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Effects of Chronic Caffeine Ingestion on Growth and Myocardial Function (42114)

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Abstract. Experiments were conducted to determine whether chronic caffeine consumption during early growth and development affected cardiac performance and development of adipose tissue. Dams were fed a nutritionally complete diet with or without the addition of 10 mg/kg caffeine during lactation. After weaning, the pups were maintained on this diet until they were sacrificed at 88 days of age. Body weight at the time of sacrifice was comparable for both groups. The hearts from caffeine-fed animals were significantly ($P < 0.05$) larger based on both dry and wet weights although the dry weight/wet weight ratios were similar. Ventricular function curves were generated on each heart using an isolated working heart preparation. The isolated hearts of caffeine-fed rats exhibited a significant reduction in cardiac output, stroke volume, mean aortic pressure, and estimated myocardial work when compared to controls. The rats fed caffeine had greater plasma triglyceride levels with no significant differences in adipocyte size or number in the epididymal and perirenal depots. It is concluded that chronic caffeine intake from birth may alter cardiac function of the offspring.

The pharmacologic effects of caffeine, a trimethylxanthine, have received considerable attention due to its daily ingestion by a large portion of the population (1, 2). Acute caffeine consumption can directly affect the central nervous system, cardiac muscle, cardiac output (2–4), blood pressure, heart rate (1), catecholamine release, and renin activity (2, 5, 6). These reports, however, have been inconsistent with regard to caffeine's effect on these specific factors (7). In addition, caffeine increases free fatty acid mobilization from adipose tissue following its ingestion in man (8, 9). Reports concerning the chronic effects of caffeine on the cardiovascular system are rare but have suggested that the organism rapidly develops a tolerance to caffeine's acute actions and the effects do not persist (5, 10).

While caffeine is known to have acute effects on the cardiovascular system, it is important to establish whether chronic ingestion during the early developmental periods (i.e., lactation, early growth) may adversely affect the heart. Little has been published regarding the chronic effects of caffeine on growth and development. This is especially important since caffeine has been found in mother's milk (11, 12) and is thus available to the suckling infant.

The purpose of the present study was to determine whether caffeine consumption during early growth periods has a long-term effect on cardiac performance at maturity. In order to separate external influences from those of the myocardium, an isolated working rat heart preparation was used. In addition, since caffeine is known to activate the sympathetic nervous system and elevates plasma free fatty acids (8, 9, 13, 14), we also examined the effect of chronic caffeine consumption on the development of adipocyte size and number in two adipose depots in the rat.

Materials and Methods. Timed pregnant Sprague–Dawley rats (Holtzman Co., Madison, Wis.) were fed Purina laboratory chow until delivery. After birth, several litters were combined if the time of delivery was within a range of 8 hr. Eight randomly selected pups were assigned to each dam. Half the dams which were fed a nutritionally complete diet with 20% protein (15) *ad libitum* served as controls. The remaining dams were pair-fed to the control group with the 20% protein diet supplemented with caffeine (10 mg/kg). This dose of caffeine was chosen so that it would fall within the range of the daily consumption by the American public. During the lactation period, pups received caffeine through the mother's milk (11, 12). When all the pups were weaned at day 22, only

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male animals were used for the experiment. These animals continued to receive their respective diet until they were killed at Day 88 postbirth. The caffeine supplemented diet was made every 10 to 14 days and the amount of caffeine in the diet was adjusted according to increased body weight and food intakes. Each rat was housed individually and water was provided *ad libitum*.

Approximately 1 week before the animals were to be killed, they were fasted overnight, a blood sample from the tail vein was taken, and plasma triglyceride concentrations were determined by an automated procedure (16). Two days prior to sacrificing, individual resting metabolic functions were determined by placing the fasted animal in a metabolic chamber which was connected to a Noyons-Diaferometer, an O_2–CO_2 analyzer. After a 30-min resting period, O_2 consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were determined and the respiratory quotient (RQ) was calculated (13).

