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METABOLIC AND CARDIOVASCULAR RESPONSES TO EXERCISE WITH
CAFFEINE

The Ohio State University

PH.D.

1979

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METABOLIC AND CARDIOVASCULAR RESPONSES
TO EXERCISE WITH CAFFEINE

DISSERTATION

Presented in Partial Fulfillment of the Requirements
for the Degree Doctor of Philosophy in the
Graduate School of The Ohio State University

By

Michael Matthew Toner, B.A., M.S.

The Ohio State University

1979

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To the living memory of my father, J. Charles Toner
his love and support still embraces my heart,

To my mother, Dorothy, whose love and security
allowed me to venture beyond,

Especially to my darling Kate, her glorious love
makes my world turn;

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Chapter I

Introduction

The human organism engages many processes to enable itself to be separate from the environment in which it lives. It has been the physiologist's role to study these complex processes that allow for such a distinction. One approach in this endeavor is to observe the responses of the whole-body to the stresses to which it is subjected. By doing this, one can gain insight into the direction to be undertaken by in vivo and in vitro animal studies. Furthermore, whole-body physiological studies can also complement or contrast the theoretical mechanisms which are generated by isolated preparations.

In addition, as knowledge is gained about the interaction of a stress and its subsequent physiological responses, one is challenged to impose additional stresses. In this way, the scope of the responses can be determined, as well as the contrastable effects of more than a single variable upon the organism.

In this regard, the present investigation has been undertaken to evaluate the effects of exercise and caffeine on the cardiovascular system.

Many in vitro preparations have indicated that caffeine has a positive inotropic influence on cardiac tissue (5,6,9, 10,27,48). This would suggest to some degree that in the intact animal there may be an increase in stroke volume and, possibly, cardiac output with caffeine ingestion.

An additional mechanism of action of caffeine on the intact innervated heart preparation has been suggested by several investigators (63,65). Caffeine by inhibiting the enzyme phosphodiesterase, increases the levels of cyclic AMP. Therefore, in addition to the direct effect on cardiac tissue as previously mentioned, caffeine increases the inotropic state of the heart by enhancing sympathetic tone via the heart's beta receptors.

Caffeine has also been shown to elevate circulating catecholamines (52) which increase sympathetic activity and, subsequently, cardiac output (26).

Direct, in vivo studies have shown that there are cardiovascular adjustments following caffeine ingestion during rest. The adjustments are mediated through changes in cardiac output (25,61), stroke volume (25), and arteriovenous oxygen difference (25,59).

The chronotropic effects of caffeine are variable. Caffeine has been shown to stimulate the parasympathetic nervous system, possibly through increased activity at the brainstem level (24,58). Increased vagal tone would tend to

lower heart rate. It has also been shown to stimulate the sympathetic system as previously described. This would tend to raise heart rate.

The effects of both caffeine and exercise have been the recent topics of studies involving human performance (16,29) and earlier works have been reviewed by Perkins and Williams (49). However, the effects of both stresses on the cardiovascular system has not been well documented.

A recent study by Ivy et al. (29) suggested that caffeine may alter the cardiovascular system during exercise. These data show that there is a change in oxygen pulse during a caffeine trial which suggests either an increase in stroke volume and/or an increase in arteriovenous oxygen difference. As of this paper, however, the only parameter to be measured in the evaluation of the cardiovascular response to exercise with caffeine has been heart rate (16,29,49).

It seems reasonable to suggest that caffeine, from a theoretical standpoint of in vivo and in vitro studies, may have a cardiovascular effect during exercise as mediated through a change in cardiac output, stroke volume, heart rate and/or arteriovenous oxygen difference.

Delimitations of the Study

Eight volunteers from the male population of The Ohio State University and neighboring community served as subjects for this experiment.

Four discontinuous maximum oxygen uptake tests were performed by each subject on four separate occasions. Each subject was required to ingest 97% decaffeinated coffee, with or without 350 mg of anhydrous caffeine added. The two caffeine and the two placebo trials were counterbalanced and double-blinded to ensure internal validity.

Statement of the Problem

Caffeine affects many physiological systems within the body. It is the intent of this study to examine the effect it has on the cardiovascular system. This is evaluated through measures of cardiac output, stroke volume, heart rate and arteriovenous oxygen difference, in addition to metabolism. These measures are obtained during a test of one's physical work capacity.

1. Decaffeinated Condition (D) - All subjects performed two exercise trials one hour after ingesting 97% decaffeinated coffee.
2. Caffeinated Condition (C) - All subjects performed two exercise trials one hour after ingesting 97% decaffeinated coffee with 350 mg of caffeine added.

Chapter II

Review of Literature

Caffeine has been the topic of many investigations since its discovery in coffee in 1821 by Robequet and Pelletier as discussed by Allen (2). This purine-based compound is ingested by a large portion of the world's population in many different beverages. Its action on the body is widespread.

The focus of this review on caffeine is in two parts. The first part concerns the description of caffeine's action on the biological system. This includes references which pertain to cardiac tissue. The second part entails the interaction of caffeine and the cardiovascular system.

Mechanism of Action of Caffeine on the Biological System

Caffeine and Cyclic AMP. Caffeine or 1,3,7-trimethylxanthine is a member of a class of xanthine compounds which have stimulating effects on many organ systems in the body. Its mechanism of action is dependent upon the action of an intracellular intermediate known as adenosine 3',7'-monophosphate (cyclic AMP). It is therefore essential in a discussion of caffeine to show the relationship between the two compounds. More importantly though, one must consider

the roles that are played by cyclic AMP within the organism, since these are the roles associated with caffeine.

Butcher and Sutherland (8) showed that caffeine inhibited the enzyme phosphodiesterase between 5 and 70% in extracts of beef heart. These reactions were dosage dependent. Phosphodiesterase was shown in an earlier work by Sutherland and Rall (62) to be capable of destroying the activity of cyclic AMP. This suggests that increases in the level of caffeine will increase cyclic AMP activity by inhibiting the enzyme which deactivates it.

The formation of cyclic AMP is catalyzed by the enzyme adenylyl cyclase and is converted from adenosine triphosphate (ATP) (54).

These references seem to suggest in part, that cyclic AMP levels are determined by the activity levels of these two enzymes - adenylyl cyclase which forms it and phosphodiesterase which inactivates it.

The action of caffeine on myocardial contractility may be mediated through inhibition of phosphodiesterase and the subsequent increase in cyclic AMP. Kukovetz and Pock (34), in 1967, showed that in guinea-pig hearts, 1500 μg of caffeine increased the isotonic contractions by nearly two-fold. Imidazole (a phosphodiesterase stimulator) reduced the contractions of caffeine but were still higher than control values. The author suggested that caffeine and imidazole

acted at the same site, phosphodiesterase to increase contractility.

Cyclic AMP and Adrenergic Receptors. Cyclic AMP has been related to adrenergic receptors. Alpha-adrenotropic (adrenergic) and beta-adrenotropic are the two classes of receptors (1) and "are now distinguished by the order in which the various catecholamines most strongly affect and by their specificity for different blocking drugs" (60). Beta-adrenergic receptors have two subclasses, a β_1 -receptor which is prevalent in myocardium and β_2 -receptor of vascular and most other smooth muscle (46).

β_1 -adrenergic receptors are stimulated by epinephrine, predominately, and its neurotransmitter norepinephrine. Stimulation of these receptors increases the contractile state of the myocardium (55). The mechanism by which the catecholamines work through these β_1 -receptors in increasing the contractility of the contractility of the cardiac muscle has been linked with cyclic AMP. This has been supported by a number of studies which have been reviewed by Sutherland et al. (63) but a causality has not been established (46).

Stimulation of the autonomic sympathetic ganglia may increase myocardial contractility above normal when caffeine is administered by increasing cyclic AMP levels at the beta-receptors.

Caffeine and Circulating Catecholamines. Cyclic AMP acts as a mediator between hormones and the physiological responses in the target organs (63). For instance, in the case of lipolysis in the adipose tissue, epinephrine or norepinephrine stimulate adenyl cyclase which increases cyclic AMP levels. This stimulates breakdown of triglycerides to free fatty acids and glycerol (7,15).

Circulating catecholamines have been shown to be elevated in the blood after caffeine administration. Robertson et al. (52) for instance has shown that after 250 mg of caffeine, subjects increased circulating epinephrine and norepinephrine, three and two-fold respectively, above control levels. The affect of these elevated catecholamines has been described by Sarnoff and Mitchell (55). They have shown that norepinephrine increased myocardial contractility. Logan and Cotten (35) isolated right ventricle strips from guinea-pigs and dogs. The results indicated that methylxanthines and norepinephrine both increase contractile force.

