Effects of Temperature and Drugs on Frog Heart

<table>
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<th>Mechanism</th>
<th>Effect on heart rate</th>
<th>Effect on contractility</th>
<th>Clinical applications</th>
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<tr>
<td>Digoxin (Digitalis)</td>
<td>Decreases heart rate</td>
<td>Increases</td>
<td>Used to regulate arrhythmias in atrial fibrillation or flutter</td>
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<tr>
<td>Atropine</td>
<td>Increase</td>
<td>Increase</td>
<td>Dilates pupils, used to treat bradycardia, 2⁴⁵ &amp; 3⁴⁵ degree heart block, cardiac arrest</td>
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<tr>
<td>Caffeine</td>
<td>Increase</td>
<td>Increase</td>
<td>Treat apnea, bronchopulmonary dysplasia, &amp; fecal incontinence</td>
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<td>Acetylcholine</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Parasympathetic response</td>
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<tr>
<td>Epinephrine</td>
<td>Increase</td>
<td>Increase</td>
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<tr>
<td>Nicotine</td>
<td>Increase</td>
<td>Increase (in high concentrations)</td>
<td>Being investigated as anti-migraine drug, ADD, Alzheimer’s, Parkinsons</td>
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<tr>
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<td>Stops heart</td>
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Although these chemicals have fairly consistent behavior when investigated alone, they can produce a variety of effects when used in living systems and when used in conjunction with, or following the administration of, other chemicals. The following article describes how difficult it can be to assign one type of response to a particular chemical! At the end of this long paper and the equally long list of references, you will find a small blurb on “vagal inhibition”.

**Haemodynamic and cardiovascular effects of caffeine**

Amer Suleman M.D., Nasir Hameed Siddiqui M.D.

**GENERAL INTRODUCTION.**
Waking up in the morning with a cup of coffee is a part of Western culture and caffeine has become one of the most popular and accepted stimulants. Caffeine has been recognized as the most widely used psychoactive drug in the world⁴. It has been estimated that 80% of U.S. civilian population above the age of 20 years drinks caffeine and related methylxanthines on a regular basis⁵. About 90% of this amount results from drinking coffee.
Chronic daily consumption is the usual pattern of intake of caffeine, and although majority of these individuals drink one to three cups a day, the mean for all coffee drinkers is 3.2 cups, or 272 mg of caffeine per day. Coffee is extracted from the fruit of *Coffea arabica* and related species. At least half the population of the world consumes tea prepared from the leaves of *Thea sinensis*, a bush native to southern China and now extensively cultivated in other countries. Cocoa and chocolate are extracted from the seeds of *Theobroma cacao*.

Cola-flavored drinks usually contain considerable amounts of caffeine, in part because of their content of extracts of the nuts of *Cola acuminata* (the guru nuts chewed by the natives of the Sudan) and in part because of the addition of caffeine as such in their production. Caffeine is often incorporated into therapeutic preparations. The caffeine containing beverages have been popular on the basis of the ancient belief that these beverages had stimulant and antisoporific actions that elevated mood, decreased fatigue, and increased capacity for work. Depending upon the alkaloid content of the coffee bean and the method of brewing, 1 cup of coffee contains 75 to 200 mg of caffeine, while 1 cup of tea contains about 50 mg of caffeine and 1 mg of theophylline; cocoa contains about 250 mg of theobromine and 5 mg of caffeine per cup. A 12-oz (360-ml) bottle of a cola drink contains 30 to 50 mg of caffeine, half of which is added by the manufacturer as the alkaloid.

<table>
<thead>
<tr>
<th>Table One: AMOUNT OF CAFFEINE IN COMMON SOURCES</th>
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<tr>
<td><strong>INSTANT COFFEE</strong></td>
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<td>WEAK</td>
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<td>MEDIUM</td>
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<td><strong>NON-ININSTANT COFFEE</strong></td>
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<td><strong>DECAFFEINATED COFFEE</strong></td>
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<td><strong>TEA</strong></td>
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<td><strong>CHOCOLATE</strong></td>
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<td>DRINKS</td>
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<tr>
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<td><strong>COLA DRINKS</strong></td>
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Adapted from Shirlow 1983.

Personal characteristics and environmental factors influence coffee consumption. Heavy usage (more than five cups a day) was found to be more prevalent in middle aged adults, in men, and in employed individuals, particularly members of two occupational groups: managers/administrators and craftsmen/kindred workers. Increases in coffee consumption were also found to be systematically related to periods of heightened occupational
demands among naval company commanders. Given such ubiquitous use of caffeine by individuals who are exposed to substantial occupational stress, investigation of its cardiovascular and related effects is warranted, particularly during periods of heightened stress.

