measures were obtained only after all tasks were completed, rather than in response to each task, may have decreased the chances of observing significant correlations.

Analyses of subjective ratings of "arousal", "difficulty", and "stressfulness" immediately following each stressor were carried out using 2 Drug x 3 Task (mental arithmetic, cold pressor, leg exercise) repeated measures MANOVAs for each measure. These analyses revealed significant task effects for ratings of "arousal" (Wilks' lambda=.66, $F(2,46)= 12.00$, $p<.01$) and "stressfulness" (Wilks' lambda= .57, $F(2,46)=17.17$, $p<.01$), and a marginally significant task effect for "difficulty" (Wilks' lambda= .90, $F(2,46)=2.51$, $p<.10$). These task effects reflect higher ratings on all subjective measures following the cold

pressor as compared to the other tasks. There were no other significant effects.

Finally, there was no significant difference in mean percentage of mental arithmetic problems correctly solved on the caffeine versus placebo days (55.4% and 58.3%, respectively).

Discussion

The findings of the present experiment extend the results of previous studies by providing original evidence that caffeine and stress combine to produce additive increases in blood pressure to several different types of stressors. Moreover, these results suggest that although additive increases in blood pressure appear consistent across stressors, the underlying cardiovascular adjustments may be quite different. Specifically, during the mental arithmetic task caffeine produced significantly greater increases in both FBF and HR. These changes suggest that the additive increases in blood pressure observed during the mental arithmetic task were related to 1) an increase in peripheral vasoconstriction produced by caffeine that combined in an additive fashion with the increase produced by stress, and 2) an increase in cardiac output and decreases in vascular resistance in the large muscles that were produced by synergistic interactions between caffeine

and stress, that is, reactions that were greater than those produced by the sum of caffeine alone and stress alone. A synergistic interaction between caffeine and stress influencing systemic vascular resistance has been reported previously in response to an active coping reaction-time task (Pincomb et al., 1988). Similarly, Lane and Williams (1987) reported synergistic interactions between caffeine and stress in FBF and FVR in response to a mental arithmetic task. In contrast, caffeine did not appear to potentiate increases in cardiac output in response to either the cold pressor or leg exercise stressors in the present study which, presumably, did not affect beta-adrenergic activity to the same extent as mental arithmetic. Collectively, the nature of the variables involved (i.e., HR and FBF), the stressor (mental arithmetic), and the interactions suggests that caffeine may potentiate activity at beta-adrenergic receptor sites in some unspecified manner. In contrast, the additive increases in BP produced by caffeine and stress during cold pressor and leg exercise appear to be due to additive effects of caffeine and stress on vasoconstriction.

Since caffeine can induce additive blood pressure increases to a range of stressors, caffeine may exacerbate the potentially detrimental effects of a variety of stressful tasks. More important, perhaps, is the finding that the cardiovascular effects of caffeine appear to

interact in a synergistic fashion with those produced by active coping stressors, which stimulate sympathetic, beta-adrenergic activity, but not with passive coping stressors. This finding may be of clinical significance given that repeated, exaggerated beta-adrenergic responsivity has been hypothesized to be related to increases in peripheral resistance and sustained elevations in blood pressure (Obrist, 1981), possibly through changes in the arterioles (Folkow, 1987) or by intrinsic autoregulatory mechanisms (Coleman, Granger, & Guyton, 1971).

Although the mechanism of caffeine-induced potentiation of sympathetic, beta-adrenergic responsivity to stress remains to be elucidated, recent evidence suggest that caffeine effects on neuroendocrine responsivity may play a role in this relationship. Lane, Adcock, Williams, and Kuhn (1990) reported that caffeine potentiated epinephrine responses to a mental arithmetic stressor. As well, there is physiological evidence of caffeine's ability to enhance beta-adrenergic receptor-mediated activity via blockade of catecholamine uptake (Kalsner, Frew, & Smith, 1975). Caffeine's ability to produce a combination of enhanced catecholamine release and reuptake blockade may explain the observed potentiation in cardiovascular measures which reflect sympathetic, beta-adrenergic activity.

The present findings of significantly greater levels of

anxiety and anger following the stressors on the caffeine versus placebo day suggest that the ingestion of caffeine prior to a stressful task may potentiate negative emotional responses to that task. Consistent with this hypothesis, Lane and Williams (1987) reported that caffeine potentiated subjective levels of fear following a mental arithmetic stressor. As well, these findings appear to parallel Henry and Stephens' (1980) observation of increased aggressive behaviour in mice in stressful social environments when they received only caffeinated water. Presently, the notion that caffeine may exacerbate emotional responses to stress has only limited empirical support. Nonetheless, this appears to be a promising line of inquiry given that existing evidence has been obtained despite the use of stressors which have not been chosen specifically for their ability to produce negative emotional reactions. Future studies should focus on stressors known to elicit particular patterns of emotional reactivity in order to examine the relationship between caffeine's effects on physiological and emotional responses to psychological stressors. Such research would enhance our understanding of the potential contributions of central and peripheral mechanisms to cardiovascular responsivity to caffeine, and may provide an important link between studies of cardiovascular reactivity, emotional reactivity, and risk for cardiovascular disease.

Table 1

Descriptive Characteristics of Subjects

Variable	Mean (SD)
Age (years)	21 (4)
Height (cm)	177 (7)
Weight (Kg)	72 (9)
Caffeine use (mg/day)	148 (195)
Smoking[a] (cig/day)	16 (8)

[a] Values are for 7 smokers.

Table 2: Means and Standard Errors of Cardiovascular Variables throughout the Study on Placebo (PLA) and Caffeine (CAF) days.

		Period					
		PRE-DRUG	POST-DRUG	MATH	COLD PRESSOR	LEG EXERCISE	RECOVERY
SBP	PLA	119(1.0)	117(0.9)	129(1.9)	133(1.8)	129(1.4)	119(1.2)
	CAF	119(1.0)	122(1.0)	135(1.7)	137(1.7)	134(1.4)	125(1.3)
DBP	PLA	67(1.1)	67(1.1)	77(1.5)	84(1.7)	80(1.2)	67(1.2)
	CAF	67(1.0)	73(1.1)	81(1.3)	87(1.6)	83(1.2)	73(1.2)
MAP	PLA	83(1.0)	82(0.8)	94(1.5)	99(1.8)	95(1.3)	83(1.0)
	CAF	83(0.9)	88(0.9)	97(1.4)	104(1.6)	100(1.1)	88(1.2)
HR	PLA	65(1.7)	64(1.4)	77(2.0)	73(1.8)	77(1.6)	63(1.4)
	CAF	63(1.4)	61(1.4)	76(1.8)	70(1.6)	74(1.4)	61(1.3)
TEMP	PLA	32.4(0.4)	31.0(0.5)	29.7(0.5)	29.4(0.6)	30.1(0.6)	29.9(0.7)
	CAF	32.1(0.5)	29.3(0.6)	28.2(0.6)	27.9(0.5)	28.4(0.6)	28.5(0.7)
FBF	PLA	2.29(0.2)	2.17(0.1)	2.88(0.2)	2.39(0.2)	2.23(0.2)	2.12(0.2)
	CAF	2.29(0.2)	2.24(0.1)	3.36(0.2)	2.91(0.2)	2.57(0.2)	2.16(0.2)
FVR	PLA	45.0(3.5)	48.4(4.1)	39.9(3.1)	53.2(4.9)	56.1(6.6)	49.1(3.8)
	CAF	44.4(3.3)	47.9(3.6)	35.7(2.6)	48.1(4.5)	54.1(5.9)	50.5(3.8)
ZRSA	PLA	0.07(0.2)	0.05(0.2)	-0.29(0.1)	0.10(0.2)	-0.37(0.1)	-0.11(0.1)
	CAF	0.06(0.2)	0.29(0.2)	-0.19(0.1)	0.22(0.2)	-0.08(0.1)	0.28(0.2)