Caffeine will also work synergistically with the catecholamines. Rall and West (50) showed that caffeine with norepinephrine will increase the contractile force of rabbit atria more than with either administered separately. The conclusions of this study indicated that the potentiating effect of the methylxanthines "would be due to the inhibition of cyclic 3,5-nucleotide phosphodiesterase which, in turn,

would lead to a greater accumulation of cyclic 3',5'-AMP at any effective concentration of the catecholamines" (50).

Caffeine and Calcium. Another mechanism by which caffeine enhances the inotropic state of the myocardium is mediated through calcium movement. Blinks et al. (5) showed that caffeine was unlike other cardiac inotropes in that the developed force during contraction was prolonged. In addition to this it was shown that the initial rapid increase in pressure (dp/dt) was not affected. The data strongly suggested that caffeine was capable of inducing an influx of calcium through the cell membrane and inhibiting the sequestration of calcium into the sarcoplasmic reticulum.

Later, De Mello's work (19) with post-extrasystolic potentiation suggested that caffeine increased calcium release from the terminal vesicles, in addition to the increase in cell membrane influx and the decrease in re-uptake. Penna and Valenzuela (48) supported this with their work on post-extrasystolic potentiation. In these cases, caffeine increased the force of isometric contractions in guinea-pig ventricle and cat papillary muscle.

Additional Work. The inotropic effect of caffeine has been shown in isolated muscle preparations in isometric contractions (5,10,19,48) in a variety of animal tissue (e.g. kitten and cat papillary and atria, guinea-pig ventricle and whole heart, dog heart, and rabbit atria).

Papillary muscles from dogs, cats, rabbits and rats were used by Bodem and Sonnenblick (6) in 1975 to study isometric contraction. Caffeine increased the peak tension and velocity of shortening (following preloaded and afterloaded conditions) in all but the rat, where both decreased. Instantaneous force-velocity curves (velocity on the ordinate; force on the abscissa) showed variable results: with the cat, caffeine shifted the relationship to the right; with the dog and rabbit, it was shifted upward and to the right; and in the rat it was shifted downward.

Caffeine and the Cardiovascular System

The previous section has shown that caffeine influences several animal preparations. The mechanism is not fully understood, but in cardiac muscle evidence suggests: increases in cyclic AMP levels; increases in calcium influx through cell membrane and tubular vesicles; and inhibition of calcium uptake into the sarcoplasmic reticulum.

Irrespective of mechanism, in the isolated heart muscle, caffeine is a positive inotrope.

Caffeine and the Cardiovascular System at Rest. In the whole animal, the added factor of elevated catecholamines and their synergistic relationship with caffeine should enhance the force of contraction of the heart and thus increase cardiac output and/or stroke volume.

This has been shown by the early work of Grollman (25). Four subjects were used to observe the effects of 160, 320, 650 and 970 mg of caffeine on heart rate, blood pressure, oxygen consumption, cardiac output and arteriovenous oxygen difference. Each subject was observed on one condition only. No change was shown with the smallest dose. With 320 mg, heart rate and blood pressure were unaffected while oxygen consumption and arteriovenous oxygen difference elevated. Cardiac output increased approximately 11%. The 650 and 970 mg trials showed the greatest increases. Cardiac output was elevated 18 and 20% respectively, while heart rate and arteriovenous oxygen difference went unaltered. This would also suggest an increase in stroke volume.

Starr et al. (59) in 1938 injected 500 mg of caffeine into the deltoid muscle. The results on four patients were variable. Cardiac output was increased by 14.8% on the average; stroke volume increased 19.1%, while heart rate decreased slightly. The changes were not significant, however, a methodological error was uncovered. One of the four patients, who had no change, was being administered digitalis. Cotten (17) showed that the positive inotropic state of dog myocardium produced by catecholamines was blocked by digitalis. Therefore, the individual on digitalis in a caffeine condition (i.e. a condition which elevated catecholamines) may not have an increase in cardiac output. This has a big impact on a study which depends on four subjects for its significance.

Increase in cardiac output has been shown by Stepp (61) as reviewed by Robertson et al. (52).

Caffeine also affects blood pressure which has been shown by Robertson et al. (52). Nine subjects were administered 250 mg of caffeine. The elevation in systolic and diastolic pressures were significant and were maintained for 3.5 hours. The monitored heart rate showed an initial bradycardia and after one hour, tachycardia. Each was significant. The initial bradycardia followed the rise in blood pressure, possibly indicating a baroreceptor reflex or brain-stem stimulation. The tachycardia response, in addition to elevated pressures is interesting. The authors had no explanation.

Caffeine has been shown to affect the medullary vagal nuclei (24,58).

The effect of caffeine on heart rate is variable and cannot be anticipated. The variation in resting heart rate seems to indicate a competition of parasympathetic and sympathetic systems which are both stimulated. Overriding parasympathetic tone would lead to bradycardia. Equal contributions would see no change while higher sympathetic activity would lead to tachycardia.

Caffeine and Exercise. Very little information has been gathered on the cardiovascular responses to exercise with caffeine. A recent paper by Ivy et al. (29) suggested that

a change in stroke volume and/or arteriovenous oxygen difference was evident in a caffeine condition as compared to no caffeine. Subjects were asked to complete as much work on a Fitron Cycle Ergometer within a two hour period as possible. Subjects performed significantly more work with caffeine. The oxygen consumption was significantly greater throughout the two hour period, with the same heart rate response as the decaffeinated condition. The greater oxygen pulse indicated that a cardiovascular adjustment was involved.

Perkins and Williams (49) studied the effect of three levels of caffeine on muscular endurance. The subjects were required to pedal at an initial work level of 300 kgm for one minute; an additional 100 kgm was imposed each minute, and was continued till the subject was exhausted. The average exercise time was five minutes in the placebo condition and was not altered with either 4 mg/kg, 7 mg/kg, or 10 mg/kg of caffeine. There was no significant change in maximal or submaximal heart rate or ratings of perceived exertion. The author's data suggest that caffeine has no additional physiological effect as determined by maximal endurance time to exhaustion, maximal and submaximal heart rates.

Costill's work with caffeine (16) considered heart rate changes during continuous submaximal exercise. Subjects were asked to pedal at 80% of $\dot{V}O_2$ max until exhaustion. Heart rates were not significantly different between the caffeine and decaffeinated control trials throughout the exercise.

Margaria et al. (40) showed no significant difference in maximal heart rate in three subjects after 100 mg and 250 mg of caffeine. Each subject performed five trials within each condition. However, one of the three subjects showed a significant difference in maximal heart rate between placebo and 250 mg caffeine, respectively 187.2 ± 0.75 , 189.6 ± 0.45 beats $\cdot$ min $^{-1}$. This significance was lost by combining these results with others. This shows that one of the three individuals showed sensitivity to caffeine at that dose.

Heart rate responses may not be the best indicator of circulatory changes. Stimulation of parasympathetic and sympathetic systems may not alter heart rate but may increase contractility, even during exercise.

From the standpoint that caffeine induces many changes, in heart preparations in animals, with cardiovascular adjustments in man during rest and with some indication in exercise, the topic of this investigation is to inquire into the effect of caffeine on the cardiovascular system during exercise.

Chapter III

Methods and Procedures

To evaluate the effect of caffeine on the cardiovascular system during exercise, it was necessary to involve one phase of experimentation. This consisted of discontinuous maximal oxygen uptake tests on a bicycle ergometer within two experimental conditions: low caffeine and high caffeine. All evaluations of metabolism and cardiovascular performance were obtained in the Laboratory of Work Physiology, The Ohio State University.

The metabolic measurements obtained on each subject, so as to evaluate experimental differences, were as follows:

1. Submaximal oxygen consumption ($l \cdot min^{-1}$)
2. Submaximal ventilation ($l \cdot min^{-1}$)
3. Submaximal respiratory exchange ratio
4. Maximal oxygen consumption ($l \cdot min^{-1}$)
5. Maximal ventilation ($l \cdot min^{-1}$)
6. Maximal respiratory exchange ratio

The cardiovascular parameters measured or calculated were as follows:

1. Submaximal cardiac output ($\text{l}\cdot\text{min}^{-1}$)
2. Submaximal stroke volume ($\text{ml}\cdot\text{beat}^{-1}$)
3. Submaximal $\text{a}-\bar{\text{v}}\text{O}_2$ difference ($\text{ml}\cdot\text{l}^{-1}$)
4. Submaximal heart rate ($\text{beats}\cdot\text{min}^{-1}$)
5. Maximal cardiac output ($\text{l}\cdot\text{min}^{-1}$)
6. Maximal stroke volume ($\text{ml}\cdot\text{beat}^{-1}$)
7. Maximal $\text{a}-\bar{\text{v}}\text{O}_2$ difference ($\text{ml}\cdot\text{l}^{-1}$)
8. Maximal heart rate ($\text{beats}\cdot\text{min}^{-1}$)

Experimental Design

To study the physiological effects of caffeine during exercise, eight subjects performed discontinuous exercise on a bicycle ergometer. One hour prior to the start of the exercise, subjects ingested decaffeinated coffee, with or without 350 mg of caffeine added.