**Chemistry**

Caffeine is 1,3,7-trimethylxanthine and is structurally related to uric acid. Caffeine is metabolized by demethylation and by oxidation. The major pathway in man proceeds through the formation of paraxanthine (1,7-dimethylxanthine), leading to the principal urinary metabolites, 1-methylxanthine, 1-methyluric acid, and an acetylated uracil derivative. Minor pathways involve the formation and metabolism of theophylline and theobromine. There is no evidence that the methylxanthines are converted to uric acid or that their ingestion exacerbates gout. There is inter-individual variation in the rate of elimination of methylxanthines due to both genetic and environmental factors, and fourfold differences are not uncommon. In most patients the drug obeys first-order elimination kinetics within the therapeutic range. However, at higher concentrations zero-order kinetics becomes evident because of saturation of metabolic enzymes. This prolongs the decline of caffeine concentrations. The disposition of methylxanthines is also influenced by the presence of other agents or of disease. For example, cigarette smoking and oral contraceptives produce small but appreciable increases in methylxanthine clearance. The half-life of theophylline can be quite prolonged in patients with hepatic cirrhosis, congestive heart failure, or acute pulmonary congestion and values of more than 60 hours have been observed. Caffeine has a half-life in plasma of 3 to 7 hours; this increases by about twofold in women during the later stages of pregnancy or with long-term use of oral contraceptive steroids. In premature infants, the rate of elimination of methylxanthines is quite slow.

**Cellular Basis for the Action of Caffeine.**

Three basic cellular actions of the methylxanthines have received major attention in studies to explain their diverse effects. In order of increasing importance, they are:

1. Translocations of intracellular calcium,
2. Increasing accumulation of cyclic nucleotides,
3. Blockade of receptors for adenosine.

The ability of methylxanthines to inhibit cyclic nucleotide phosphodiesterases is often cited to explain their therapeutic effects; however, there is little compelling evidence for such a view. Plasma concentrations of caffeine that raise blood pressure seem to be below the threshold for inhibition of phosphodiesterase. This fact appears to eliminate the participation of this category of actions to the therapeutic effects of methylxanthines.

At high concentrations (0.5 to 1 mM) caffeine interferes with the uptake and storage of Ca2+ by the sarcoplasmic reticulum in striated muscle. This action can account for observations that such concentrations of caffeine increase the strength and duration of contractions in both skeletal and cardiac muscle. Similar actions could enhance secretion in certain tissues. However, it is unlikely that they have an important role at therapeutic concentrations. In vitro, it has generally been found that methylxanthines (about 0.2 mM or above) cause relaxation of vascular smooth muscle in the presence of various stimulators of contraction (e.g., norepinephrine, angiotensin. K’). While relaxation probably results from a reduction of the cytosolic concentration of Ca2+ it is not clear to what extent the methylxanthines alter Ca2+ binding and transport directly or influence these functions indirectly by means of changes in cyclic nucleotide metabolism.
This would leave the anti-adenosine action as the leading candidate\textsuperscript{16,17}. Methylxanthines act as competitive antagonists at adenosine receptors at concentrations well within the therapeutic range. The effects of exogenous adenosine are very often opposite to those of the methylxanthines, and the removal of ambient adenosine in some experimental settings (by the addition of adenosine deaminase) will reproduce and obtund the actions of the methylxanthines. Plasma concentrations of caffeine that raise blood pressure seem to be within the range for antagonism of adenosine receptors\textsuperscript{18}. Several other types of actions that have received relatively little attention to date that might prove to be important in certain effects of the methylxanthines. These include their potentiation of inhibitors of prostaglandin synthesis\textsuperscript{19}, and the possibility that methylxanthines reduce the uptake and/or metabolism of catecholamines in nonneural tissues\textsuperscript{20,21}.

**PHARMACOLOGICAL PROPERTIES**

Caffeine has a wide range of pharmacological effects and has been positively associated with stimulation of cardiovascular and central nervous systems, glandular tissue, action on the kidney to produce diuresis, and relaxation of smooth muscles.

**Cardiovascular System.**

The caffeine has complex actions on the circulatory system, and the final effects largely depend upon the conditions prevailing at the time of administration, the dose used, and possibly the history of exposure to methylxanthines. *In addition to effects on the vagal and vasomotor centers in the brain stem, there is an array of more or less direct actions on vascular and cardiac tissues in combination with indirect peripheral actions that are mediated by catecholamines and possibly by the renin-angiotensin system. Therefore, the observation of a single function, for example, the blood pressure, is deceiving because the drugs may act on a variety of circulatory factors in such a way that the blood pressure may remain essentially unchanged.*

**Blood Pressure**

Placebo controlled studies have shown that caffeine decreased heart rate, increased blood pressure, and increased plasma levels of catecholamines and free fatty acids.