Table 3

Effects of Caffeine on Cardiovascular Responses to Stress: Results of MANCOVAs of Periods with Pre-Drug Covariates

	Drug	Period		Stress Order x Period	
	$F(1,41)$ [a]	$F(4,39)$ [a]	Wilks' lambda	$F(20,130)$ [a]	Wilks' lambda
SBP	48.64**	70.78**	0.12	0.86	0.66
DBP	115.22**	101.37**	0.09	0.89	0.65
MAP	63.23**	95.47**	0.09	0.74	0.70
HR	3.99+	82.88**	0.11	0.95	0.63
TEMP	15.23**	15.44**	0.39	2.11**	0.39
FBF	5.30*	14.00**	0.38	0.85	0.64
FVR	0.10	9.26**	0.49	1.29	0.52
ZRSA	8.69**	3.17*	0.69	0.83	0.58

[a] df of some analyses lower due to missing data.
+$p<.10$
*$p<.05$
**$p<.01$

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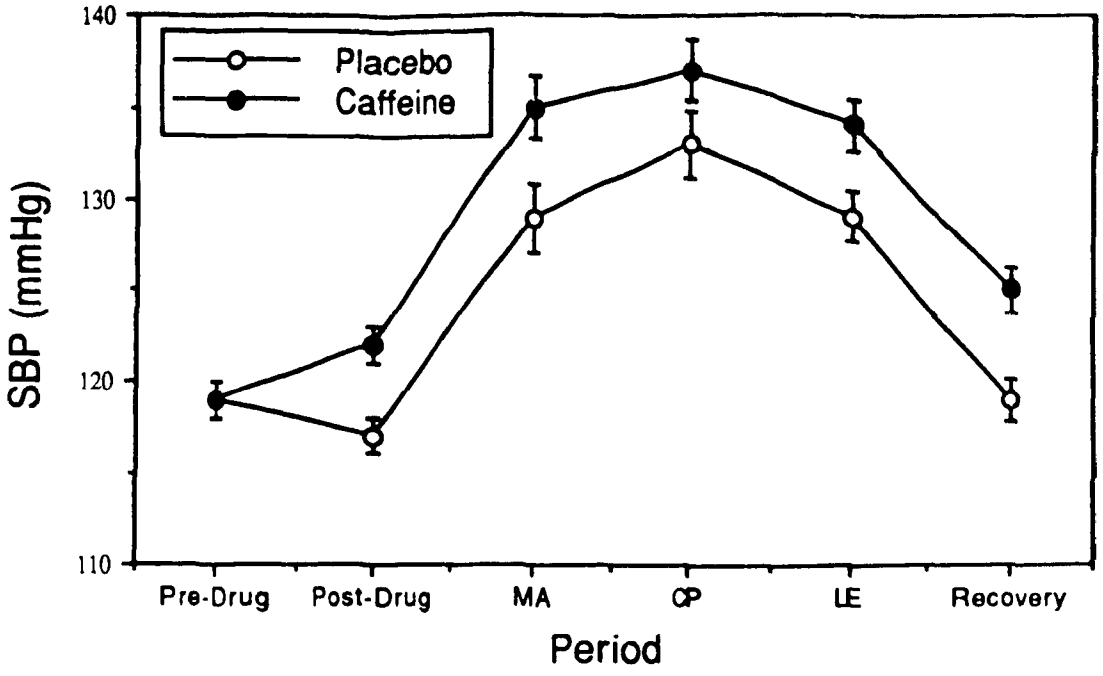
Figure Captions

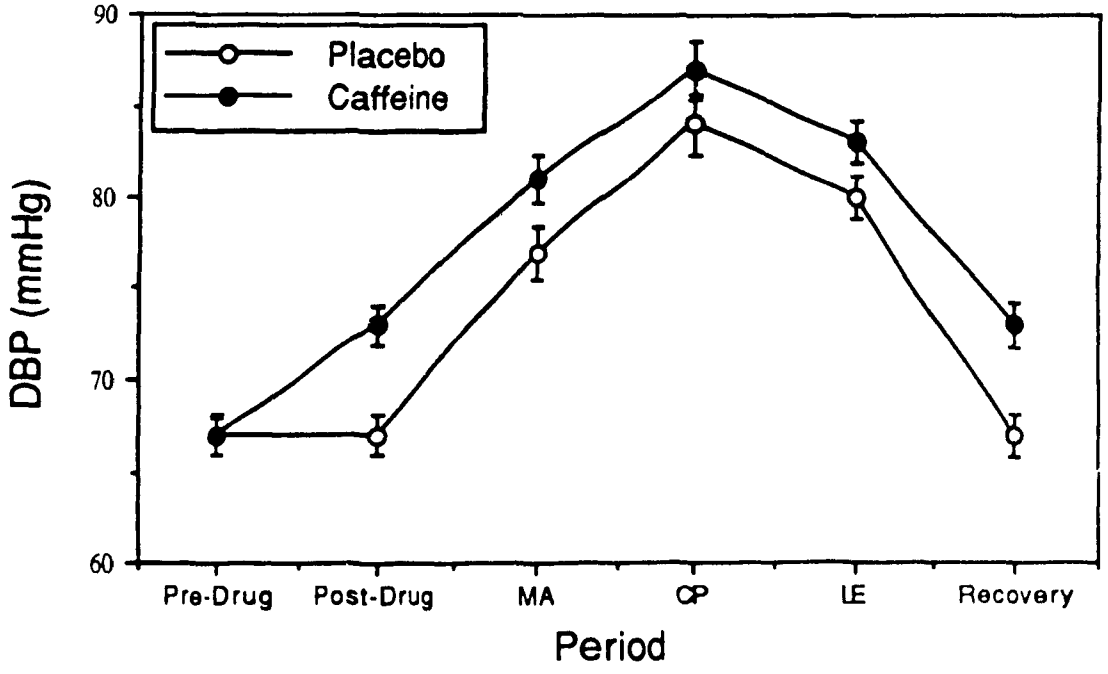
Figure 1. Systolic and diastolic blood pressure at each period (pre-drug, post-drug, mental arithmetic (MA), cold pressor (CP), leg exercise (LE), and recovery) on placebo and caffeine days.

Figure 2. Heart rate at each period (pre-drug, post-drug, mental arithmetic (MA), cold pressor (CP), leg exercise (LE), and recovery) on placebo and caffeine days.

Figure 3. Forearm blood flow and forearm vascular resistance at each period (pre-drug, post-drug, mental arithmetic (MA), cold pressor (CP), leg exercise (LE), and recovery) on placebo and caffeine days.

Figure 4. Subjective ratings of anger and anxiety (subscales of the profile of mood states questionnaire) at pre-drug, post-drug, and recovery on placebo and caffeine days.