Each subject followed this protocol on four trials. Two trials were the decaffeinated (D) condition only and two trials were the same as the decaffeinated condition but with caffeine (C) added. The four trials were counterbalanced and double-blinded to ensure internal validity.

Subjects

Eight subjects from The Ohio State University and neighboring community were involved in all aspects of the experimental conditions. Four subjects were competitive cyclists and experienced in bicycle riding. Four subjects were untrained.

Six subjects were naive coffee drinkers and did not consume other caffeinated beverages on any regular basis. The seventh and eighth subjects averaged five cups per week and rarely consumed other caffeinated beverages. This is an important consideration since it has been shown that individuals develop a tolerance to the drug (52,67).

Each subject was informed of all aspects of the experiment including the possible side and after effects of the exercise test and caffeine. Their consent was obtained on an appropriate form.

The physical characteristics of the subjects are presented in Table 1.

Discontinuous Exercise Test

To test caffeine's influence on the cardiovascular system, a discontinuous maximum oxygen uptake test, on a bicycle ergometer similar to the protocol described by McArdle et al. (35) was utilized.

The discontinuous protocol consisted of intermittent exercise and rest periods. The exercise period was five minutes and the rest period ranged from five to ten minutes.

The work intensities were different for the trained and untrained subjects, so as to obtain between five to eight levels of work on each. The trained subjects pedalled at a rate of eighty (80) revolutions per minute. The initial

Table 1
Physical Characteristics

Subjects	Age Year	Height cm	Weight kg
B.P.	34	194.0	83.3
R.D.	24	174.6	73.0
D.D.	26	177.8	73.2
M.L.	24	186.7	73.4
M.T.	26	186.7	71.4
D.B.	32	177.8	73.1
M.A.	32	188.0	89.8
P.S.	23	174.0	66.9
Mean	27.6	182.45	75.51
S.D.	± 4.3	± 7.33	± 7.35

exercise bout was $720 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ and increased to $1200 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ on the second bout. Each additional bout consisted of the addition of $240 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$.

Prior to the experimental conditions, the untrained individuals were required to familiarize themselves with the bicycle. Each performed three practice sessions within a one week period. Each session was approximately twenty minutes of discontinuous submaximal exercise.

The exercise levels for the untrained individuals consisted of a pedalling rate of 60 revolutions per minute. The initial bout was $540 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$, followed by $900 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ which was the second bout. The exercise intensity was increased $180 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ with each additional exercise task.

The discontinuous maximal test required the subject to continue with increasing exercise levels until exhaustion was reached. To control for motivation on the maximal work level, subjects were stopped at volitional exhaustion with little or no encouragement by the investigators. The individual was stopped when the pedalling frequency could not be maintained.

An evaluation of caffeine's effect on total work performance was determined by the total exercise time to the point of exhaustion, as it has been used by others in discontinuous maximal tests (38,39).

Gas Collection and Analysis

Expired gases were collected via a Collins 5-way valve in a 120 liter Collins spirometer. All volumes were corrected to standard conditions of temperature and pressure.

A two liter aliquot was obtained from the spirometer and was analyzed for fractional concentrations of oxygen and carbon dioxide. The oxygen analyzer, Beckman OM-11 and the carbon dioxide analyzer, Beckman LB-2 were calibrated prior to each analysis with gases that were chemically determined by a Lloyd-Gallenkamp gas analyzer.

Measures of oxygen consumption, carbon dioxide production and respiratory quotient were calculated from the gases obtained during collection. The methods employed to calculate these values were presented previously by Consolazio et al. (14).

Collections were obtained during the last minute of exercise within each level.

Electrocardiograph

An electrocardiogram was taken during both the D and C conditions. The electrode placement was precordial lead-V-6, manubrium sternum and the ground was placed on the deltoid muscle. The heart rate was recorded on a Hewlett-Packard electrocardiograph by way of hard wire leads.

Resting heart rates were obtained during a control period prior to and one hour following the ingestion of the

beverage. Exercise heart rates were recorded during the last fifteen seconds of each gas collection period.

Non-Invasive Technique for Measurement of Cardiac Output

Cardiac output was determined during exercise by a CO₂ rebreathing technique which was introduced by Defares (18), and modified by Jernerus (30). The technique utilizes the Fick principle which states:

$$\dot{Q} = \frac{\dot{V}O_2}{C_aO_2 - C_{\bar{V}}O_2}$$

where

$\dot{Q}$ = cardiac output (l·min⁻¹)

$\dot{V}O_2$ = oxygen consumption (ml·min⁻¹)

$C_aO_2 - C_{\bar{V}}O_2$ = content of oxygen in arterial blood minus
content of oxygen in mixed venous blood
(ml·min⁻¹)

However, in the CO₂ rebreathing procedure, instead of oxygen consumption and its transport, the CO₂ production and transport is considered as follows:

$$\dot{Q} = \frac{\dot{V}CO_2}{C_aCO_2 - C_{\bar{V}}CO_2}$$

where

$\dot{Q}$ = cardiac output in l·min⁻¹ of blood flow

$\dot{V}CO_2$ = amount of CO₂ output in ml·min⁻¹

$C_a\text{CO}_2$ = CO_2 content in arterial blood in $\text{ml}\cdot\text{min}^{-1}$

$C_{\bar{v}}\text{CO}_2$ = CO_2 content of mixed venous blood in $\text{ml}\cdot\text{l}^{-1}$

The minute production of carbon dioxide ($\dot{V}\text{CO}_2$) is determined, as described previously, by collection of expired gases.

Arterial pressure of carbon dioxide is obtained by end-tidal sampling of expired gas. This is obtained by drawing gas at a rate of $500 \text{ ml}\cdot\text{min}^{-1}$ from the mouthpiece during the time of collection. The rise in the fractional concentration of carbon dioxide with successive breaths during light and heavy submaximal exercise is illustrated in Appendix A. An average of eight to ten breaths are obtained.

The end-tidal method assumes that alveolar pressure of carbon dioxide equilibrates with the blood passing through the lungs. That is to say, one assumes that alveolar PCO_2 equals arterial PCO_2 . This procedure has been shown to be valid and reliable by direct sampling of arterial blood and by comparing cardiac output results using this technique with other methods (23,32,45,51).

The basis for this technique has been the establishment of a procedure which allows for measurement of mixed venous carbon dioxide tension by non-invasion. There are numerous cardiac output methods which consider gases in the lung (12,18,32).

The method employed by Defares (18) utilized end-expiratory sampling of successive breaths during closed system rebreathing and the determination of carbon dioxide tension within each breath. The exponential rise in carbon dioxide tension could be extrapolated to that point where the curve would asymptote. This asymptote represented the point where the lung-bag system would be in equilibrium with the carbon dioxide tension of venous blood. Thus, an estimation of mixed venous carbon dioxide tension would be obtained.

Jernerus et al. (30) later utilized the rebreathing technique of Defares and added a simple graphic technique to determine mixed venous carbon dioxide tension. Figure 1 represents an example of such a technique. The two lines are a line of identity (A) and a rebreathing line (B). The rebreathing line is the best fit line through points obtained from the rebreathing curve. Each point represents an abscissa value which is the fractional concentration of carbon dioxide on one breath, and an ordinate value which is the fractional concentration of carbon dioxide obtained on the following breath. Therefore, the points of this line are obtained by plotting (breath 1 vs breath 2), (breath 2 vs breath 3), ..., (breath n vs breath n+1).

The rebreathing line is extrapolated to the identity line to give the point where equilibrium would have been reached between the lung-bag system and the venous blood. Actual

Figure 1. Equilibrium Analysis: Identity Line(A) and Rebreathing Line(B)

equilibrium is never reached for two reasons. First, recirculation of carbon dioxide would tend to continually elevate the mixed venous content (36) and secondly, as observed from the use of the Collier method, equilibrium is never reached because of the small gradients between the lung-bag system and venous blood, this technique requires a correction factor.