The administration of 250 mg of caffeine, an amount equivalent to that in 3 cups of coffee\textsuperscript{22}, has been shown, in the lab settings, to produce a moderate rise (11-14 mm Hg) in resting systolic and diastolic pressures in normal volunteers\textsuperscript{10,11,13,23,24,25,27,26,29,30,31}, in the elderly\textsuperscript{13,15}, in hypertensive subjects\textsuperscript{12}, in patients with autonomic insufficiency\textsuperscript{22}, and with exercise in healthy subjects\textsuperscript{26,29,30}, in patients with stable coronary artery disease on their medicines including calcium channel blockers and \textsuperscript{23} and in a group of normotensive, healthy, caffeine naive persons, on ambulatory BP monitoring, persisting for two days\textsuperscript{34}, who have abstained from recent caffeine ingestion.

Frequent consumers of caffeine have been found to respond less to acute administration than caffeine-naive individuals\textsuperscript{11,24,35}. On the other hand, rises in BP, after caffeine consumption, have been reported, even in persons who continued their normal caffeine consuming habits throughout study\textsuperscript{32,36}.

Similarly a small but significant elevation of BP was found in habitual coffee drinkers using regular coffee compared to those who drank decaffeinated coffee, as the subjects were followed for 6 weeks for BP measured by the subjects themselves, outside the office setting, using semiautomated, patient activated BP device\textsuperscript{37}. Caffeine and exercise seem to have additive effects on SBP, whereas caffeine's effects on DBP are weakened\textsuperscript{29}.
It has been suggested that there are individual differences in DBP response to caffeine, at rest and during exercise. Greater response may occur in individuals with some risk factors for hypertension including parental history of hypertension, high normal resting BP (135 to 154/85 to 94 mm Hg), high percentage of total body fat and exaggerated pressor response to exercise. Also tolerance to caffeine's habitual use has not been detected during exercise or at rest in various studies specially after about 12 hours of abstinence from caffeine containing beverages. Some of the subjects with largest pressor responses to caffeine have been the ones with high caffeine consumption >800 mg/day.

Future studies will be required to describe relevant underlying hemodynamic relationships of above risk factors [parental history of hypertension, high normal resting BP (135 to 154/85 to 94 mm Hg), high percentage of total body fat and exaggerated pressor response to exercise] and caffeine's effects.

The persistence of caffeine's pressor effects during exercise may have implications for physicians who supervise exercise programs. The view that "caffeine induces dilation of peripheral vasculature during exercise...an obvious advantage during exercise" appears premature for persons susceptible to caffeine's pressor effects. However, pressor response may disappear with heavy exercise, eg work loads greater than 600 kg m/min.

In combination with psychological stress, caffeine has been shown to produce an additive increase in systolic an diastolic pressure, for example, in male college students during performance of a challenging arithmetic task, or during heightened work stress. Caffeine in moderate amounts, administered to male mice during exposure to population crowding and frequent confrontations in cramped tunnels to reach food and water produced additive increases in plasma renin, systolic blood pressure, adrenal weight, and levels of plasma corticosterone and blood urea nitrogen (Henry and Stephens, 1980).

Human studies of caffeine's effects on stress reactivity have focused on cardiovascular reactivity elicited by acute laboratory stressors. Caffeine has had consistent effects on blood pressure (BP) in these placebo-controlled studies of healthy, normal subjects, elevating resting BP levels and adding significantly (5-10 mm Hg) to the level of BP reached during exposure to the stressor. As a general rule, the studies suggest that caffeine raises BP during stress by elevating the resting baseline from which the response is measured and not by potentiating the acute BP stress response. Potentiation of cardiovascular reactivity is apparent in other variables however. Caffeine potentiated stress-related increases in cardiac output in one study and forearm blood flow and forearm vasodilation in others. Taken together, the studies suggest that caffeine can indeed influence cardiovascular stress reactivity, either by adding to the level reached during stress or by potentiating the stress response itself.

Some of the observers have failed to find any significant changes in HR, BP and urine catecholamine excretion, in subjects even on high dose 12mg/kg/day of caffeine, on regularly repeated dosing for 3 to 4 days, or significant interactions between cigarette smoking and such caffeine dosing on above CV parameters.

Epidemiological studies have found either no positive association between coffee consumption and BP or have failed to confirm it after controlling for smoking, or suggested a small contribution to elevation in SBP and DBP within three hours after caffeine consumption independent of the overall average daily consumption or variation in SBP levels in some population subgroups as well as treated hypertensives. Some studies have suggested an additive effect for SBP between coffee consumption and tobacco consumption and a significant association between DBP and coffee consumption, that might be masked by negative correlation of DBP with tobacco consumption. On the other hand, some have observed a significant...
inverse relationship between caffeine and blood pressure, with increasing caffeine consumption being associated with a progressively lower blood pressure\(^4\).

The exact duration of the caffeine free period required to make an individual once again vulnerable to the pressor effects of caffeine is unknown\(^3\). Regular consumers of moderate amounts of caffeine need not be concerned about it’s effect on blood pressure. Infrequent consumption may cause a small but significant transient increase in blood pressure which is unlikely to be harmful to an individual but might influence the diagnosis of hypertension in a patient with borderline elevated BP\(^3\). The hypertensive effect on SBP persisted for 180 min after acute administration of caffeine in borderline hypertensives, even though only it remained significant for 90 min after caffeine ingestion only\(^1\).