140
130
120
110
SBP (mmHg)
Placebo
Caffeine
Pre-Drug
Post-Drug
MA
OP
LE
Recovery
Period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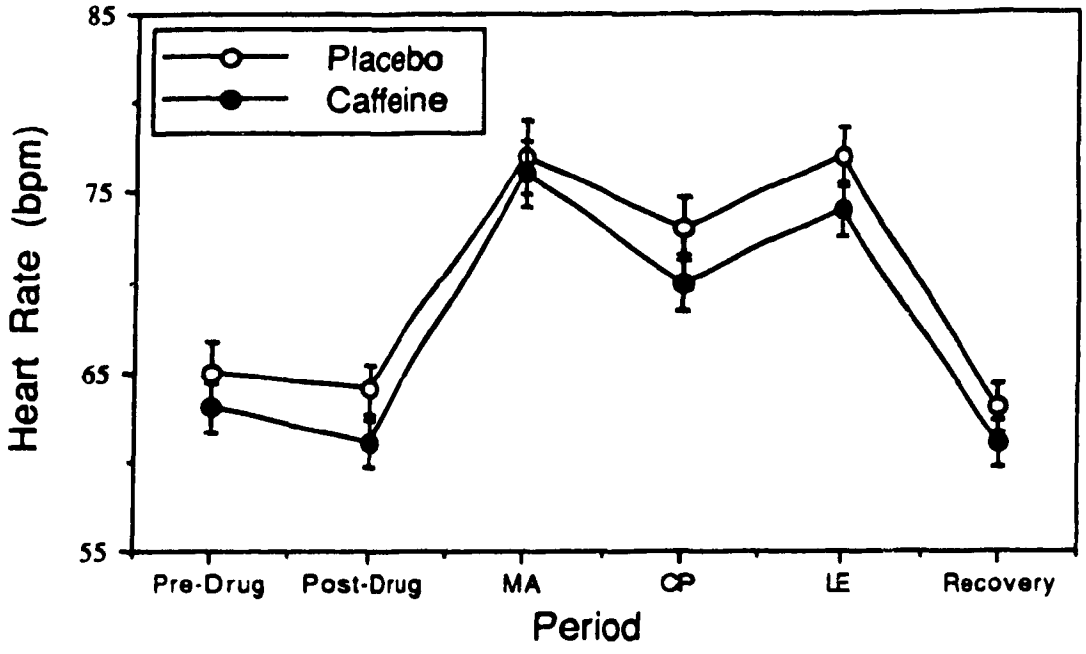
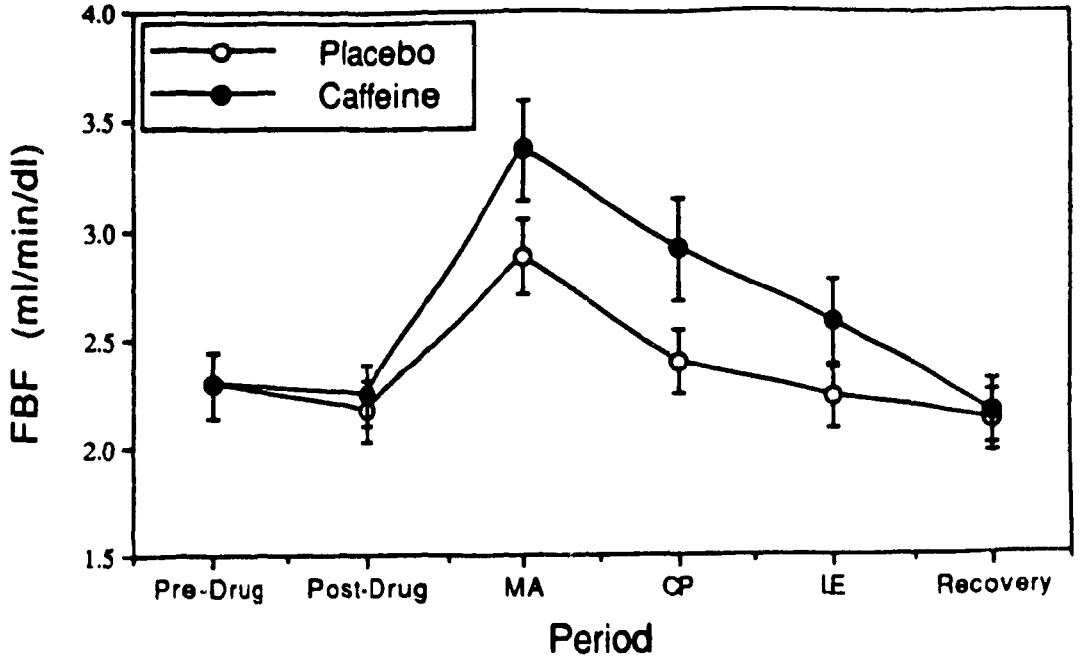
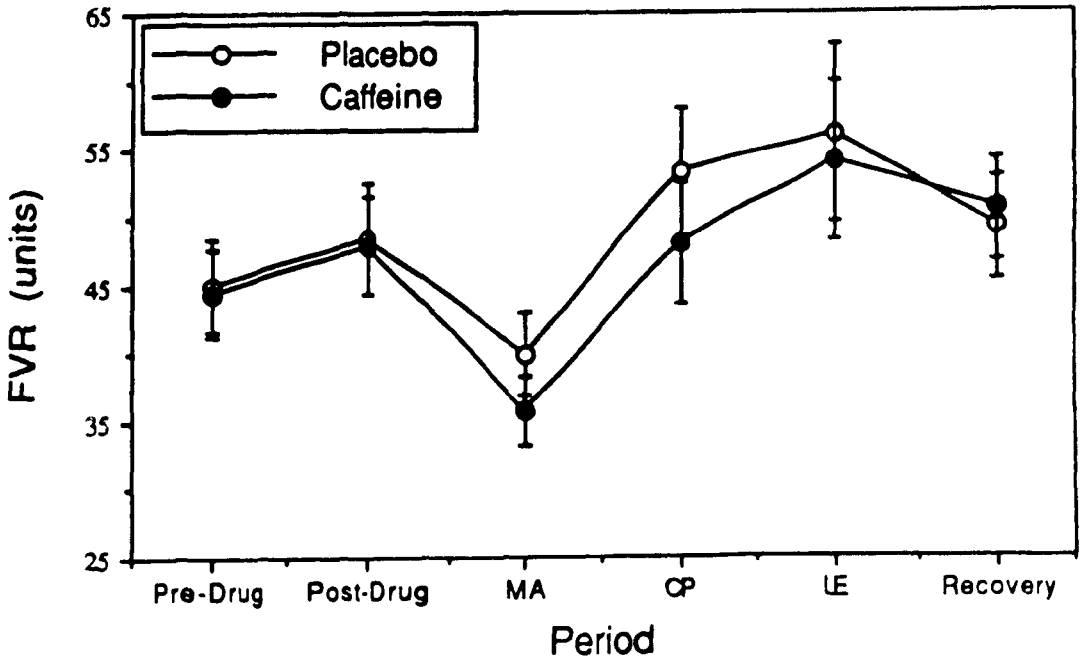
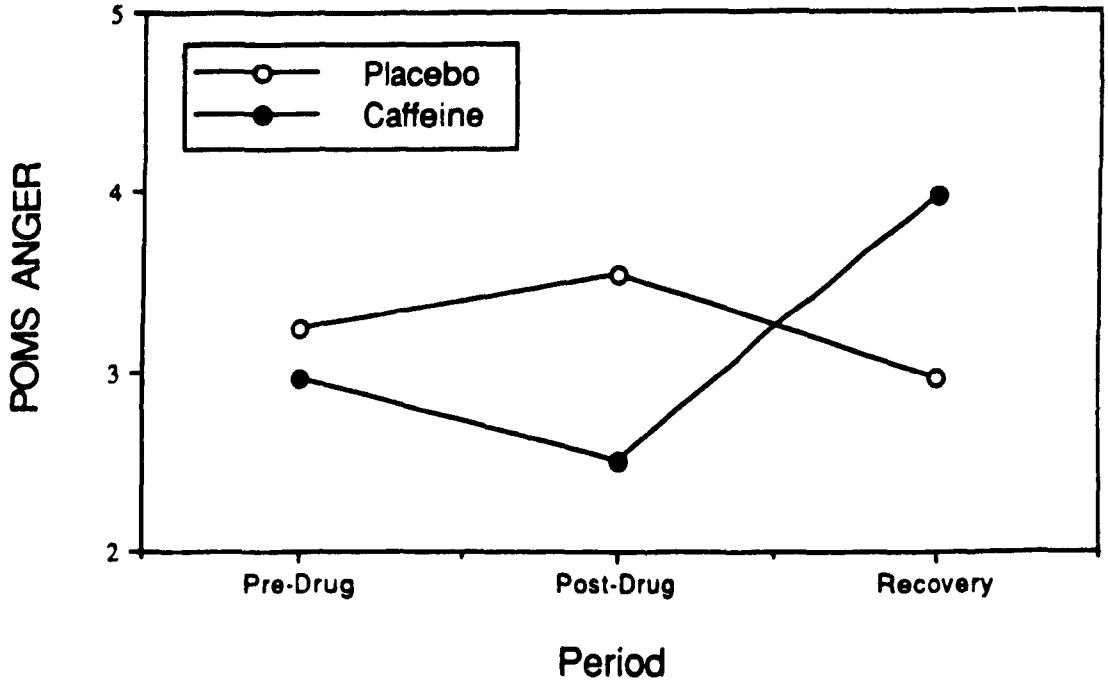
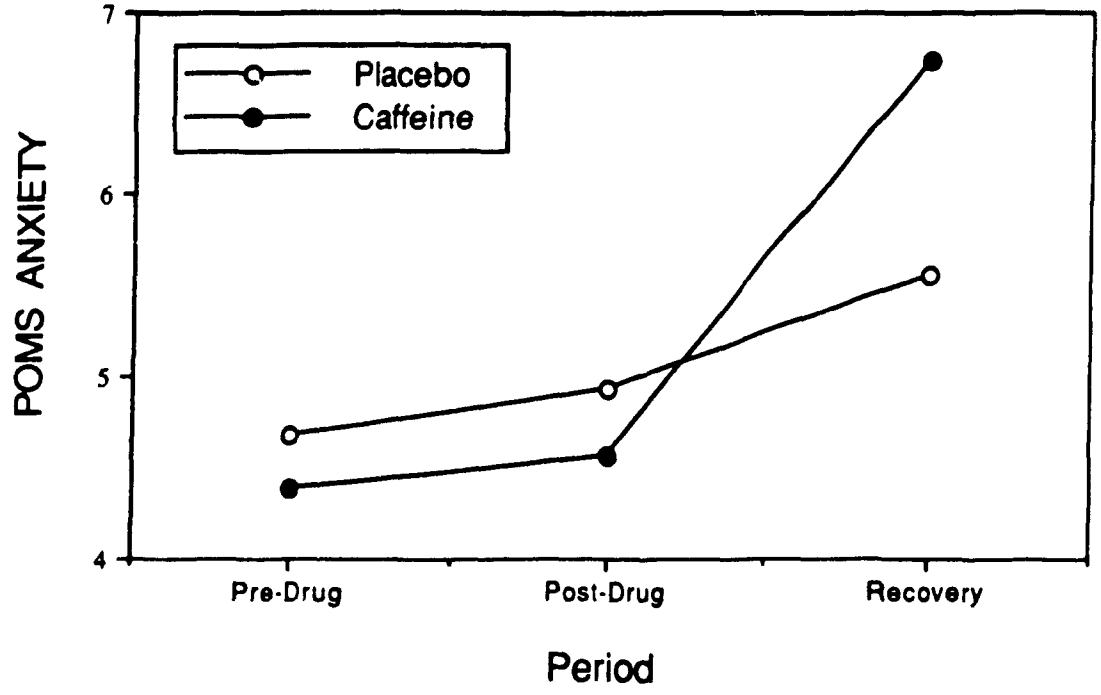
70
60
DBP (mmHg)
Placebo
Caffeine
Pre-Drug
Post-Drug
MA
OP
LE
Recovery
Period