Actual calculation of the equilibrium point is made by determining, through linear regression, the line of best fit. This line and the identity line is solved simultaneously to determine the point of intersection, or equilibrium point.

Rebreathing Apparatus and Procedure

The rebreathing apparatus is schematically shown in Appendix A. The 3-liter rebreathing bag is filled with 99.7% oxygen to a volume which is greater than the tidal volume of the subject. On signal the subject rebreathes from the bag at a rate of 50 breaths per minute. A continuous sample of gas is removed from the distal portion of the bag at a rate of 500 milliliters per minute and passed through a rapid carbon dioxide analyzer, Beckman LB-2. This sample is then returned to the bag in order to maintain a constant volume.

The output of the LB-2 is fed into a Grass-polygraph where a range of 3-9% is recorded. Both the LB-2 and the Grass recorder are calibrated prior to each measurement.

The Beckman LB-2 was found to be linear by passing gases of known carbon dioxide content from tanks previously analyzed chemically. The Grass, however, was found not to be linear throughout the full range. Corrections were made during graphic analysis.

Rebreathing curves during light and heavy submaximal exercise are shown in Appendix A and represent no more than 12-15 seconds of rebreathing. This is obtained immediately following gas collection. Calculations of cardiac output are shown also in Appendix A. Briefly, $\dot{V}CO_2$, P_aCO_2 and P_vCO_2 have been previously described. The pressures of carbon dioxide are converted to concentrations by a standard carbon dioxide dissociation curve (13). The carrying capacity of the blood for carbon dioxide is altered by the pressure of oxygen, as described by Haldane. High pressures of oxygen are used in rebreathing to ensure complete oxygenation of mixed venous blood. Therefore, the carbon dioxide dissociation curve for completely oxygenated blood is used to determine carbon dioxide content in both arterial and mixed venous blood. This procedure has been shown to be valid during both rest and exercise (51).

Experimental Beverages

The decaffeinated beverage used in Condition D consisted of 3 g of 97% decaffeinated coffee (i.e. a total caffeine content of less than 7 mg) in 230 ml of water. The caffeinated beverage used in Condition C consisted of 3 g of 97%

decaffeinated coffee, with the addition of 350 mg of caffeine anhydrous, in 230 ml of water. Two trials of each condition were counterbalanced and double-blinded to strengthen internal validity. The schedule is shown in Table 2.

The subjects were at liberty to add a non-dairy creamer and/or saccharin to the beverage. However, the same quantity of each was added in each of the four trials.

The beverages were ingested one hour prior to the start of the maximal test. This was to ensure that the caffeine levels were near peak values in the blood (4,41,52).

Statistical Analysis

To evaluate the influence of caffeine on the metabolism and the cardiovascular system during rest and maximal exercise, a mixed analysis of variance (one-within and one-between design) as described by Kennedy (31) was utilized. The decaffeinated condition was compared with the caffeinated trials, while the effect of training state was considered.

The influence of caffeine during submaximal exercise was evaluated by selecting two exercise loads that all subjects performed. A one-between, two-within design of the mixed ANOVA (31) was used.

To test the hypothesis that there were no differences between decaffeinated and caffeinated conditions, an alpha level of 0.05 had been chosen for all variables obtained.

Table 2
Testing Schedule

Subject	Condition			
	Test 1	Test 2	Test 3	Test 4
B.P.	D	C	C	D
R.D.	D	C	D	C
P.S.	D	D	C	C
M.A.	C	D	C	D
D.D.	C	C	D	D
M.L.	C	D	D	C
D.B.	C	D	D	C
M.T.	D	D	C	C

D = Decaffeinated Test

C = Caffeinated Test

To test for differences between test 1 vs test 2 in each condition, paired t-tests were performed on all variables. An alpha level of 0.05 was chosen.

Chapter IV

Results

The purpose of the study was to evaluate the impact of caffeine on the metabolic and cardiovascular response during rest and exercise. To test the hypothesis that caffeine has no effect on resting and exercising man, subjects were exposed to duplicate trials of caffeine and low caffeine conditions. All experimental conditions were the same except the level of caffeine administered.

All subjects with the exception of R.D. performed duplicate trials on both caffeine and decaffeinated conditions. R.D. performed, at random, one trial at each condition.

Paired t-tests were performed on all maximal variables to test for differences. There were no differences between T_1 and T_2 values on any variables. Each measure presented on a subject, represents the average of the two tests.

Raw data and statistical analysis tables appear in Appendix B.

Reliability of Cardiac Output by CO₂ Rebreathing During Exercise

Cardiac output was obtained on some subjects during rest and all subjects during maximal exercise. The reproducibility of the technique was evaluated on all subjects during both decaffeinated and caffeine trials. A total number of 67, T₁ vs T₂ pairs were obtained.

A correlation coefficient of 0.83 was calculated on the test-retest data. The standard error of a single cardiac output observation was ± 3.522 l/min or $\pm 20\%$ of the mean during submaximal exercise and $\pm 14\%$ at maximum.

Duplicate observations in both control and caffeine treatments during all exercise levels were obtained. The average of two measures represents one observation at each exercise level.

Validity of the Cardiac Output Results

The cardiac output results for the control condition are shown as a function of oxygen consumption in Figure 2. These data compare well with other laboratories. For instance, Magel et al. (37) tested trained and untrained athletes on a bicycle ergometer from rest through maximal exercise. The results of the present study matches closely the results obtained on their subjects.

Figure 2 Cardiac Output as a Function of Oxygen Consumption

Metabolic and Cardiovascular Responses to Bicycle Ergometry

Maximal Exercise. Maximal values of the untrained and trained cyclists appear in Table 3. Maximal oxygen consumption for the untrained subjects was $3.740 \pm 0.527 \text{ l}\cdot\text{min}^{-1}$, and was statistically less than ($p < 0.05$) the trained cyclists' value of $4.601 \pm 0.499 \text{ l}\cdot\text{min}^{-1}$.

Maximal pulmonary ventilation was statistically different ($p < 0.05$). The cyclists ventilated $144.68 \pm 22.71 \text{ l}\cdot\text{min}^{-1}$ as compared to the untrained, $117.19 \pm 8.94 \text{ l}\cdot\text{min}^{-1}$. The respiratory exchange ratios between the groups showed no difference.

The circulatory responses of the two groups were similar. There were no significant differences between the groups for cardiac output, stroke volume, heart rate and arteriovenous oxygen difference.

Submaximal Exercise. Oxygen consumptions at different power outputs are illustrated in Figure 3. These data represent all the subjects during the control condition. Each point on the graph is the oxygen consumption measured for a one minute interval between minutes two and five of exercise at the particular power output.

A correlation coefficient of 0.985 was obtained giving a coefficient of determination of 0.97. This suggests that oxygen consumption varies directly with increasing power demands, and almost all (97%) of the variance in oxygen consumption is related to the variance in power output.

Table 3
Metabolic and Cardiovascular Responses During
Maximal Exercise on a Bicycle Ergometer

Subject	$\dot{V}_{EBPTS}$ l·min ⁻¹	$\dot{V}O_2$ l·min ⁻¹	R	$\dot{Q}$ l·min ⁻¹	HR beats/min	(a- $\bar{v}$)O ₂ diff ml/L ⁻¹	SV ML
Untrained							
P.S.	108.10	3.860	1.06	24.4	189	154.2	129.1
M.T.	124.65	3.017	1.11	19.4	185	187.3	104.9
D.D.	110.92	3.801	1.07	25.1	179	166.9	139.7
M.A.	125.08	4.280	1.02	25.1	180	172.3	139.4
$\bar{X}$	117.19	3.740	1.07	23.5	183	170.2	128.3
SD	8.94	0.526	0.03	2.7	4	13	16.3
Trained							
R.D.	118.30	4.130	0.98	25.7	174	181.1	147.7
M.L.	133.80	4.412	1.06	25.5	177	182.5	144.1
D.B.	167.71	4.563	1.09	25.8	187	176.4	138.0
B.P.	158.89	5.299	1.04	28.7	170	190.1	175.0
$\bar{X}$	144.68	4.601	1.04	26.4	177	182.5	151.2
SD	22.70	0.498	0.04	1.5	7.2	5.7	16.3

Figure 3. Oxygen Consumption as a Function of Power Output on a Bike

Two submaximal workloads were chosen from the data and included all of the subjects. Load I represented a power output of $540 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ and $720 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ for the untrained and trained, respectively. The power output of Load II for the untrained was $1260 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ and $1200 \text{ kg}\cdot\text{m}\cdot\text{min}^{-1}$ for the trained cyclists.