**Heart Rate**

Although after acute caffeine ingestion, an increase in heart rate\(^4\), or no change\(^1\), or even no change\(^1\) has been reported, the commoner response may be slight decrease in heart rate, in laboratory settings\(^1\), presumably due to direct vagal stimulation\(^3\), baroreceptor reflex\(^3\), or effect on the sinoatrial node\(^3\). Not surprisingly, inconsistent effect has been reported in patients with autonomic failure, who have diminished baroreflexes, in response to caffeine\(^3\). It has been suggested that Caffeine probably has a direct cardioacceleratory effect and elicits a vagally mediated bradycardia by baroreflex activation consequent to its pressor effect (Bock J, Buchholtz J. Uber das Minutenvolum des Herzens beim Hunde und uber den Einfluss des Coffeins auf die Grosse des Minutenvolums. Arch Exp Pathol 1920; 88:192-215) Heart rate was slowed in a dose related manner, started at 30 min and lasted till 3 hours. The mean decrease was 10 bpm in group receiving 8.8 mg/kg at 30 min. Bradycardia was the only parameter that correlated with time course of plasma caffeine levels. There was no consistent correlation between heart rate and BP, thus bradycardia is not due to baroreflex, but possibly due to direct central vagal stimulation\(^1\). Thus the administration of 250 to 350 mg of caffeine may produce small decreases in heart rate and modest increases in both systolic and diastolic blood pressure. Such doses may have no effect on these parameters in those who consume caffeine regularly.

**ARRHYTHMIAS**

At higher concentrations (>10 mg/kg/day) caffeine produces definite tachycardia\(^5\); sensitive individuals may experience other arrhythmias\(^5\), such as premature ventricular contractions. Arrhythmias may also be encountered in persons who use caffeine-containing beverages to excess. However, it appears that the risk of inducing cardiac arrhythmias in normal subjects is quite low\(^1\), and that patients with ischaemic heart disease or pre-existing ventricular ectopy can usually tolerate moderate amount of caffeine without provoking an appreciable increase in the frequency of arrhythmias. No significant arrhythmias were observed during maximal exercise stress test in old individuals with stable angina on medical therapy\(^3\).

**MYOCARDIUM**

Substantial increases in circulating epinephrine (+207%), NE (+75%), and plasma renin activity (+57%) have been documented after a 250 mg dose in normal subjects\(^1\). Thus it might be expected that caffeine would potentiate exercise induced increases in myocardial oxygen consumption by a net increase in peak systolic pressure or peak heart rate, or both. An increase in myocardial oxygen demand at any given workload would be expected to reduce exercise duration in patients with coronary artery disease. Both angina and marked elevation in left heart filling pressure, with secondary pulmonary congestion, would be potential consequences\(^3\). Caffeine might also be expected to produce abnormal diastolic relaxation\(^3\). In study by Paulus\(^5\) the observed increases in left ventricular end diastolic pressure during pacing induced ischemia persisted more than three times as long after
caffeine pretreatment than with myocardial ischaemia alone. Tolerance to caffeine has been documented in some studies\textsuperscript{11}, an individual's previous use of caffeine may be a determinant of the pharmacodynamics of caffeine.

In dogs with coronary stenoses, large doses of intravenous caffeine potentiate impaired left ventricular diastolic relaxation, resulting in marked elevation of left ventricular diastolic pressure\textsuperscript{57}. In isolated heart muscle, caffeine and other methylxanthines prolong the time course of ventricular relaxation by reducing the rate of intracellular calcium sequestration during diastole by sarcoplasmic reticulum\textsuperscript{33,58,59}.

There is controversy as to whether circulating catecholamines or plasma renin activity is increased significantly in caffeine-naive subjects; however, it is generally agreed that little change occurs in chronic users.

While some studies have shown elevated cardiac output and stroke volume\textsuperscript{49}, in other studies caffeine has not been shown to have significant effects on LV ejection fraction and cardiac index, in young healthy men, at rest, or during exercise\textsuperscript{30}.

Selected patients with history of stable angina pectoris had no significant change in total exercise duration, time to onset of angina and time to onset of 0.1 mV of ST depression. Rate pressure product at onset of angina and onset of 0.1 mV of ST depression were not significantly different after caffeine ingestion. In response to exercise, echocardiographic measures of LVSF and LVDF were similar in both groups, in all but two patients who showed worsening of diastolic function at rest and further worsening with exercise after caffeine. There was no significant increase in frequency or severity of atrial or ventricular arrhythmias\textsuperscript{13}.