Just prior to sacrifice, the animals were injected intraperitoneally with 500 U heparin followed by sodium pentobarbital (50 mg/kg body wt). The hearts were excised, placed in cold saline, and then placed on the aortic cannula for determination of cardiac performance. Also, both the epididymal and perirenal depots were removed in their entirety, rinsed in saline, and weighed. Adipocytes were isolated and both cell size and number per fat pad were determined as previously described (17).

The cardiovascular performance of the caffeine-fed and control groups was examined by using the isolated working heart preparation as previously described (18, 19). Retrograde perfusion of the coronaries was initiated using an oxygenated, nonrecirculating Krebs-Henseleit bicarbonate buffer with glucose. Perfusion was continued for approximately 10 min while the left atrial appendage and the pulmonary artery were cannulated. After the cannulation procedures were completed, antegrade perfusion via the left atrial cannula was begun.

For the first 5–10 min of antegrade perfusion, the heart was perfused at a preload pressure of 15 cm H_2O above the level of the left atrial cannula to allow for pressure stabilization. The hearts were not paced and the workload was varied by changing the preload pressure (left atrial filling pressure). The afterload was maintained by keeping the aortic overflow tube at 70 cm H_2O. After stabilization, the hearts were perfused at left atrial filling pressures of 10, 15, 20, 25, and then back to 15 cm H_2O. Each left atrial filling pressure was maintained for 5 min before measurements were recorded.

The perfusion medium used in this experiment was a modified Krebs-Henseleit bicarbonate buffer (pH 7.4), equilibrated with 95% O_2–5% CO_2 at 37°C. Final concentration of salts in the buffer were (in m*M*) NaCl 118, KCl 4.7, $MgSO_4$ 2.4, KH_2PO_4 1.2, $NaHCO_3$ 25, NaEDTA 1.0, and $CaCl_2$ 2.8. Glucose (5.5 m*M*) was added to the buffer as the only substrate. The buffer was recirculated throughout each experiment using new buffer for each heart.

After the 5-min equilibration period at each preload pressure, coronary and aortic flow were measured using graduated cylinders. All flow related measurements were normalized to the dry weight of the heart. Oxygen in the left atrial buffer reservoir and the coronary effluent were measured with an oxygen probe connected to an oxygen monitor (Yellow Springs Instruments, Models 5331 and 53, respectively). Oxygen consumption and external efficiency were calculated (19, 20) with oxygen consumption being expressed as millimoles oxygen consumed per hour per gram dry heart weight and external efficiency as a percentage. An estimation of myocardial work (double product) was calculated as cardiac output ($\dot{Q}$) times peak systolic pressure (PSP).

Data are expressed as means ± SEM. A two-way analysis of variance with repeated measures design was used to evaluate the differences between groups (control and caffeine-fed) and various preload pressures (10, 15, 20, and 25 cm H_2O). A Newman–Keuls multiple range test was used to determine significant differences between means. Correlations were used to determine relationships between variables while regression analysis was used to evaluate oxygen consumption and coronary flow in relation to estimated myocardial work. Statistical differences were considered significant at $P < 0.05$ (21, 22).

Results. In examining the physical char-

acteristics of the animals used in this study, there were no significant differences in body weight between the two groups at the time of sacrifice (Table I). Also, no significant differences in body weight were observed during growth and development (birth to 88 days) between the control and caffeine-fed animals. Whole-body oxygen consumption ($\dot{V}_{O_2}$) for the caffeine-fed animals was significantly increased by 16% during rest while the respiratory quotient (RQ) was not significantly different from controls (Table I). There were no differences in either adipocyte size or number in either of the two depots examined. In contrast, plasma triglyceride was significantly increased in the caffeine-fed group (Table II). With regard to heart weight, the caffeine-fed animals had a significant 19% increase in dry and wet heart weight while the dry heart weight/body weight ratios were 8% greater ($P < 0.05$) than the controls. The dry to wet heart weight ratio was similar between groups (Table I).