The average oxygen uptakes for the untrained subjects at the two loads in the control state were 1.571 ± 0.138 and $3.084 \pm 0.078 \text{ l}\cdot\text{min}^{-1}$. The trained subjects showed comparable values at both levels 2.005 ± 0.111 and $3.007 \pm 0.224 \text{ l}\cdot\text{min}^{-1}$.

There were no differences in the R values between the two groups, although differences ($p < 0.01$) were seen between the two loads in each group.

Differences were seen in the heart rate responses between the cyclists.

Metabolic and Cardiovascular Responses to Caffeine Ingestion

Metabolic Responses. Maximal values on all metabolic values are presented in Table 4.

Analysis of variance yielded a non-significant F-ratio of 2.51 for oxygen consumption during rest between the caffeine and control conditions. Caffeine did not affect the oxygen uptake of either group at the two submaximal power outputs, as indicated by a non-significant F-ratio of 0.20.

Table 4

Comparison of Maximal Metabolic Responses
to Caffeine and Control Conditions

Variable		Control	Caffeine	
				$\bar{X}$
Max $\dot{V}O_2$ ml·min ⁻¹	UT	3.758(0.494)	3.859(0.544)	3.809(0.519)
	T	4.601(0.499)	4.780(0.421)	4.691(0.460) *
	$\bar{X}$	4.180(0.497)	4.320(0.483) †	
Max $\dot{V}_{E\text{BTPS}}$ l·min ⁻¹	UT	117.19(8.94)	118.76(17.24)	117.98(13.09)
	T	144.68(22.71)	155.12(16.24)	149.90(19.48) *
	$\bar{X}$	130.94(15.83)	136.94(16.74)	
Max R	UT	1.06(0.05)	1.06(0.02)	1.06(0.04)
	T	1.04(0.05)	1.03(0.01)	1.04(0.03)
	$\bar{X}$	1.05(0.05)	1.05(0.02)	
Max exer- cise time min	UT	28.25(6.75)	28.67(5.15)	28.46(5.95)
	T	26.47(4.65)	28.60(4.25)	27.54(4.45)
	$\bar{X}$	27.36(5.70)	28.64(4.7)	

$\bar{X}$ (Sd)

† $p < 0.05$ from control

* $p < 0.05$ from untrained

UT = untrained

T = trained

There was a slight though significant increase in maximal oxygen consumption in the trained subjects. The untrained subjects did not increase significantly. Analysis of variance showed that there was no interaction of training and treatments.

Maximal pulmonary ventilation was not altered by caffeine as indicated by an F-ratio of 1.01. In addition, the maximal respiratory exchange ratio was unaffected. Exercise time to exhaustion was not changed during the caffeine condition as compared to the control.

During submaximal exercise, caffeine had no statistical effect on oxygen consumption during the two levels. However, a treatment by load interaction was significant ($p < 0.01$).

Tukey procedures showed that the interaction means were not significant. The significant F-ratio was a function of the large oxygen consumption difference between the loads.

Respiratory exchange ratios were not statistically different between the control and caffeine treatments at either level of submaximal exercise.

Cardiovascular Responses. Maximal cardiovascular responses to control and caffeine conditions are presented in Table 5.

Maximal heart rates were elevated during the caffeine condition as it was indicated by a significant ($p < 0.01$) F-ratio of 40.00. The untrained subjects averaged 184 and

Table 5

Comparison of Maximal Cardiovascular Responses to
Caffeine and Control Conditions

Variable		Control	Caffeine	
				$\bar{X}$
Max HR beats· min ⁻¹	UT	183(4.6)	190(3.6)	186.5(4.1)
	T	177(7.3)	180(5.8)	178.5(6.6)
	$\bar{X}$	180(6.0)	185(4.7)♦	
Max $\dot{Q}$ l·min ⁻¹	UT	23.5(2.7)	23.9(3.1)	23.7(2.9)
	T	26.4(1.6)	26.9(2.6)	26.7(2.2)
	$\bar{X}$	25.0(2.1)	25.4(2.9)	
Max (a- $\bar{v}$) Diff ml·l ⁻¹	UT	170.2(13.7)	170.5(14.4)	170.4(14.1)
	T	182.5(5.7)	188.5(2.5)	185.5(4.1) *
	$\bar{X}$	176.4(9.7)	179.5(8.5)	
Max SV ml	UT	124.5(17.7)	122.9(18.2)	123.7(18.0)
	T	151.2(16.4)	149.3(15.3)	150.3(15.9)
	$\bar{X}$	137.9(17.1)	136.1(16.8)	

♦ p < 0.01 from control

UT = untrained

* p < 0.05 from untrained

T = trained

190 beats·min⁻¹, in the control and caffeine conditions respectively. In the trained the increase was smaller, 177 to 180 beats·min⁻¹,

Maximal cardiac output, stroke volume and arteriovenous oxygen difference were not statistically significant between the control and caffeine condition.

During submaximal exercise, an interaction between the treatment and load conditions for heart rate was active ($p < 0.01$). The Tukey procedure showed that the significant interaction was a function of the large difference in heart rates between loads and not truly an interaction.

Chapter V

Discussion

There was a slight increase in oxygen consumption during the caffeine trial at the maximal power output. The explanation for this can be speculated from two viewpoints. First, caffeine increases the maximum oxygen consumption on the bike. Second, the oxygen consumption during the control condition was not a maximum and that the increase in oxygen consumption reflects the stimulating effects of caffeine on an individual. Therefore the individual pushed to maximum under the influence of caffeine.

Both are plausible explanations from these data and both must be explored for their credibility and their implications.

Experimental design may have contributed to the increase. The subjects were taken to volitional maximum which included little or no encouragement by the experimenters. It would be possible that the subjects were not at maximum during the control trial.

The maximal heart rate responses are comparable with data from other laboratories which utilized subjects (43,37, 47). The trained subjects tended to have slightly lower maximal rates than have been reported.

The respiratory exchange ratios were similar during both conditions. It would be expected that the R values would have been lower in the control than the caffeine trial if the control trials were not maximal.

To ensure that the maximal values in each condition were not a function of the testing order, each subject was administered the conditions at random. Each subject had an opportunity to receive either the C or D trials on any two testing days. Table 2 shows that on the Test 1 day, equal numbers of caffeine and decaffeinated trials were administered.

These factors do not rule out the possibility that the control trial was not a maximal value. Maximal work time was not statistically different between conditions. Statistical significance may not reflect physiological significance however. A slight increase in power output must be evaluated for its physiological potential.

The principle criteria for establishing a maximal oxygen consumption, in addition to heart rate and R values, has been the plateau of the oxygen consumption with increasing power demands (i.e. as one increases the power load, there is a point where the oxygen consumption does not increase). In some cases at the highest output, this value has been shown to decrease. In all but one case in the present study, the last oxygen consumption was less than that predicted for an increase in power.

This still may not be enough to conclude that one has reached maximum. Unlike exercise on a treadmill, bicycle ergometry does not require the subject to maintain the power output. At the highest exercise level the subject might have fallen off the pedal frequency. The power output would drop between 21 and 30 kg·m (depending upon the given individual) for each revolution that was missed in a minutes time. If a number of revolutions were missed, then the power output would drop significantly followed by a drop in oxygen consumption. This would be a spurious indication that the maximal oxygen consumption had been reached. It is impossible from these data to support or refute this possibility.

If the subject had not reached maximum on the control trials, then the data would imply that caffeine enabled the subjects to maintain the pedalling rate and increase the oxygen consumption to maximum. Caffeine is considered to be a better CNS stimulant than a cardiovascular stimulant (24). It has also been shown to stimulate locomotion in mice which may have been caused by stimulation of central catecholamine receptors (66). Perkin's review of literature on caffeine and muscular endurance (49) had equivocal findings. Her data did not show improvement in muscular endurance with caffeine as measured by exhaustion time, heart rate and ratings of perceived exertion. The present study implies near maximal aerobic power, not short duration supra-maximal tasks such as the muscular endurance evaluation

employed by Perkins and Williams. Caffeine may have had a neurological effect that stimulated subjects to reach maximum aerobic capacity on the bike. This is in contrast to subjects who were not encouraged to push at all on the test.

The increase in maximal heart rate followed the increase in oxygen consumption.

It is also possible that the subjects were at maximum during the control trials and that the increase in $\dot{V}O_2$ was above this. The following section considers this possibility.