85
75
65
55
Heart Rate (bpm)
Placebo
Caffeine
Pre-Drug
Post-Drug
MA
OP
LE
Recovery
Period


Placebo
Caffeine
FBF (ml/min/dl)
4.0
3.5
3.0
2.5
2.0
1.5
Pre-Drug
Post-Drug
MA
CP
LE
Recovery
Period


Placebo
Caffeine
FVR (units)
65
55
45
35
25
Pre-Drug
Post-Drug
MA
CP
LE
Recovery
Period


Placebo
Caffeine
POMS ANGER
5
4
3
2
Pre-Drug
Post-Drug
Recovery
Period


Placebo
Caffeine
POMS ANXIETY
7
6
5
4
Pre-Drug
Post-Drug
Recovery
Period

In the preceding studies evidence was obtained to support the notion that caffeine and laboratory stressors combine to produce additive increases in blood pressure in regular caffeine consumers. Further, despite consistent additive effects on pressor responses to a variety of different stimuli, assessment of additional indices of cardiovascular activity revealed that caffeine may potentiate cardiovascular responses to stressors which elicit significant beta-adrenergic sympathetic activity. This finding provides insight into one potential mechanism whereby caffeine consumption may promote structural or physiological adaptations in the peripheral vasculature leading to sustained elevations in blood pressure. The final paper "Cardiovascular responses to occupational stress and caffeine in telemarketing employees" provides an assessment of the effects of caffeine on cardiovascular responses during performance of a challenging occupational activity (telephone sales). Because the telephone sales staff were remunerated on the basis of total weekly sales, and since these individuals were accustomed to daily caffeine consumption at work, it was believed that this environment would provide an ecologically-valid assessment of the effects of caffeine and psychosocial stress on regular caffeine consumers. As well, this study presented an ideal opportunity to assess the influence of the Type A behavior pattern on cardiovascular responses to stress and caffeine,

given the competitive and interpersonal nature of the naturalistic stressor of telephone sales.

Cardiovascular Responses to Occupational Stress and Caffeine in Telemarketing Employees

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Cardiovascular responses to the combination of caffeine and a challenging occupational activity were examined using a within subject double-blind design. Seventeen female and 11 male telemarketing employees received drinks that did and did not contain 250 mg of caffeine on two consecutive days with order of presentation counterbalanced across subjects. Repeated measurements of systolic and diastolic blood pressure, heart rate, and digital blood volume pulse were obtained during a pre-drug resting baseline and a post drug working period on each day. Repeated measures analyses of variance revealed significant main effects of Period on all measures of cardiovascular activity, indicating that occupational demands elicited significant cardiovascular adjustments. Only systolic blood pressure revealed a significant Drug × Period effect, indicating that responses were significantly greater on the caffeine versus placebo day. The changes in diastolic blood pressure and heart rate, although not significant, were consistent in direction with the results from previous laboratory studies. There were no significant differences between males and females in cardiovascular response to the combination of stress and caffeine.

INTRODUCTION

Caffeine is one of the most widely consumed drugs in North America. The results of a survey published by Bonham and Leaverton in 1979 (1) suggested that 80% of U.S. adults over 20 years of age drink coffee on a regular basis. Moreover, caffeine is obtained from a variety of other sources including tea, cocoa, chocolate, many soft drinks, and a number of medications.