A similar lack of effect of caffeine on exercise duration, time to 0.1 mV ST depression, and heart rate blood pressure product was demonstrated by Piter in patients in whom medications were withheld on the day of the testing. However a significant increase in exercise duration before the onset of angina was noted\textsuperscript{60}. Caffeine has been shown to increase circulating free fatty acids and glycerol during exercise in normal subjects, with associated improvements in exercise duration\textsuperscript{61,62}, maximum oxygen consumption\textsuperscript{50}, resting metabolic rate\textsuperscript{63}, or perceived exertion\textsuperscript{64}. Some authors have not observed these changes\textsuperscript{65}. Enhanced peripheral lipolysis may not be noted at lower workloads achieved in patients with ischaemic heart disease, especially in presence of B-blockers\textsuperscript{66}.

**HUMORAL EFFECTS/ MECHANISMS**

Humoral or sympathetically mediated vasoconstriction has been suggested\textsuperscript{11,14} as the major effect at dose of 250 mg. Increases in circulating epinephrine (+207%), NE (+75%), and plasma renin activity (+57%) have been documented after a 250 mg dose in normal subjects, at rest.\textsuperscript{10} Additive increases in epinephrine with exercise have been noted\textsuperscript{30}. Some studies found a stronger relationship between caffeine and NE rather than caffeine and Epinephrine\textsuperscript{67,68}. Others have been unable to demonstrate these elevations in normotensives\textsuperscript{11,69}, and in borderline hypertensives\textsuperscript{12}.

Activation of renin angiotensin system has been presented as the predominant physiologic effect\textsuperscript{10,11}. Though some have noted no change in plasma renin activity after acute caffeine administration\textsuperscript{12}, in normotensives\textsuperscript{13}, and in borderline hypertensives\textsuperscript{12}, and in patients with autinic insufficiency\textsuperscript{32} or a fall in PRA\textsuperscript{14}.

Many observers have not been able to link catecholamine or PRA responses to the pressor effects\textsuperscript{12,13,30,32}. No study, to our knowledge, has demonstrated an association between caffeine induced changes in renin and blood pressure elevations. Alternatively caffeine's adenosine antagonistic actions\textsuperscript{16} have been suggested\textsuperscript{89} to cause elevated systemic vascular resistance\textsuperscript{31,90,91}. The vasodilator and the depressor effects of adenosine and the effect of increasing plasma norepinephrine and PRA, can be blocked by relatively low dose of caffeine, in young, healthy human subjects\textsuperscript{31}.

Theophylline enhances the production of endogenous adenosine in the heart as well as antagonizes the capacity of this autacoid to dilate coronary arteries (see Berne et al., in Symposium. 1987b). Vasodilating effects of adenosine seem to be mediated by a subclass of adenosinergic (A2-receptors), which are related to stimulation of cAMP formation\textsuperscript{92}.

Most effects of therapeutic doses of caffeine, on regional and peripheral blood flow and vascular resistance, are variable and depend upon the locale of the vascular bed and the experimental conditions employed. Conflicting patterns of haemodynamic effects have been observed.
In study by Smits, coffee did not increase FBF in their subjects. Also FVR did not fall whereas DBP rose. This might suggest increased SVR. This is in concordance with studies showing increased peripheral vascular resistance in normal regular caffeine consumers, at rest\textsuperscript{30,29} and during exercise\textsuperscript{30}, and in contrast to other studies where a fall in SVR has been reported\textsuperscript{49,93}. However, it has been shown that drug related elevation in SVR might get less pronounced during heavier exercise\textsuperscript{29,30}. The xanthines can increase coronary blood flow in man. However, it has been repeatedly demonstrated that methylxanthines cause a marked increase in cerebrovascular resistance with an accompanying decrease in cerebral blood flow and oxygen tension. This apparently reflects the anti-adenosine action of the xanthines, and prominent role of adenosine in cerebrovascular autoregulation.

Several studies confirm that caffeine's pressor response at rest may be attributed to heightened systemic vascular resistance\textsuperscript{26,28,30}. In contrast, during work on challenging mental tasks, caffeine elevates BP by potentiating the cardiac stimulatory properties of the task\textsuperscript{29,28}. This suggests that the methylxanthines have little direct action on the major resistance vessels. It is more likely that any change in peripheral vascular resistance results from interplay of the effects on the brainstem and the heart, with modification or reinforcement by autonomic reflexes, changes in the concentrations of circulating catecholamines and interaction with autoregulatory local hormones.

**Relation to Myocardial Infarction.**

For the past 20 year coffee consumption has been implicated as a risk factor for the development of ischemic heart disease but there has been controversy over a possible deleterious effect of caffeine in the etiology of acute myocardial infarction. Coffee consumption has been associated an increased risk of myocardial infarction\textsuperscript{94,95,96,97,98,99}. On the other hand, the results of a number of studies indicate that coffee drinking is associated with little, if any, increased incidence of coronary heart disease\textsuperscript{82}. Several epidemiologic surveys have failed to confirm, in particular after controlling for cigarette smoking\textsuperscript{43,44,45}, the suggestion by the Boston Collaborative Drug Surveillance Program\textsuperscript{79,80} that an association exists between coffee consumption and coronary heart disease\textsuperscript{100,81,101}.