The slight increase in oxygen consumption during maximal exercise in the caffeine condition is contrary to the earlier findings of Margaria et al. (40). In that study three individuals were exposed five times to 100 and 250 mg of caffeine. There was no statistical significance between the caffeine or control trials on a maximal oxygen consumption test. Close examination of each individual's data shows that one of the three subjects had a significantly higher oxygen consumption on the treadmill during the 250 mg trials as compared to the placebo controls, 51.70 ± 0.80 ml/kg·min and 49.14 ± 0.38 ml/kg·min, respectively. It is important to note here that this is the same subject who had the elevated maximal heart rate in the review chapter. In Margaria's data the significance of this subject was lost when pooled with two who had no responses.

The sensitivity of individuals to caffeine is variable. There are many who will manifest the symptoms of caffeine's effects, given a small cup of coffee (e.g. sleeplessness, nervousness, gastrointestinal response, etc.) while others have no responses after drinking many cups. This may, in part, be associated with exposure to the drug. As with many stresses that are imposed for extended periods of time, the body increases its tolerance to them. This has been shown in the case of caffeine (67). In Margaria's study since it was not stated, the individual tolerance to the drug may not have been controlled. It is also important to note that the exercise was performed on the treadmill which required the subject to do the work.

In the present study, all but two subjects (M.A. and M.T.) were naive coffee drinkers and with little exposure from other sources. These two subjects showed no increases in maximal oxygen uptake as compared to the 100 to 300 milliliter increase in the six others.

The increase in maximal heart rate may indicate an increase in circulation. Since $\dot{V}O_2$ max and maximal heart rate were the only variables to increase, then their relationship is plausible.

The standard error of the estimate of cardiac output was 14% at maximum. Since the increase in $\dot{V}O_2$ at maximum was just over 3%, then any changes of that magnitude in

cardiac output could have been masked in the high error of the technique.

Faulkner et al. (22) suggested that lower maximum oxygen uptakes on a bicycle ergometer were attributable to lower cardiac outputs. The increase in circulation may contribute to the oxygen supply to the exercising musculature.

Caffeine has been shown to increase epinephrine levels during exercise (56). Circulation of the catecholamine may induce additional dialation in skeletal muscle by stimulating beta-receptors, as would the direct action of caffeine. Clausen (11) suggests that sympathetic nervous constriction limits blood flow to active muscles.

The increase in maximal heart rate is not easily explained, since heart rate control mechanisms are not completely understood. The S-A node is the center of rhythmicity of the heart. Nervous innervation include both parasympathetic and sympathetic systems which are stimulated by higher centers, baroreceptive reflexes and circulating hormones.

Caffeine is primarily a central nervous system stimulant (24). It has been shown at the maximal oxygen consumption that the sympathetic system is the primary nervous influence for control of heart rate (20). It is possible that caffeine may have a central and/or local nervous effect on cardiac rate during maximal exercise by increasing sympathetic discharge.

The unchanged heart rate during the submaximal loads may suggest an increase in the parasympathetic activity in addition to the increased sympathetic tone. The effective result would be no change in rate. The increase in heart rate at maximum reflects the lack of contribution of the parasympathetic system to maximal rates.

Respiratory exchange ratios were unchanged during submaximal exercise. This is contrary to the work of Costill et al.(16). Costill had shown that caffeine significantly lowered the R values after 10 minutes of exercise at 80% of $\dot{V}O_2$ max. This trend continued for over one hour of work. The contradiction may have been in design differences. Costill's subjects were 6-12 hours post-absorptive. In the present study the subjects did not ingest food for at least 3 hours. Since caffeine tends to increase the epinephrine/norepinephrine ratio during rest (52), and since it increases significantly the epinephrine level above a control exercise level (56), then the differences in the post-absorptive periods may reflect the different responses of the respiratory exchange ratios. Epinephrine stimulates the mobilization of carbohydrates to increase plasma glucose levels as does caffeine. In Costill's study the glucose levels were not significantly different. The long post-absorptive period may have reduced the availability of carbohydrate and thus the effectiveness of epinephrine (64) and caffeine. In the

present study the R values may not have been different if plasma glucos levels were elevated, in response to the short post-absorptive period.

The more plausible explanation concerns the type of exercise. Costill used continuous whereas the present study involved discontinuous work bouts. Norepinephrine levels have been shown to return to control levels within 10 minutes following 10 minutes of exercise at 40% $\dot{V}O_2$ max (33). This response may not have allowed the synergistic action of caffeine and the catecholamines to elicit a change in the substrates for energy production.

There was no change in stroke volume during submaximal or maximal exercise. Elzinga and Westerhof (21) have suggested that "the effect of an increase in inotropic state on stroke volume depends on the initial contractile state of the heart and on the pressure level at which it functions." Stroke volumes attain near maximal values at work levels of 40% $\dot{V}O_2$ max (3). The present study supports this, since there were no differences between Load I, Load II or maximal stroke volumes. This must indicate that the inotropic state is near maximum, since exercise with caffeine did not increase the stroke volume above the level of the exercise control. It also supports Elzinga's conclusion provided that the left ventricular pressure was the same in the control and caffeine trials.

Chapter VI

Summary and Conclusion

The purpose of the study was to investigate caffeine's effect on the cardiovascular system during exercise. There has been evidence to suggest that stroke volume and/or cardiac output would be altered during exercise following the ingestion of caffeine. Metabolic variables were also obtained and were compared to other studies.

Eight subjects from The Ohio State University and neighboring community volunteered to be subjects in each aspect of the experiment. Four discontinuous maximum oxygen uptake tests on a bicycle ergometer were required of each subject. Prior to each test, the subject ingested a decaffeinated beverage with or without 350 mg of caffeine added. Two caffeine and two decaffeinated trials were administered randomly throughout a three week period.

Cardiac output during exercise was determined by a CO₂ rebreathing procedure. Values of stroke volume and arterio-venous oxygen difference were calculated from cardiac output, heart rate and oxygen consumption.

There was an average increase in the maximal oxygen consumption of $140 \text{ ml} \cdot \text{min}^{-1}$ ($p < 0.05$) during the caffeine condition. The maximal heart rate was elevated by an average of $5 \text{ beats} \cdot \text{min}^{-1}$ ($p < 0.01$). There were no other changes associated with caffeine and exercise. This included the other maximal metabolic and cardiovascular variables, in addition to all submaximal parameters.

Conclusions

Within the limitation of this study, the following conclusions were derived:

1. The maximum oxygen consumption on a bicycle ergometer was increased after caffeine ingestion as compared to the control condition.
2. The maximal heart rate response was elevated during the caffeine condition.
3. Caffeine did not affect maximal values of pulmonary ventilation, respiratory exchange ratio, stroke volume, cardiac output or arteriovenous oxygen difference.
4. The maximal exercise time (total exercise time during the discontinuous test) went unaltered after caffeine.
5. There were no metabolic or cardiovascular changes associated with caffeine during submaximal discontinuous exercise on the bicycle ergometer.

6. The responsiveness of an individual to caffeine might have been related to prior exposure to the drug. The data seem to show that the subjects with normally low caffeine intake, had the greatest responses.

7. Cardiac output determination by carbon dioxide rebreathing was within 20% of the mean during submaximal exercise and 14% at maximum. Two trials are necessary to obtain a realistic estimate of cardiac output. In the present study, the technique is valid as compared against other laboratories.

8. The slight increase in oxygen consumption (3%) indicates that either the subjects did not reach maximum on the control trial, or the increase above the maximum control trial represents a change in cardiac output or arteriovenous oxygen difference; this change was undetectable by the CO₂ rebreathing technique.

Recommendations

As a consideration for future investigations a few points should be considered. As described in this and other studies, the subjects should be naive to caffeine. The literature is equivocal as to caffeine influence on metabolism and cardiac performance during exercise. These discrepancies may be attributable to the lack of control of this variable.

Tolerance to the drug may also complicate the determination of the proper dosage. A variety of weight dependent dosages

as administered by Perkins and Williams seems appropriate. The statistical treatment may have to be altered somewhat. An individual may respond at one dose but not another. That is, the threshold for responses may be quite different between individuals in a group. Statistical significance may not be obtained, as was the case with Margaria's data. Repeated measures on the same individual at different dosages may be an appropriate consideration.

Caffeine may not have affected stroke volume during submaximal and maximal exercise simply because the power levels were too high. The lowest submaximal exercise level was at 40% of $\dot{V}O_2$ max, a level considered by some to elicit maximal stroke volume. Caffeine may change the response between rest and 40% $\dot{V}O_2$ max. A dye-dilution technique for estimating cardiac output would be more accurate at those low levels.