Although evidence of caffeine's influence on resting cardiovascular activity has existed for many years (2), it is only within the past few years that investigators have begun to study the effects of caffeine on cardiovascular adjustments produced by stress, and their relationship to cardiovascular disease. For example, Henry and Stephens (3) reported that when mice living in a competitive social environment were administered coffee instead of normal drinking water, they exhibited an intensification of stress-related increases in blood pressure, adrenal weight, corticosterone, and plasma renin. As well, there were significant increases in morbidity and mortality rates among mice receiving coffee. In humans, caffeine and short-term stress have been shown to produce cumulative increases in both systolic (SBP) and diastolic blood pressure (DBP) (4–6), as well as cumulative and synergistic effects on a variety of other indices of cardiovascular activity (7–9).

While there are a number of reports of caffeine's ability to exacerbate cardiovascular responses to stress in humans

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there are several limitations to these studies One limitation is the restricted range and non-naturalistic nature of psychological stressors which have been used In fact, with only one exception (10), all of the previous studies used laboratory stressors, such as challenging mental arithmetic tasks Pincomb et al (10) published the first report of the effects of caffeine on cardiovascular responses to a naturalistic stressor In this study, male medical students were tested for the effects of caffeine on cardiovascular activity during a period of low stress (a week with no exams) and high stress (final exam week) The results indicated that exam stress alone produced increases in SBP and heart rate (HR), but not DBP Caffeine alone produced significant increases in both SBP and DBP and a decrease in HR Finally, consistent with the results of previous laboratory studies, the increases in SBP produced by caffeine combined in an additive fashion with the increases produced by stress Although laudable in its use of naturalistic testing, one problem with this study is that the experimental design did not allow measurement of cardiovascular activity concomitant with performance of a stressful task In fact, all measurements were obtained while subjects were "quietly studying course work " Although studying of course work during the final exam week was considered a stressful task compared to studying at other times, the degree to which the results obtained in this study are comparable to those of laboratory studies is unclear

A second limitation of the research on cardiovascular responses to stress and caffeine relates to the exclusion of females as subjects Since it remains to be seen whether women respond to the combination of stress and caffeine in a manner similar to men, the present study included both males and females

In summary, the present study was designed to examine the cardiovascular responses of men and women to the combination of caffeine and a challenging, real-life occupational activity Measurements of blood pressure, HR, and blood volume pulse were obtained before and during work in a group of telemarketing employees Administration of either caffeine or a placebo followed a pre-work resting baseline period The subject then began work as normal Measurements of cardiovascular activity were obtained again 45 min later while the subject was at work Since all employees were paid on the basis of total sales, it was expected that the task of telephone sales would elicit significant cardiovascular responses. Although a post-drug resting baseline period would have been interesting in order to evaluate the nature of caffeine-stress interaction effects, such a period was not feasible given the constraints of the naturalistic setting. Therefore, the main question this study addressed was not whether caffeine interacts with stress in an additive or synergistic fashion, but whether caffeine enhances cardiovascular responses to a naturalistic stressor in males and females who are regular users of caffeine

METHODS

Subjects

Twenty-eight healthy normotensive subjects were recruited from five telemarketing companies in the Montreal area Descriptive characteristics of the final sample of 17 females and 11 males are shown in Table 1 Each subject received $25 00 for participating in the study

Apparatus

Measurements of SBP DBP and HR were obtained using a portable Lumiscope (model 1070) digital sphygmomanometer. According to the manufacturer the device is accurate within ±3 mm Hg for blood pressure and ±3 bpm for HR. The cuff was placed on the subject's non-dominant arm. Digital blood volume pulse (DBVP) measurements were obtained using a portable Thought Technology biofeedback module (HR/BVP100T). The photoplethysmographic transducer was attached to the second finger of the subject's dominant hand.

Procedure

All subjects were tested on two consecutive working days. Testing occurred at the beginning of the subject's working day in order to enhance adherence to a variety of restrictions including fasting for 6 hr and avoidance of caffeine, alcohol, nicotine, and non-prescription drugs for 12 hr prior to the experiment.

Upon arrival at work the subject was familiarized with the experimental procedures and informed consent was obtained. Once the blood pressure cuff and the finger photoplethysmograph were attached, two casual blood pressure readings were obtained. An average resting SBP of 140 mm Hg or greater and/or DBP of 90 mm Hg or greater was considered grounds for discontinuation. However, no subject exhibited such a resting blood pressure level.

While the subjects sat at their desks and engaged in casual conversation with the experimenter, baseline measurements were taken for a 10-min period. The subjects were encouraged to carry on a casual conversation during the pre-work resting baseline in order to control for the effects of speech on cardiovascular activity during work. A total of five readings of SBP, DBP, and HR were recorded at 2-min intervals. DBVP readings were obtained every 30 sec during the odd minutes for a total of 10 readings. Following the baseline period, the subject received grapefruit juice that either contained or did not contain 250 mg of caffeine. The caffeine was administered in a double-blind fashion, with order of presentation counterbalanced across subjects. Grapefruit juice was chosen based on previous evidence that it masks the somewhat bitter taste of caffeine (11). The subjects were then instructed to begin work as they would normally. After allowing 45 min for the absorption of caffeine into the bloodstream, the experimenter returned to each subject's office and resumed physiological recording while the subject continued to work. All measurements were obtained for 10 min according to the same schedule used during the resting baseline period.

After the physiological measures were obtained during work, the subjects rated the preceding period in terms of difficulty, the subjective level of arousal, and stressfulness of the job using visual analog scales. As well, they completed a questionnaire between the first and second sessions. The questionnaire requested information concerning each subject's medical history, consumption of caffeinated beverages and cigarette smoking, and included the Jenkins Activity Survey (JAS) Form C (12).

Testing on the second day was identical to the first with the exception that the subject received whatever he or she did not get (placebo or caffeine) the previous day.

TABLE 1. Descriptive Characteristics of Subjects

Variable	Mean (SD)	
	Males (N = 11)	Females (N = 17)
Age (years)	26 (12)	25 (9)
Height (cm)	175 (8)	163 (5)
Weight (kg)	67 (9)	63 (16)
Caffeine use (mg/day)	271 (188)	300 (267)
Smoking[a] (cig/day)	21 (14)	22 (11)
Telemarketing experience (months)	19 (22)	8 (14)

[a] Values are for 10 male and 8 female smokers.

Data Reduction and Analysis

The recorded values of SBP, DBP, HR, and DBVP were averaged to obtain mean resting and working levels for both caffeine and placebo days. The experimental design for the analysis of the combined effects of stress and caffeine included the within-subject factor of Drug with two levels (caffeine/placebo), the within subject factor of Period with two levels (resting/working), and the between subject factor of Order with two levels (caffeine on day 1/placebo on day 2, and vice-versa). Therefore, for each cardiovascular measure a 2 Drug (Condition) ×

2 Period × 2 Order repeated-measures analysis of variance (ANOVA) was conducted. In addition, a series of ANOVAs was conducted to assess the effects of sex on change in each of the cardiovascular response measures on caffeine and placebo days. Change scores were calculated by subtracting mean resting from working values on each day, and 2 Sex (male, female) × 2 Drug Condition (change on caffeine day, change on placebo day) ANOVAs were conducted. Finally, partial correlations controlling for possible age and sex effects were computed between the self-report ratings, JAS Type A score, and changes in cardiovascular activity on each day.

RESULTS AND DISCUSSION

Mean levels of cardiovascular activity on the placebo and caffeine days are displayed in Table 2.

Results of the repeated measures ANOVAs used to analyze the effects of caffeine, stress, and order of drug presentation are presented in Table 3.

Significant Period main effects were observed for all measures, indicating that occupational demands elicited significant cardiovascular adjustments. Specifically, as can be seen in Table 2, elevations in SBP, DBP, and HR, and decreases in DBVP were observed in response to occupational activity on both placebo and caffeine days. Although not surprising, there are, in fact, very few controlled demonstrations of the impact of real-life stressful events on cardiovascular activity (13–15), and this is one of the main contributions of the present study.