There is also an association between coffee consumption and raised cholesterol concentrations, reported in people who drink boiled coffee\textsuperscript{83,85}, and also in populations where boiled coffee is rarely consumed\textsuperscript{88,84}. Some of these studies have suggested that the risk of coronary heart disease increases disproportionately with increasing levels of coffee consumption\textsuperscript{96,98,88}.

**MECHANISMS OF CAFFEINE TOLERANCE:**

Caffeine and other methylxanthines competitively inhibit the binding of adenosine receptor ligands in brain tissue (Snyder \textsuperscript{81}). This action has been proposed as the mechanism of well documented behavioral stimulant effects of caffeine\textsuperscript{81,84}. Chronic daily administration of caffeine leads to the development of tolerance to many effects of drug on the behavior\textsuperscript{82,83,88}. It has also been associated with an increase in the number of adenosine binding sites in the brain\textsuperscript{83,85,86,88}, suggesting that upregulation of adenosine receptors is the cellular basis of caffeine tolerance (Marangos \textsuperscript{85}; Snyder \textsuperscript{85}). Chronic treatment with caffeine may not uniformly affect all subtypes of adenosine receptors or adenosine binding sites in different regions and upregulation of adenosine receptors is not the mechanism of tolerance to caffeine. Other effects of caffeine (inhibition of phosphodiesterase and release of stored calcium) may become important with continuous administration of caffeine (Holtzman \textsuperscript{91}).
DISCUSSION

Caffeine has a wide range of pharmacological effects and has been positively associated with stimulation of cardiovascular and central nervous systems, glandular tissue, action on the kidney to produce diuresis, and relaxation of smooth muscles. Caffeine has physiological effects similar to those observed in association with psychological or psychosocial stress. In addition to its many other stimulant effects, the dietary consumption of caffeine can intensify the physiological responses elicited by psychological stressors in the laboratory and possibly in everyday life and potentially increase the pathogenic consequences that have been attributed to exaggerated stress reactivity. Because caffeine consumption and stress are both common features of contemporary life, a caffeine related potentiation of these harmful effects of stress could have especially important implications for the development of cardiovascular disease. Human studies of caffeine's effects on stress reactivity have focused on cardiovascular reactivity elicited by acute laboratory stressors. Taken together, the studies suggest that caffeine can indeed influence cardiovascular stress reactivity, either by adding to the level reached during stress or by potentiating the stress response itself.

The habitual consumption of caffeine leads to the development of tolerance to the drug's cardiovascular and neuroendocrine effects. The extent of any potential pathogenic consequences of caffeine/stress interactions should be directly related to caffeine and stress exposure, but if daily consumption of the drug leads to tolerance to its effects, the negative effects on health attributable to caffeine should be minimal. The most frequently cited studies offer evidence that the effects of an acute caffeine dose on resting levels of blood pressure, catecholamines, and plasma renin activity may disappear after several days of chronic administration of high caffeine doses e.g. 750 mg/day. However, other studies have shown significant caffeine effects on cardiovascular and neuroendocrine stress reactivity, similar in magnitude, in habitual caffeine consumers and in individuals described as "caffeine-naive".

A pressor response to caffeine taken in the morning can still be seen in the regular coffee drinkers, particularly those with lower morning concentrations of caffeine. No relationship was seen between maximum SBP changes with caffeine or placebo and subject's (elderly healthy men and women) mean daily consumption of caffeine. The comparisons of habitual moderate caffeine consumers and light consumers failed to find even non-significant trends linking level of habitual caffeine consumption to reduced caffeine effects. The habitual group consumed more caffeine than expected on average (6.6 mg/kg), close to levels estimated for the highest 10% of adults. If even at these higher daily doses, habitual consumption plays such a small role in modulating caffeine effects, it might be reasonable to conclude that tolerance is not present. It has been suggested that a person's daily caffeine intake (within a broad range of 0-1000 mg/day) is probably not meaningfully related to the magnitude of caffeine's effects.