Subjects should be pushed at the highest work level so as to ensure that the maximal oxygen consumption has been reached. A counter should be placed on the ergometer to monitor pedal frequency. In this way, the exact power output can be determined during the last level of the test.

Appendix A

Figure 4 Sampling of End-tidal Gas for Carbon Dioxide
During light (A) and heavy (B) Submaximal Exercise

Figure 5
Carbon Dioxide Rebreathing During light (A) and heavy (B) Submaximal Exercise

Figure 6 Schematic Representation of Experimental Apparatus

DATA SHEET FOR CARDIAC OUTPUT CALCULATION

Cardiac Output

NAME M.A. AGE 32 HT 188.0 cm WT 89.8 kg

TEST NO. 2 EXERCISE LEVEL 2.5 DATE 4 May 1979

FINAL READING 367 mm TEMP. 23°C

INITIAL READING 23 mm PRESSURE 744 mm Hg

UNCORRECTED READING 344mm X 133.2ml/mmSTPD FACTOR .874

UNCORRECTED VOLUME $\frac{45.82 \text{ l}}{\quad}$ $P_A = P_b - 47 = \underline{697 \text{ mm Hg}}$

VOLUME STPD 40.05 l H.R. 135

Gas Analysis

$$\% \text{ CO}_2 \quad \underline{4.75} \quad \% \text{ O}_2 \quad \underline{15.61} \quad \% \text{ N}_2 \quad \underline{79.64}$$
$$\% \text{ CO}_2 - .04\% = \% \text{ CO}_2 \text{ expired } \underline{4.71} \quad \% \text{ O}_2 \text{ consumed } \underline{5.495}$$
$$\dot{V}O_{2STPD} \frac{1886}{R \quad .86} \text{ ml/min} \quad \dot{V}O_{2STPD} \frac{2201}{R \quad .86} \text{ ml/min}$$
$$P_a \text{CO}_2 = \% \text{CO}_2 \text{ End-Tidal} \times \frac{P_A}{5.91} = \frac{41.19}{697} \text{ mm Hg}$$
$$P_{\bar{V}}CO_2 = \% CO_2 \text{ Equil} \times P_A = \frac{69.49}{9.97 \times 697} \text{ mm Hg}$$
$$C_a \text{CO}_2 = \frac{49.00}{100} \text{ vol. \%} \quad C_v \text{CO}_2 = \frac{60.05}{100} \text{ vol. \%}$$
$$\dot{Q} = \frac{\dot{V}CO_2 \text{ ml/min}}{C_{\bar{v}}CO_2 \text{ ml/l} - C_aCO_2 \text{ ml/l}} = \frac{17.1}{} \text{ l/min}$$
$$\text{S.V.} = \frac{\dot{Q}}{\text{H.R.}} = \frac{126.7}{\text{ml}}; \text{ a-}\bar{v}\text{O}_2 \text{ Diff.} = \frac{\dot{V}\text{O}_2}{\dot{Q}} = \frac{128.7}{\text{ml/l}}$$

Appendix B

Table 6
Maximal Oxygen Consumption ($l \cdot min^{-1}$)

	No Caffeine	Caffeine
UNTRAINED	3.860	3.959
	3.090	3.064
	3.801	4.160
	<u>4.280</u>	<u>4.253</u>
	3.758 ± 0.494	3.859 ± 0.544
TRAINED	4.130	4.471
	4.412	4.536
	4.563	4.722
	<u>5.299</u>	<u>5.390</u>
	4.601 ± 0.499	4.780 ± 0.421
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	3.1117	1	3.1117	6.60 *
Error	2.8272	6	0.4712	
Treatment	0.0784	1	0.0784	6.89 *
Train x Treat	0.0060	1	0.0060	0.53
Error	0.0682	6	0.0113	

* $p < 0.05$

Table 7

Maximal Pulmonary Ventilation (BTPS) ($\text{l} \cdot \text{min}^{-1}$)

	No Caffeine	Caffeine
UNTRAINED	108.10	119.09
	124.65	94.42
	110.92	133.09
	<u>118.30</u>	<u>135.53</u>
	117.19	118.76
	8.94	17.24
TRAINED	118.30	135.53
	133.80	148.06
	167.71	167.27
	<u>158.89</u>	<u>169.62</u>
	144.68	155.12
	22.71	16.24
$\bar{X} \pm \text{Sd}$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	4077	1	4077	9.35 *
Error	2615	6	435	
Treatment	144	1	144	1.01
Train x Treat	78	1	78	0.55
Error	853	6	142	

* $p < 0.05$

Table 8

61

Maximal Respiratory Exchange Ratio

	No Caffeine	Caffeine
UNTRAINED	1.11	1.07
	1.07	1.07
	1.02	1.04
	<u>1.06</u>	<u>1.06</u>
	1.06 ± 0.05	1.06 ± 0.02
TRAINED	1.04	1.02
	1.06	1.04
	0.98	1.03
	<u>1.09</u>	<u>1.04</u>
	1.04 ± 0.05	1.03 ± 0.01
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	0.0017	1	0.0017	1.42
Error	0.0076	6	0.0012	
Treatment	0.0002	1	0.0002	0.40
Train x Treat	0.0000	1	0.0000	0.01
Error	0.0036	6	0.0006	

Table 9

62

Maximal Heart Rate (beats·min⁻¹)

	No Caffeine	Caffeine
UNTRAINED	185	189
	179	189
	180	187
	<u>190</u>	<u>194</u>
	183.5 ±5.1	189.8 ±3.0
TRAINED	170	174
	177	179
	174	179
	<u>187</u>	<u>188</u>
	177.0 ±7.3	180.0 ±5.8
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	238.09	1	238.09	4.23
Error	337.33	6	56.22	
Treatment	74.66	1	74.66	48.17 †
Train x Treat	9.52	1	9.52	6.14
Error	9.33	6	1.55	

† p < 0.01

Table 10
Maximal Cardiac Output ($l \cdot \text{min}^{-1}$)

	No Caffeine	Caffeine
UNTRAINED	24.4	25.4
	19.4	19.3
	25.1	25.4
	<u>25.0</u>	<u>25.6</u>
	23.5 <u>+2.7</u>	23.9 <u>+3.1</u>
TRAINED	25.7	25.9
	25.3	23.6
	25.8	28.6
	<u>28.7</u>	<u>29.3</u>
	26.4 <u>+1.6</u>	26.9 <u>+2.6</u>
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	551.9	1	551.90	1.05
Error	3152.4	6	525.41	
Treatment	46.4	1	46.41	0.94
Treat x Train	31.8	1	31.80	0.64
Error	297.7	6	49.62	

Table 11
Maximal Stroke Volume (ml)

	No Caffeine	Caffeine
UNTRAINED	129.1	130.9
	139.7	135.4
	104.9	102.1
	<u>139.4</u>	<u>135.8</u>
	124.5	122.9
	<u>±17.7</u>	<u>±18.2</u>
TRAINED	147.7	144.7
	144.1	131.8
	138.0	152.1
	<u>175.0</u>	<u>168.4</u>
	151.2	149.3
	<u>±16.4</u>	<u>±15.3</u>
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	2412.2	1	2412.2	5.58
Error	2591.5	6	431.9	
Treatment	10.4	1	10.4	0.31
Train x Treat	0.1	1	0.1	0.00
Error	202.2	6	33.7	

Table 12

65

Maximal $(a-\bar{v})O_2$ Diff ($ml \cdot l^{-1}$)

	No Caffeine	Caffeine
UNTRAINED	154.2	153.4
	187.3	164.0
	166.9	183.7
	<u>172.3</u>	<u>181.0</u>
	170.2	170.5
	<u>± 13.7</u>	<u>± 14.4</u>
TRAINED	181.1	190.5
	182.5	188.5
	176.4	185.0
	<u>190.1</u>	<u>190.0</u>
	182.5	188.5
	<u>± 5.7</u>	<u>± 2.5</u>
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation				
Training	919.60	1	919.60	6.73*
Error	820.03	6	136.67	
Treatment	40.00	1	40.00	0.50
Train x Treat	31.64	1	31.64	0.40
Error	478.24	6	79.70	

* $p < 0.05$

Table 13
Maximal Exercise Time (min)