Cardiac output ($\dot{Q}$) in the working heart increased significantly with preload pressure for both groups (Fig. 1). Hearts from caffeine-fed rats had a significantly lower $\dot{Q}$ than the control group at preloads of 10, 15, and 20 cm H_2O. At the highest preload pressure, 25 cm H_2O, $\dot{Q}$ for the hearts from caffeine-fed animals appeared to be depressed, however, the difference was not significant. Since there were no significant differences in *in vitro* heart rate (HR) between the controls (174 ± 4 beats/min) and the caffeine-fed group (185 ± 4 beats/min) at any preload pressure, the stroke volume (SV) for the experimental group was significantly less than for the controls at all left atrial filling pressures (Fig. 1). Coronary flow (CF) was not significantly different between the controls and the hearts from the caffeine-fed group (Fig. 1). However, the CF/$\dot{Q}$ ratio for the caffeine-fed group was significantly greater (80–87%) at all preload pressures than the CF/$\dot{Q}$ ratio for the controls (75–78%).

Peak systolic pressure (PSP) increased with each increment of preload pressure for both groups. Hearts from the caffeine-fed rats had a lower but not significantly different PSP than control hearts (121.9 ± 2.8 and 130.8 ± 2.6 mm Hg, respectively). Diastolic pressure was significantly lower in the hearts from

TABLE I. BODY WEIGHT, HEART WEIGHT, RESPIRATORY QUOTIENT, AND RESTING OXYGEN CONSUMPTION OF CONTROL AND CAFFEINE-FED RATS

		Body wt (g)	Wet heart wt (mg)	Dry heart wt (mg)	Dry heart wt/body wt	Dry heart wt/wet heart wt	RQ	$\dot{V}_{O_2}$ (ml/min)	$\dot{v}_{O_2}$ (ml/min/kg)
Control	$\bar{X}$	375	1554	282	0.754	18.13	0.76	5.34	13.16
($n = 8$)	SEM	15	47	10	0.015	0.27	0.01	0.48	0.68
Caffeine fed	$\bar{X}$	411	1846*	336*	0.818*	18.23	0.74	6.49*	15.31*
($n = 8$)	SEM	12	55	10	0.015	0.31	0.02	0.27	0.89

Note. Values represent mean ($\bar{X}$) ± SEM. Numbers in parentheses represent the n per group.
* Treatment significantly different from control value, $P < 0.05$.

TABLE II. ADIPOSE TISSUE AND PLASMA TRIGLYCERIDE DATA ON CONTROL AND CAFFEINE-FED RATS

		Epididymal depot				Perirenal depot				
		Wt (g)	Diameter (μm)	TG/cell (μg)	No. cells ($\times 10^6$)	Wt (g)	Diameter (μm)	TG/cell (μg)	No. cells ($\times 10^6$)	Plasma TG (mg/dl)
Control ($n = 7$)	$\bar{X}$	5.76	84.89	0.373	11.35	8.37	93.94	0.498	11.63	83.74
	SEM	0.87	4.14	0.055	1.46	1.20	4.04	0.064	1.21	12.02
Caffeine fed ($n = 8$)	$\bar{X}$	7.68	82.82	0.400	13.26	9.44	88.32	0.483	12.35	144.46*
	SEM	0.89	4.51	0.069	1.73	0.84	3.33	0.063	1.72	20.34

Note. Values represent mean ($\bar{X}$) ± SEM. Numbers in parentheses represent the n per group.
* Treatment significantly different from control value, $P < 0.05$.

caffeine-fed animals at 10 cm H_2O when compared to the control hearts (34.5 ± 2.4 and 42.6 ± 2.0 mm Hg, respectively). Mean aortic pressure was significantly less for the caffeine-fed group at preloads of 10, 15, and 20 cm H_2O (Fig. 2).

The double product ($\dot{Q} \times$ PSP) and stroke work ($\dot{Q} \times$ PSP/HR), which were used to estimate myocardial work, increased with preload pressure in both the caffeine-treated and control groups. Hearts from caffeine-fed rats exhibited a significantly lower double product at left atrial filling pressures of 10, 15, and 20 cm H_2O than the control hearts (Fig. 3). Stroke work displayed similar significant differences as double product at preloads of 10, 15, and 20 cm H_2O.

Myocardial oxygen consumption in hearts from the caffeine-fed group was significantly less at a preload pressure of 10 cm H_2O (Fig. 4). With increasing preload pressures, no significant differences between groups were observed.