TABLE 2. Means and Standard Errors of Cardiovascular Variables at Different Points in the Study

		SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	DBVP[a] (units)
Placebo day	Resting	108.7 (2.0)	72.1 (2.2)	74.1 (2.1)	57.4 (2.5)
	Working	111.6 (2.2)	78.0 (1.6)	78.6 (2.4)	46.6 (2.2)
	Change	2.9 (1.8)	5.9 (1.8)*	4.5 (1.4)*	−10.8 (3.2)*
Caffeine day	Resting	107.3 (2.0)	71.6 (1.9)	73.3 (2.6)	57.3 (2.6)
	Working	117.8 (1.8)	80.4 (1.8)	76.8 (1.9)	48.1 (2.8)
	Change	10.5 (1.5)*	8.8 (1.6)*	3.5 (1.6)*	−9.2 (2.9)*

[a] Low values are associated with high arousal.
* Significantly greater (or, in the case of DBVP, lower) than 0, $p < 0.05$.

TABLE 3. Effects of Caffeine on Cardiovascular Activity at Rest and during Work

Source	SBP	DBP	HR	DBVP
Order	1.56	0.71	0.43	4.82*
Drug	7.55*	0.76	0.52	0.16
Period	28.53**	29.72**	13.82**	17.33**
Order × Drug	1.63	0.77	1.17	0.00
Order × Period	0.06	0.26	1.58	1.25
Drug × Period	11.47**	1.84	0.27	0.16
Order × Drug × Period	0.53	0.40	0.56	0.15

* $p < 0.05$
** $p < 0.01$
$f(1,36)$

Furthermore, most studies have used uncommon real-life stressors such as dental procedures (14) and parachuting (15).

As can be seen in Table 3 only SBP displayed a significant Drug × Period interaction, indicating that SBP responses were significantly greater on the caffeine versus placebo day. The increment in SBP response produced by the addition of caffeine to stress was just over 7 mm Hg, which is identical to the additive effect of caffeine on SBP observed in previous laboratory studies of both naive and regular users of caffeine (5, 8). As can be seen in Table 2, the observed changes in DBP and HR, although not significant, were consistent in direction with the results from previous laboratory investigations (5, 6, 9). That is, subjects displayed larger DBP elevations on the caffeine versus placebo day, while their HR responses were slightly smaller on the caffeine day. It is possible that the preservation of naturalistic conditions prevented the equalization of occupational stress on the two days, and stronger drug effects were masked by variations in stressor intensity. Although there were no significant differences between the placebo and caffeine days in self-reported difficulty of work, stress of work, or subjective levels of arousal, individuals often reported higher values of these variables on one of the two days. Regardless, the present findings are consistent in two important respects with results obtained by Pincomb et al. (10) in their study on the effects of caffeine under naturalistic conditions. First, caffeine and stress combined to produce cumulative increases in SBP. Second, a drug effect was observed despite the fact that subjects included regular users of caffeine, and responsivity to caffeine was measured after only 12 hr abstinence. This result is consistent with evidence that many regular users of caffeine do not exhibit tolerance to its cardiovascular effects at rest (16, 17).[1]

The results from the four 2 Drug Condition × 2 Sex ANOVAs of change scores revealed no significant interaction effects, indicating no differences in response between males and females to the combination of stress and caffeine. As would be expected given the results of the previous ANOVAs, the SBP analysis revealed a significant main effect of Drug ($F(1,26)=10.70$, $p < 0.01$). Since this study represents the first report of cardiovascular responses to stress and caffeine in women, these results are important in suggesting that previous findings may generalize to the female population.

The partial correlations between self-ratings of work stress, work difficulty, arousal, and changes in cardiovascular activity are presented in Table 4. As can be seen in Table 4, significant correlations were observed between several ratings and cardiovascular response to work on the placebo day. Specifically, HR response was significantly correlated with ratings of job difficulty and stressfulness, while SBP response was significantly correlated with subjective arousal and marginally correlated with perceived job difficulty. Interestingly, ratings of occupational

[1] DBVP revealed a significant main effect of Order. Inspection of the data revealed that subjects who received Order 1 (caffeine/placebo) had higher resting baselines on both days than subjects who received Order 2 (placebo/caffeine). It is perhaps due to this higher initial baseline that these subjects showed greater reductions in DBVP under stress.

TABLE 4 Partial Correlations between Self-ratings and Changes in Cardiovascular Measures

Variable	Placebo day				Caffeine day			
	SBP	DBP	HR	DBVP	SBP	DBP	HR	DBVP
Difficulty rating	0 36*	0 04	0 46**	0 21	0 07	−0 04	−0 03	−0 18
Arousal rating	0 40**	0 04	0 32	0 15	0 02	−0 10	−0 08	0 16
Stress rating	0 22	0 24	0 46**	−0 03	−0 02	−0 02	−0 02	0 05
Type A score	−0 03	0 17	−0 12	0 21	0 50**	0 14	0 59**	0 49**

$p < 0.10$ ** $p < 0.05$ two-tailed

demands were not significantly correlated with cardiovascular response to work on the caffeine day This may have been due to individual differences in sensitivity to the effects of caffeine, which masked relationships with the subjective state ratings Perhaps of greater interest, JAS Type A score and SBP, HR, and DBVP responses to the combination of stress and caffeine, but not stress alone, were significantly correlated The significant positive correlations for both SBP and HR suggest that Type A individuals responded with greater cardiac responses to the combination of stress and caffeine The seemingly counterintuitive positive correlation between Type A score and DBVP response was most likely a product of this elevated cardiac output The absence of a relationship between Type A and cardiovascular responsivity to stress and caffeine in previous investigations (6, 8) may have been due to the reliance on a laboratory stressor. Furthermore, it seems reasonable to suggest that the interpersonal, competitive nature of the naturalistic stressor task used in the present study—telephone sales—would be more likely to elicit Type A behavior than the mental arithmetic task used by Lane and Williams (6, 8)

In summary, the results of the present investigation indicate that caffeine may enhance cardiovascular responses to a naturalistic stressor Moreover, this conclusion appears valid for both males and females who regularly consume caffeine, and may be most noticeable among Type As

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General Conclusions and Directions for Future Research

Because the research in this thesis is presented as a compilation of articles, conclusions derived from the results obtained in each study are provided in their respective discussion sections. Therefore, in the following pages a brief synthesis of the findings from the three studies will be presented in order to arrive at a set of general conclusions. In addition, issues which remain to be addressed in the caffeine-stress literature will be presented as directions for future research.

One consistent finding in the studies presented is that the pressor effects of caffeine and psychological stress combine to produce elevated levels of blood pressure in regular caffeine consumers. While this appears to be an additive, as opposed to synergistic, relationship across different types of stressors, the increases in blood pressure observed in response to the combination of these stimuli deserve serious attention. Pincomb and colleagues (Pincomb, Lovallo, Passey, Brackett, & Wilson, 1987; Pincomb, Lovallo, Passey, & Wilson, 1988) observed that the combination of caffeine and stress produced a significant increase in blood pressure, with peak systolic blood pressure levels reaching into the borderline hypertensive range in some individuals. They noted that such effects could be of clinical significance if they reflect responses

in everyday life. While it remains to be determined whether frequent exposure to elevated blood pressure levels leads to pathophysiological consequences, the observation that regular caffeine consumers exhibit higher blood pressure levels in response to occupational stress and caffeine (France & Ditto, 1989) suggests that there is ample opportunity for such a process to occur. Moreover, epidemiological investigations indicate that an increase in blood pressure of 10 mmHg, which is well within the range produced by the combination of stress and caffeine, is associated with a 30% increase in risk for cardiovascular disease (Page, 1983). Although the epidemiological findings are based on resting levels of blood pressure and therefore may not hold for measures of blood pressure responsivity to chronic stress and caffeine, they nonetheless highlight the importance of even small changes in blood pressure level. Finally, in addition to caffeine's ability to produce cumulative blood pressure responses to different stressors, caffeine has been shown to potentiate other physiological responses to stress.