	No Caffeine	Caffeine
UNTRAINED	21.5	23.2
	28.0	28.7
	35.0	33.5
	<u>28.2</u>	<u>29.2</u>
	28.2 <u>±5.5</u>	28.7 <u>±4.2</u>
TRAINED	30.6	33.9
	28.8	28.5
	20.0	23.5
	<u>26.4</u>	<u>28.5</u>
	26.5 <u>±4.6</u>	28.5 <u>±4.3</u>
$\bar{X} \pm Sd$		

Analysis of Variance

Source of Variation	SS	df	MS	F-ratio
Training	3.45	1	3.45	0.08
Error	257.49	6	42.91	
Treatment	6.63	1	6.63	5.36
Train x Treat	2.48	1	2.48	2.00
Error	7.42	6	1.23	

Table 14

Oxygen Consumption (l/min) During Submaximal Exercise

		Load I		Load II	
		No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED		1.370	1.489	3.026	2.950
		1.592	1.584	3.017	3.039
		1.650	1.523	3.182	3.174
		1.670	1.769	3.112	3.085
		1.571	1.591	3.084	3.062
		± 0.138	± 0.125	± 0.078	± 0.093
TRAINED		1.990	2.011	3.325	2.850
		1.939	1.973	2.830	2.611
		1.924	1.846	2.871	2.850
		2.165	2.482	3.000	3.094
		2.005	2.078	3.007	2.851
		± 0.111	± 0.278	± 0.224	± 0.197
$\bar{X} \pm Sd$					
Analysis of Variance					
Source of Variance		SS	df	MS	F-ratio
Training		0.1998	1	0.1998	2.94
Error		0.4073	6	0.0678	
Treatment		0.0034	1	0.0034	0.20
Train x Treat		0.0032	1	0.0032	0.18
Error		0.1044	6	0.0174	
Load		11.3276	1	11.3276	569.40†
Treat x Load		0.7311	1	0.7311	36.75†
Error		0.1193	6	0.0198	
Train x Load		0.0369	1	0.0369	4.12
Train x Load x Treat		0.0172	1	0.0172	1.92
Error		0.0538	6	0.0089	

† $p < 0.01$

Table 15

68

Respiratory Exchange Ratio During Submaximal Exercise

	Load I		Load II	
	No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED	0.82	0.79	0.95	0.93
	1.02	0.95	1.06	1.07
	0.89	0.89	1.00	1.00
	0.86	0.88	0.94	0.96
	0.90 ± 0.09	0.88 ± 0.07	0.98 ± 0.06	0.99 ± 0.06
TRAINED	0.82	0.80	0.91	0.87
	0.81	0.84	0.84	0.85
	0.90	0.90	0.93	0.94
	0.84	0.86	0.87	0.89
	0.84 ± 0.04	0.85 ± 0.04	0.89 ± 0.04	0.89 ± 0.04
$\bar{X} \pm Sd$				

Analysis of Variance

Source of Variance	SS	df	MS	F-ratio
Training	0.0406	1	0.0406	3.68
Error	0.0662	6	0.0110	
Treatment	0.0000	1	0.0000	0.09
Treat x Train	0.0003	1	0.0003	0.57
Error	0.0032	6	0.0005	
Load	0.0406	1	0.0406	57.50†
Treat x Load	0.0072	1	0.0072	10.19
Error	0.0042	6	0.0007	
Train x Load	0.0001	1	0.0001	0.52
Train x Load x Treat	0.0004	1	0.0004	2.10
Error	0.0012	6	0.0002	

† $p < 0.01$

Table 16

Heart Rate (beats/min) During Submaximal Exercise

	Load I		Load II	
	No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED	110	93	169	158
	127	121	181	189
	109	110	163	162
	114	123	161	170
	115.0 ±8.3	111.8 ±13.7	168.5 ±9.0	170.0 ±13.8
TRAINED	125	112	150	139
	112	99	130	127
	107	104	145	144
	110	113	125	123
	113.5 ±7.9	107.0 ±6.7	137.5 ±11.9	133.3 ±9.9
$\bar{X} \pm Sd$				

Analysis of Variance

Source of Variance	SS	df	MS	F-ratio
Training	2719.53	1	2719.53	9.71*
Error	1679.68	6	279.94	
Treatment	81.28	1	81.28	1.32
Train x Treat	38.28	1	38.28	0.62
Error	370.68	6	61.78	
Load	13081.53	1	13081.53	154.53†
Treat x Load	1875.78	1	1875.78	22.16†
Error	507.93	6	84.65	
Train x Load	22.78	1	22.78	2.04
Train x Treat x Load	2.53	1	2.53	0.23
Error	66.93	6	11.15	

†p < 0.01

*p < 0.05

Table 17

70

Cardiac Output (L/min) During Submaximal Exercise

	Load I		Load II	
	No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED	13.2	10.3	21.7	16.3
	17.3	15.8	16.5	17.6
	15.3	12.6	26.7	18.9
	14.0	15.5	20.0	17.3
	15.0 ± 1.7	13.6 ± 2.6	21.2 ± 4.2	17.5 ± 1.1
TRAINED	16.4	16.1	17.2	16.4
	14.1	14.5	19.5	14.7
	17.1	22.7	16.8	17.4
	14.9	17.3	21.3	21.0
	15.6 ± 1.3	16.2 ± 1.2	20.2 ± 2.4	17.4 ± 2.7
$\bar{X} \pm Sd$				

Analysis of Variance

Source of Variance	SS	df	MS	F-ratio
Training	2.205	1	2.205	0.30
Error	43.485	6	7.247	
Treatment	27.011	1	27.011	5.75
Train x Treat	4.061	1	4.061	0.86
Error	28.197	6	4.699	
Load	127.999	1	127.999	14.92†
Treat x Load	10.125	1	10.125	1.18
Error	51.474	6	8.579	
Train x Load	15.961	1	15.961	7.63*
Train x Load x Treat	0.551	1	0.551	0.26
Error	12.547	6	2.091	

† $p < 0.01$ * $p < 0.05$

Table 18

(a-v)O₂ Diff (ml/l) During Submaximal Exercise

	Load I		Load II	
	No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED	104.5	143.9	142.4	182.6
	93.6	101.5	182.8	164.2
	108.4	122.0	119.7	171.1
	121.5	114.1	155.9	178.3
	107.0	120.4	150.2	174.1
	± 11.5	± 17.8	± 26.4	± 8.1
TRAINED	121.3	124.9	193.3	173.8
	131.1	136.9	146.0	177.7
	112.5	122.4	127.8	173.5
	150.5	143.5	140.6	148.0
	129.4	131.9	151.9	168.3
	± 16.4	± 10.0	± 28.6	± 13.6
$\bar{X} \pm Sd$				

Analysis of Variance

Source of Variance	SS	df	MS	F-ratio
Training	445.5	1	445.5	2.13
Error	1257.4	6	209.5	
Treatment	1573.6	1	1573.6	4.43
Train x Treat	167.4	1	167.4	0.47
Error	2131.2	6	355.2	
Load	12136.8	1	12136.8	22.70†
Treat x Load	721.9	1	721.9	1.35
Error	3207.4	6	534.5	
Train x Load	924.0	1	294.0	1.53
Train x Load x Treat	5.2	1	5.2	0.03
Error	1155.9	6	192.6	

† p < 0.01

Table 19
Stroke Volume (ml) During Submaximal Exercise

	Load I		Load II	
	No Caffeine	Caffeine	No Caffeine	Caffeine
UNTRAINED	115.3	109.4	128.3	102.8
	137.1	131.0	91.3	98.3
	140.6	114.6	163.8	117.7
	122.6	127.1	155.9	97.0
	128.9 ± 11.96	120.5 ± 10.2	134.8 ± 32.8	103.9 ± 9.5
TRAINED	131.3	143.3	114.9	118.0
	131.3	152.4	150.4	116.9
	160.0	162.0	156.9	120.8
	134.3	153.7	171.1	170.3
	139.7 ± 13.6	152.9 ± 7.7	148.3 ± 23.9	131.5 ± 25.9
$\bar{X} \pm Sd$				

Analysis of Variance

Source of Variance	SS	df	MS	F-ratio
Training	3540.6	1	3540.6	6.47*
Error	3282.5	6	547.0	
Treatment	920.2	1	920.2	4.54
Train x Treat	633.6	1	633.6	3.12
Error	1216.8	6	202.8	
Load	272.6	1	272.6	0.52
Treat x Load	2.1	1	2.1	0.00
Error	3172.6	6	528.7	
Train x Load	1378.1	1	1378.1	8.10*
Train x Load x Treat	28.1	1	28.1	0.17
Error	1020.2	6	170.0	

*p < 0.05

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