Myocardial oxygen consumption ($r = 0.74$, $P < 0.05$) and coronary flow ($r = 0.88$, $P < 0.05$) correlated well with all indices of myocardial work tested. However, there were no significant differences in the slopes or intercepts between the control and caffeine-fed hearts when myocardial oxygen consumption or coronary flow were examined as a function of myocardial work.

Discussion. Caffeine is a common component of beverages such as coffee, tea, cola, and other carbonated soft drinks as well as in many popular, over-the-counter medications (23). Caffeine is a potent stimulant of the central nervous system when administered acutely and produces both positive inotropic and chronotropic effects on the heart. Caffeine also has a variety of hormonal and metabolic effects in acute studies (2, 24). In contrast, the chronic ingestion of caffeine has received little attention experimentally, especially during the period of early growth and development. The manner in which continuous intake of caffeine during this period may affect the cardiovascular system of the growing offspring is also presently not known. Caffeine easily diffuses into breast milk (11, 12) and with the growing number of women who nurse their infants (which has increased to 55%) (11), it then becomes extremely impor-

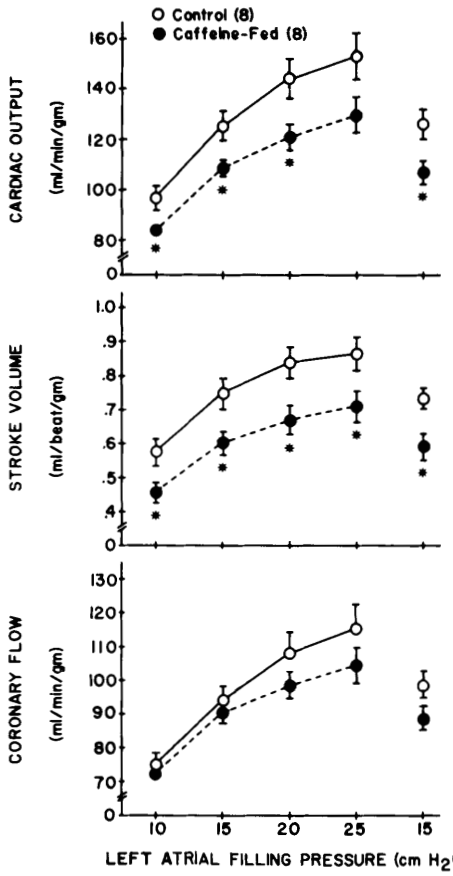

FIG. 1. Changes in cardiac output, stroke volume, and coronary flow (mean ± SEM) in the isolated working heart at various left atrial filling pressures in control and caffeine-fed rats. Number of hearts per group is given in parentheses. All flows are expressed in terms of dry heart weight. *Treatment is significantly different from control value, $P < 0.05$.

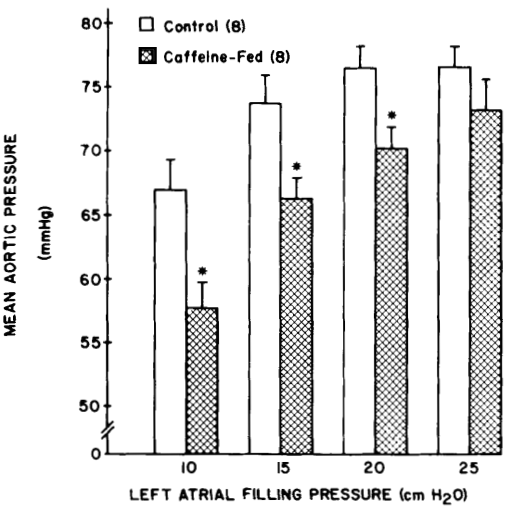

FIG. 2. Changes in mean aortic pressure (mean ± SEM). Number of hearts for each condition is shown in parentheses. *Treatment is signficantly different from control value, $P < 0.05$.

tant to determine the effects of early caffeine intake by newborns through the milk as well as continuous intake of caffeine by them after weaning.