On long term use, compared with placebo, caffeine persistently produced a 5/8 mm Hg rise in blood pressure at 30 min, though a much smaller rise at 30 min., and much weakening of response after one hour. Although BP fell after the meal, post prandial BP remained significantly higher after caffeine vs placebo (p<0.05 for SBP and DBP). In many epidemiological studies, coffee drinkers had higher SBP and DBP. Also among treated hypertensives who were excluded from calculations, S and DBP were higher among coffee drinkers. The presence of significant caffeine effects might depend on 12 to 24 hours of abstinence. In most of the studies, acute CV reactivity to caffeine was apparent, and no influence of regular caffeine use on physiological responses was seen e.g. after about 12 hours of abstinence, when tested comparing healthy students below (50-190 mg/d; M=11 5 mg/d + 10 SEM) vs above (199-1,582 mg/d; M=407 mg/d + 141 SEM) the median for average daily caffeine consumption; after 17 hrs of abstinence tolerance was apparently lost completely; BP elevations were similar in the caffeine naive subjects and in habitual consumers post 12 hours of abstinence; S.B.P. and D.B.P. in young, healthy, male volunteers, 1-6 cups per day regular coffee drinkers, after 36 hours of abstinence, were elevated 3 to 6 mm Hg, and elevation persisted for 4 hours of observation. Denaro 9167 suggested that on average dosing of caffeine for 5 days produced persistent activation of the sympathetic nervous system, an effect especially pronounced with high dose (12 mg/kg/day) caffeine; however, development of tolerance was suggested during the day. Probably overnight
abstinence allowed tolerance to abate somewhat so that the individuals became sensitive to the catecholamine-releasing effect of caffeine by the next morning\textsuperscript{67}. The overnight period of abstinence is consistent with normal patterns of caffeine consumption in habitual consumers. If caffeine tolerance is lost overnight, an equal loss of tolerance would be expected to occur every night in habitual consumers.

A pressor response to morning caffeine doses can particularly be seen in the regular coffee drinkers with lower morning concentrations of caffeine\textsuperscript{52,11}. Overnight period of abstinence produced pre-drug caffeine levels below 1 µg/ml in most studies. The low initial level may be important. In (Robertson \textsuperscript{81})\textsuperscript{11} 250 mg caffeine raised the BP of regular coffee drinkers by 4.2 mm Hg only if initial plasma level was below 1 µg/ml. A negative correlation between the initial level of caffeine in plasma and magnitude of BP response to an acute caffeine dose has been reported\textsuperscript{52}. Smits has shown that hemodynamic effects of caffeine may be influenced by the residual plasma caffeine concentration, which in turn is a function of individual clearance rates\textsuperscript{52}. A report of tolerance to acute caffeine dose after several days of chronic administration\textsuperscript{11} may be due to a high dose (750 mg/day), coupled with subjects' unusually slow rate of caffeine elimination (t\textsubscript{1/2}= 10 hrs vs normal 3-5 hrs), which might have maintained significant caffeine levels and effects throughout the study. There might be a relatively flat dose response curve for these caffeine effects. Thus acute caffeine effects may be detected only if the initial caffeine levels are below some threshold probably 1 µg/ml.

Regular caffeine users who are physically active respond to an acute caffeine challenge by increasing plasma epinephrine and fat oxidation. Even on increasing caffeine consumption by 500 mg/day for 6 weeks caffeine challenge still increased fat oxidation, though epinephrine response was less\textsuperscript{71}. This might suggest that even if tolerance develops, it might not be complete tolerance to all the effects\textsuperscript{74}. Support for the notion that tolerance to caffeine may be incomplete comes from several different types of research. The pressor effects of caffeine persist after 7 days of dosing in patients with autonomic failure\textsuperscript{32}. A pressor response to caffeine taken in the morning was in the regular coffee drinkers, particularly those with lower morning concentrations of caffeine\textsuperscript{52,11}.

All the CV and biochemical effects are variable at individual level in most of the studies\textsuperscript{23,27}. Individual responses to caffeine even after 5 days of use varied, at least one third of the study population (3/9) still had elevations of SBP, DBP, FFA and NE, and only 1/9 subject showed some tolerance\textsuperscript{67}. Individual variation in the extent of development of tolerance to effects of caffeine may underlie individual differences to adverse effects of caffeine on health\textsuperscript{67}. Similar interindividual variation should be expected in studies by Robertson\textsuperscript{11}. Their (Robertson's) subjects continued to show a trend towards higher levels of SBP and DBP and lower HR while on caffeine\textsuperscript{67}. Robertson did not look to determine if complete tolerance developed\textsuperscript{67}. They measured catecholamines for only four hours after the dose and subjects in their placebo group were different from caffeine group\textsuperscript{67}. The administration of 3.5 mg/kg of caffeine resulted in a wide range of observed plasma caffeine levels in the experimental subjects\textsuperscript{70}. Given that most studies correlations are based on observations of independent subjects, they may also reflect individual differences in the overall response to the drug\textsuperscript{70}.

Caffeine metabolism has been shown to be dose dependent under multiple dosing conditions; also the primary metabolites of caffeine, the dimethylxanthines, which may also have pharmacological actions, are subject to dose dependent metabolism as well\textsuperscript{73}. With high levels of consumption of caffeine, possibly related in part to saturable metabolism of caffeine and other dimethylxanthines, tolerance may not fully compensate for some of the pharmacological effects of caffeine and its metabolites\textsuperscript{67}.