In the second study presented (France & Ditto, 1990), caffeine potentiated heart rate and forearm blood flow responses to a mental arithmetic stressor. These findings corroborate those of previous investigations in which caffeine potentiated heart rate (McDougall, Musante, Castillo, & Acevedo, 1988; Pincomb et al., 1988; Strickland,

Myers, & Lahey, 1989) and forearm blood flow (Lane & Williams, 1985; 1987) responses to active coping stressors. Moreover, this study suggested that the synergistic effects of caffeine may involve beta-adrenergic sympathetic activity, given that 1) potentiation was observed on measures which reflect beta-adrenergic activity, and 2) this pattern of effects was observed for mental arithmetic, which is known to stimulate beta-adrenergic activity, but not for cold pressor or isometric exercise stressors.

Interestingly, a pattern of beta-adrenergic sympathetic activity enhancement was not observed in the first study presented, which also used a mental arithmetic task (France & Ditto, 1988). In this study caffeine and stress produced additive increases in diastolic blood pressure and digital blood volume pulse responses, but failed to produce either additive or synergistic effects on measures of cardiac sympathetic activity (i.e., heart rate and pulse transit time). Based on previous evidence of the importance of task involvement in determining cardiac stimulation effects, this failure was attributed to the fact that the mental arithmetic stressor may not have been sufficiently demanding. Obrist and colleagues (1978) reported that a shock-avoidance reaction-time task elicited significant cardiac sympathetic activity when the task was difficult, but not when it was easy or impossible. These results were explained on the basis of degree of subject involvement in

the task. That is, the difficult task required effortful, active coping; the easy task was perceived to require little significant effort; and the impossible task was perceived to be beyond control. In sum, the degree to which a task requires effortful, active involvement is an important determinant of beta-adrenergic sympathetic reactivity. Therefore, the failure to observe a caffeine-induced potentiation of cardiovascular activity in the first study may have been due to the use of a combination of easy, difficult, and impossible math problems, which attenuated subject involvement in the task and consequent beta-adrenergic stimulation. This hypothesis is supported by the fact that the mental arithmetic task used in the first study elicited an average heart rate increase of only 5 bpm in the no-caffeine condition (France & Ditto, 1988), while the mental arithmetic task used in the subsequent study elicited an average increase of 13 bpm on the no-caffeine day (France & Ditto, 1990).

The combined results from the first and second studies lead to a potentially important insight into caffeine's effects on cardiovascular responsivity to stress. These results suggest that when the prevailing stimulus conditions elicit significant beta-adrenergic sympathetic activity (e.g., effortful, active coping stressors), caffeine may potentiate responses in cardiovascular measures which reflect beta-adrenergic activity. In contrast, caffeine does

not potentiate cardiovascular responses to passive coping stressors or active stressors which fail to evoke significant task involvement, presumably because there is insufficient stimulation of beta-adrenergic activity.

If caffeine enhances beta-adrenergic sympathetic activity, what mechanism(s) might account for this effect? There is some evidence that such an effect may be related to caffeine's influence on catecholamine activity. A number of studies have indicated that caffeine can produce significant increases in plasma epinephrine and norepinephrine levels at rest (Lane, Adcock, Williams, & Kuhn, 1990; Pincomb et al., 1988; Robertson et al., 1978; Smits, Pieters, & Thien, 1986; Smits, Thien, & van't Laar, 1985). While the cardiovascular effects of caffeine at rest may not be dependent on plasma catecholamine levels, given that significant changes in resting blood pressure and heart rate responses to caffeine have been observed in adrenalectomized patients (Smits et al., 1986), caffeine-induced plasma catecholamine elevations may have an impact on stress-induced sympathetic stimulation. To date, two studies have reported that caffeine-induced increases in catecholamine levels combine in an additive and/or synergistic fashion with stress-induced increases (Lane, Adcock, Williams, & Kuhn, 1990; Pincomb et al., 1988). Pincomb and colleagues (1988) observed that caffeine and an appetitive reaction-time stressor combined to produce additive increases in plasma

norepinephrine levels. Plasma epinephrine levels were not obtained. Caffeine also potentiated heart rate, stroke volume, and hence, cardiac output, responses to the stressor. In addition to additive increases in plasma norepinephrine levels in response to caffeine and a mental arithmetic task, Lane et al. (1990) observed that caffeine potentiated stress-related increases in plasma epinephrine levels. There were no significant correlations between neuroendocrine measures and any of the cardiovascular measures obtained. While cardiovascular measures were restricted to blood pressure and heart responses, this study used the same mental arithmetic task which had previously been shown to potentiate forearm blood flow responses following caffeine consumption (Lane & Williams, 1985; 1987). In sum, investigators have reported both enhancement of catecholamine activity and potentiation of cardiovascular activity during active coping stressors. Unfortunately, assessment of the relationship between neuroendocrine responsivity and potentiation of beta-adrenergic activity will require the simultaneous assessment of catecholamine activity and a wider range of cardiovascular responses than has been reported to date. In addition, it should be noted that the relationship between caffeine-induced increases in catecholamine secretion and potentiation of stress-induced increases in beta-adrenergic activity may not be adequately addressed by correlational analyses, since plasma

catecholamine levels may not accurately reflect sympathetic synaptic activity (Folkow, DiBona, Hjemdahl, Toren, & Wallin, 1983).

One related possibility is that caffeine's potentiation of cardiovascular activity is not due to elevated plasma catecholamine levels, but to direct effects of caffeine at adrenergic synapses. In line with this hypothesis, caffeine has been shown to enhance the effects of catecholamines on beta-adrenergically mediated cardiac stimulation and smooth muscle relaxation (Kalsner, 1971; Kalsner, Frew, & Smith, 1975), which could account for both heart rate and forearm blood flow potentiation effects. Kalsner and colleagues (1975) indicated that the potentiation of beta-adrenergically mediated responses were attributable to an inhibition of catecholamine uptake and a consequent increase in catecholamine concentration at receptor sites. Therefore, future studies on the mechanism(s) by which caffeine potentiates cardiovascular responsivity to stress should focus on activity at adrenergic receptor sites. In this regard, a critical test of the hypothesis that caffeine potentiates cardiovascular responsivity to stress via enhancement of beta-adrenergic receptor activity could involve the administration of beta-adrenergic receptor blockers. Such an investigation could provide important insight into the role of beta-adrenergic activity in the cardiovascular effects of caffeine and stress, especially

given the availability of drugs which preferentially block cardiac beta-1 adrenergic receptors (e.g., metoprolol) as well as drugs which produce non-selective beta-adrenergic receptor blockade (e.g., propranolol). Likewise, the potential role of alpha-adrenergic receptor activity in mediating cardiovascular responses to caffeine at rest and during passive coping stressors could be investigated using alpha-adrenergic blocking agents.