The present results demonstrate that the hearts of animals fed caffeine from birth can be distinguished from control hearts with respect to heart weight and cardiac performance. The increased heart weight in the caffeine-fed animals might be attributed to several factors such as volume- and/or pressure-overload hypertrophy (25), increased catecholamine release (26, 27), increased renin activity (2, 6), and increased growth hormone levels (28). However, data are not presently available to determine the relative importance of the above factors on cardiac hypertrophy. Although the body weights for both groups were not significantly different, the caffeine-fed animals had a mean body weight 9% greater than that of the controls. Due to the between-group and within-group variability in body weight, no definitive con-

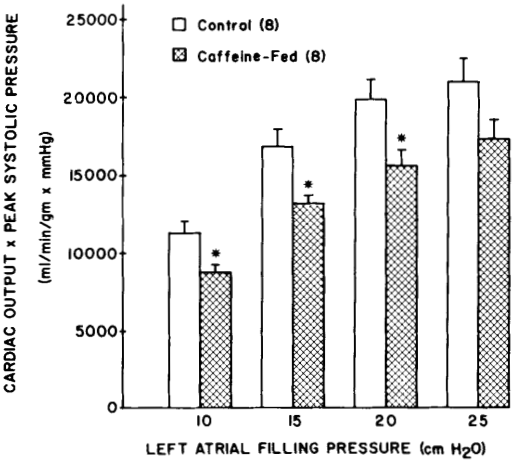

FIG. 3. Changes in estimated myocardial work (mean ± SEM). Number of hearts per group is given in parentheses. *Treatment is significantly different from control value, $P < 0.05$.

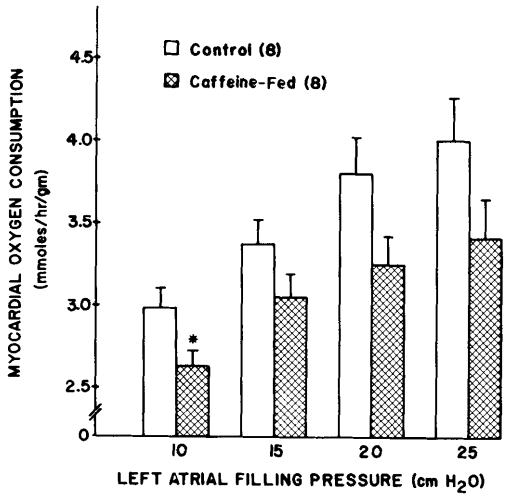

FIG. 4. Changes in myocardial oxygen consumption (mean ± SEM). Number of hearts for each condition is shown in parentheses. *Treatment is significantly different from control value, $P < 0.05$.

clusion can be drawn as to the contribution of body weight on cardiac performance and heart weight.

The larger hearts of the caffeine-fed animals may account for some of the findings in this experiment. For example, with the finding of increased heart weight in the animals fed caffeine, it was not surprising that coronary flow (ml/min/g dry heart wt) and the coronary flow/cardiac output ratio would be the same in both groups. If myocardial hypertrophy is due to an increase in muscle tissue, this may be accompanied by an increased vascularization resulting in greater coronary flow. On the basis of dry heart weight, the caffeine-fed hearts displayed a number of differences in cardiac performance from the control group. First, cardiac output and stroke volume were decreased in the hearts of caffeine-treated animals at most preload pressures. Also, decreased myocardial work was observed at these preload pressures in the caffeine-fed animals. These decreases can, in part, be accounted for by differences in pressure development in the caffeine-fed and control groups. At the preload pressures where work and cardiac output were reduced, there were reductions in mean aortic pressure. The hearts of the caffeine-fed animals could not generate as much pressure as the controls. Therefore, at the fixed resistance used in our apparatus, cardiac output, stroke volume, and the work performed were reduced. Additionally, there was a significant decrease in oxygen consumption in the hearts of the caffeine-fed animals at the lowest preload pressure (10 cm H_2O) and in most experiments at the other preload pressures.