Most of the studies have examined effects of single dose of caffeine, or of the doses given at regular intervals, whereby significant effects of caffeine dosed in an irregular manner throughout the day, or only part of the day, can not be excluded\textsuperscript{41}. This pattern with the heaviest consumption in the morning and decreasing consumption throughout the day, may be a more common pattern among general population\textsuperscript{41}. It has been shown in animal studies that temporal spacing of caffeine dosing, rather than magnitude of dose, is important. Whereas continuous administration (caffeine added to
the only accessible drinking water) may lead to tolerance, intermittent administration (every 48 to 72 hours) sensitizes the animals to stimulatory effects of caffeine76.

Caffeine can influence cardiovascular stress reactivity. Caffeine raises BP during stress by elevating the resting baseline from which the response is measured76. Caffeine consumption may add to the blood pressure elevations seen in medical students, fluctuating their peak SBP into borderline hypertensive range (140-159)77 or telephone marketing workers77 during periods of occupational stress. Potentiation of stress reactivity is apparent in other variables also e.g. stress-related increases in cardiac output26, forearm flow26,39, forearm vasodilation39 and neuroendocrine reactivity. The observed interactions of caffeine and stress may be present even in individuals who habitually consume moderate amounts of caffeine70. Significance of caffeine stress interactions in laboratory to cardiovascular and neuroendocrine reactivity in everyday psychosocial environment remains to be demonstrated, however, it might be reasonable to assume that it may raise BP during more natural stressors as well70. Caffeine use might increase potential health consequences from prolonged exposure to occupational stress77.

Acute elevation of BP after caffeine administration alone, or during psychologic stress, could be clinically significant/relevant in management of BP25, particularly in subgroups of patients with cardiovascular disease, and people with impaired excretion of methylxanthines e.g. cirrhotics and users of oral contraceptives27. Similar elevations could potentially eliminate or reverse the therapeutic effects of a number of the antihypertensive medications currently in use. Time sequence & duration of caffeine induced changes are important factors in assessing potential health effects. Coffee drinking has been implicated as an independent risk factor for coronary heart disease78,79,80,81,43. Possible mechanisms include increased blood pressure36,13,47,26, glucose intolerance82 and elevated cholesterol83,84,85,88 and exaggerated cardiovascular86 and neuroendocrine stress reactivity, through effects on lipid metabolism87. Thus caffeine could possibly accelerate cardiovascular disease development. Given the prevalence in everyday life of caffeine consumption and stress, opportunities of caffeine and stress interaction are common and their detrimental effects on health may be widespread.

If potentially harmful combined effects of the very common features of contemporary life are confirmed by future research, the awareness could lead to significant improvements in prevention of cardiovascular effects25. The discrepancies regarding tolerance can be resolved only with further studies. Almost all the studies have been short term studies, on a very small sample of a highly selected population, revealing great interindividual and interstudy variation. These limitations complicate extrapolation of experimental data, in lab, to general population of coffee drinkers. Caffeine dose of 3.5 mg/kg equals 250 mg for a 160 lbs subject, and is found in 10-15 oz of brewed coffee. Thus effects of significant magnitude could be expected to occur from dietary caffeine intake of majority of adults in US, given average daily intake of 3-4 mg/kg. Certain population subgroups e.g. elderly13, pregnant females, cirrhotics, persons with higher BMI, high normal resting BP and parental history of hypertension29 may be particularly susceptible to the effects of caffeine. Stratification of epidemiologic data on caffeine consumption may help to resolve this question. Ubiquitous consumption of caffeine coupled with it's significant effects on human body suggest that time sequence and duration of caffeine induced changes, effects of habitual caffeine use, caffeine/stress interactions and other potential health effects deserve further investigation.

REFERENCES


And now a word on “vagal inhibition”. If you attempt to find out what this term means by searching on the internet, you will find that it has several different meanings, which can be very confusing! This excerpt from a blog on http://www.bio.net/bionet/mm/neur-sci/1999-April/037752.html was written by Dr. Frank Le Fevre in response to a question about vagal inhibition.

The vagus nerve sends projections to much of the body visceral organs. It originates in the brain stem and is very important in the control of heart rate, gastric motility, digestive, and metabolic activities. When the vagus sends messages to the heart, the heart rate slows. When the vagus sends messages to salivary glands, they secrete saliva. Vagal stimulation of the pupil causes the aperture to close (mydriasis.)

One common term used in conjunction with vagal function is vagal tone. Increased vagal tone results in a slower heart rate, salivary secretions, and pupillary constriction. Decreased vagal tone has the opposite effects. It is possible to inhibit the actions of the vagus which would decrease vagal tone, but that is probably not what is implied by vagal inhibition.

You see vagal inhibition a potentially sloppy phrase. Vagal inhibition of the heart slows the heart rate. Inhibition of the vagus accelerates the heart rate.

What did you observe when you tapped the intestines of the frog? Think about your options as stated above, and decide how you would explain this phenomenon.