In addition to potential direct effects of caffeine on adrenergic receptor activity, caffeine may indirectly influence adrenergic receptor activity via stimulation of plasma cortisol levels. Cortisol is capable of exerting diverse effects on catecholaminergic activity, including enhanced synthesis, inhibition of degradation, and increased receptor sensitivity (Jazayeri & Meyer, 1988; Kvetnansky, 1980). Therefore, since caffeine has been shown to produce both additive and synergistic increases in plasma cortisol responses to stress (Lane et al., 1990; Pincomb et al., 1987; 1988), it is possible that caffeine enhances beta-adrenergic activity via cortisol stimulation. Further, Lovallo and colleagues (1989) observed that caffeine produced significantly greater increases in cortisol plasma responses to the combination of caffeine and stress in hypertension-prone men. Therefore, cortisol stimulation may be an important mechanism in determining cardiovascular responses to stress and caffeine, and may be of particular

concern in individuals who are predisposed to hypertension.

Regardless of the mechanism(s) ultimately responsible for the observed potentiation of beta-adrenergic sympathetic responses to active coping stressors, this finding may be of clinical significance. Repeated, exaggerated beta-adrenergic responsivity to active coping stressors has been related to increases in peripheral resistance and sustained elevations in blood pressure. Obrist (1981) hypothesized that, in certain individuals, active coping stressors elicit metabolically-exaggerated increases in cardiac output and may provoke subsequent physiological adjustments such as intrinsic autoregulatory mechanisms (Coleman, Granger, & Guyton, 1971) and possibly structural changes in the arterioles (Folkow, 1987). Such physiological adjustments could, in turn, lead to sustained elevations in blood pressure. While Obrist (1981) focused primarily on exaggerated cardiovascular responsivity to active coping stressors in offspring of hypertensives, the present findings suggest that other factors, such as caffeine, may elicit exaggerated cardiovascular responsivity to stress and as such may contribute to the pathogenic process of hypertension development.

Although the preceding studies have focused on cardiovascular responses in attempt to understand the potential pathogenic consequences of caffeine-stress interactions, it is also possible that caffeine may combine

with psychological stress to enhance risk for cardiovascular disease by influencing kidney functioning. Renal activity exerts significant control over blood pressure levels through its influence on vascular resistance and blood volume levels. Both caffeine and psychological stress have been shown to independently affect renal activity. While caffeine is usually described as a diuretic, there have also been contrary findings suggesting that caffeine may increase sodium and potassium excretion rates but not urine output in healthy males (Massey & Berg, 1985). Psychological stimuli also influence renal functioning since alpha-adrenergic sympathetic activity has a direct impact on sodium reabsorption (Zambraski, DiBona, & Kaloyanides, 1976) and beta-adrenergic activity can alter sodium balance and vascular resistance through its influence on renin release (Zanchetti, Stella, Leonetti, Morganti, & Terzoli, 1976). In an initial investigation of caffeine and stress effects on renal functioning, Pincomb and colleagues (1987) collected urine samples following a stress protocol on both a caffeine and a placebo day. The main finding was that caffeine exerted a natriuretic, rather than a diuretic, effect since it increased sodium and potassium clearance and decreased free water clearance. Additional analyses revealed that individuals who demonstrated high heart rate reactivity to a previously administered cold pressor task showed decreased glomerular, sodium, and potassium filtration rates

following the protocol, and that caffeine tended to further decrease glomerular and sodium filtration rates in these individuals. Finally, there were no significant differences in renal functioning in individuals at high-risk versus individuals at low-risk for hypertension as defined by a parental history of hypertension and high resting blood pressure level. However, the restricted sample of high-risk men (n=9) may have limited the generalizability of these findings. This possibility is supported by previous evidence of significantly larger decreases in sodium excretion rates in individuals genetically at-risk for hypertension following exposure to an active coping stressor (Light, Koepke, Obrist, & Willis, 1983). In any case, these initial investigations support the notion that an ultimate understanding of the effects of caffeine and psychological stress on cardiovascular activity will require a careful consideration of the role of changes in renal activity.

One potentially important consideration for future research on caffeine-stress interactions is the ecological validity of the stressors presented. The results of the third study presented (France & Ditto, 1989) suggest that responses to caffeine and psychological stress observed in the laboratory studies may generalize to real-life responses of regular caffeine consumers. Moreover, in contrast to previous laboratory studies which did not find an increase in responsivity to stress and caffeine in Type A

individuals, Type A individuals responded with greater cardiac responses to the combination of caffeine and a naturalistic occupational stressor. In revealing that cardiovascular responsivity may be modulated by individual characteristics and environmental circumstances which may not be adequately replicated in the laboratory (e.g., occupational demands), these results highlight the need to verify our findings under naturalistic conditions. Therefore, beyond the benefit of verifying the generalizability of laboratory findings, naturalistic testing has the added advantage of presenting a psychosocial environment which may elicit unique physical and psychological responses. Another important characteristic of the field study is that observations are obtained in the context of natural patterns of exposure to the stimuli of interest. This characteristic may be particularly important for future research on the combined effects of caffeine, smoking, and psychological stress on cardiovascular activity. Because individual patterns of exposure to these stimuli may differ along varying dimensions (dose, frequency, synchronicity of exposure), attempts to precisely mimic these effects under laboratory conditions would require unduly complex designs and would be of dubious generalizability to the normal experience of smokers who consume caffeine. Finally, naturalistic paradigms may provide an ideal method of assessing psychological responses

to the combination of stress and caffeine.

Possibly due to the existing tendency to focus on laboratory stressors, there is presently limited evidence of caffeine's ability to influence subjective, emotional responses to psychological stress. Henry and Stephens (1980) provided anecdotal evidence that caffeine increased aggressive behavior in mice living under a stressful psychosocial environment. Lane and Williams (1987) indicated that caffeine enhanced subjective fear ratings following a mental arithmetic stressor. Finally, in the second study presented (France & Ditto, 1990), subjects reported significantly higher levels of anxiety and anger following a stress protocol on the caffeine day versus the placebo day. While these findings are little more than suggestive leads for further inquiry, they are particularly compelling given that the stressors used in the human laboratory studies were not chosen specifically for their ability to elicit emotional responsivity. If caffeine is capable of exacerbating prevailing emotional states, a significantly larger effect may be observed in response to stressors chosen specifically for their ability to elicit emotional reactivity. Given the practical and ethical difficulties inherent in any attempt to elicit significant emotional responses in the laboratory, the use of naturalistic testing methods may be particularly helpful in this regard. For example, the observed relationship between Type A score and

cardiovascular response to caffeine during occupational stress (France & Ditto, 1989), but not during laboratory stressors (Greenstadt, Yang, & Shapiro, 1988; Lane & Williams, 1985; 1987), may have been related to the greater likelihood of observing Type A behavior characteristics (e.g., interpersonal competitiveness, hostility) under naturalistic testing circumstances. Although speculative, this example highlights the potential for real life stressors to elicit more intense, genuine emotional responses than are likely to be observed in the laboratory. Consistent with an emphasis on the importance of emotional responses to daily life stressors, a recent study reported that anger expression mediated the impact of occupational stress on the development of hypertension (Cottington, Matthews, Talbott, & Kuller, 1986). Future research on the effects of caffeine on emotional responsivity will be important in at least two respects. First, this information will allow an assessment of the possibility that caffeine's effects on sympathetic activity may, in part, be mediated by its impact on central nervous system activity. Second, given the hypothesized role of anger in mediating risk for both hypertension and heart disease (Diamond, 1982; Siegel, 1984), caffeine's ability to exacerbate negative emotional responsivity to stress would provide further support for the role of caffeine and psychological stress as contributors to the development of cardiovascular disease.

In sum, research on caffeine-stress interactions is still in its infancy. Researchers are only beginning to understand the various cardiovascular, neuroendocrine, renal, and psychological responses to these stimuli. Further studies will be instrumental in addressing the relationships among the various physiological and psychological responses, and in elucidating the relationships between these effects and risk for cardiovascular disease.

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