The increased heart weight in the caffeine-fed animals may account for the differences in cardiac performance from the standpoint of a change in the length–tension relationship (i.e., Starling curve) of the larger hearts. The Starling relationship predicts that with a given increase in preload pressure or left end diastolic volume, cardiac output will be increased (29, 30). At almost all preload pressures, the caffeine-fed animals produced less cardiac output than the control animals. One reason for a shift in the Starling curve is a change in contractility. At preload pressures of 10, 15, and 20 cm H_2O, a decrease in contractility may explain the decreased flow and work values in the caffeine-treated hearts. Numerous explanations in the literature have been reported which could change contractility: release of calcium, increased heart weight, and the number of myofibrils (1, 25, 31). A possible reason for the change in contractility was the increased heart weight in the animals fed caffeine. Although we did not measure left ventricular end diastolic volume, if the increase in heart weight represented an increase in volume, then the heart would have to create more tension for the same pressure (i.e., Law of LaPlace). Since it did not, a reduced pressure was observed (30). It is premature, however, to conclude whether the increased heart weight (and perhaps volume) and the associated reduced cardiac performance represented impaired performance since the nature of the working heart apparatus may be such that the larger hearts are only required to develop a certain amount of pressure at a given preload pressure to meet the resistance placed upon it. It has been reported that larger hearts produce less pressure and perform less work than a smaller heart at a given preload (20).

In this regard, it is important to note that the differences observed in the two groups at lower preloads were less pronounced at the highest preload pressure (25 cm H_2O) ex-

amined in this experiment. At this higher preload, values of flow, work, and pressure were not statistically reduced in the caffeine-fed animals. Perhaps the length–tension relationship in larger hearts is such that an increase in preload pressure is needed to generate pressures comparable to normal-sized hearts. Compliance may have been altered in the caffeine-fed hearts because it is not uncommon to find increased chamber stiffness resulting from pressure- or volume-overload hypertrophy (32). In such instances, very high ventricular filling pressures may be required to maintain adequate diastolic sarcomere stretch (32) for greater ventricular diastolic filling and systolic ejection.

With regard to metabolic parameters and FFA availability to the heart, caffeine consumption produced an elevation in resting whole-body oxygen consumption ($\dot{V}_{O_2}$), a slight reduction in RQ, and an elevation in fasting plasma triglyceride levels. The observed changes in oxygen consumption and the respiratory quotient are consistent with observations following caffeine intake by human volunteers in approximately the same dose levels (4 and 8 mg/kg) (13, 14). Conversely, our values were obtained from fasted rats and may have represented a long-term adaptation in increasing the metabolic rate under these specific nutritional conditions. The reduction in RQ following caffeine ingestion was consistent with other reports (13, 14) resulting in a concomitant increase in plasma free fatty acid (FFA) levels.

Because of the pronounced effect of caffeine on FFA mobilization (8, 9, 13, 14), the epididymal and perirenal depots were examined to determine if this caffeine dosage would affect adipocyte size or number. Our nonsignificant findings regarding adiposity were consistent with other studies in the rat in which dosages of 50 mg/kg produced no alterations in these parameters (33). However, when caffeine was added in higher doses (65 and 150 mg/kg) to the diet, the adipocyte number and size in the perirenal depot decreased in spite of the fact that there were no significant differences in food consumption (33). Thus, significantly higher doses of caffeine may be necessary in order to elicit a significant change in adiposity. The fact that adipose tissue lipolysis was probably increased in our study may be deduced from the fact that RQ was decreased somewhat and fasting plasma triglycerides were significantly increased. This latter observation is consistent with an increased FFA mobilization resulting in an increase in plasma very low density lipoprotein secretion to recycle the FFA back to the adipose tissues for storage.

The precise physiological significance of chronic caffeine administration on the heart is apparently complex. Continuous caffeine consumption results in mild cardiac hypertrophy which causes a depressed myocardial function at fixed preload pressures when observed on an isolated working heart preparation. The increased heart mass may be attributed to several *in vivo* stimulations as previously discussed. The administration of caffeine to young animals during early growth and development may affect the myocardium in such a way as to decrease contractility and hence work of the heart. At this time, we have no evidence that this occurs *in vivo.* However, this would be difficult to observe because of the many compensatory mechanisms.

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1. MacCornack FA. The effects of coffee drinking on the cardiovascular system: Experimental and epidemiological research. Prev Med **6**:104–119, 1977.
2. Rall TW. Central nervous system stimulants: The xanthines. In: Gilman AG, Goodman LS, Gilman A, eds. The Pharmacological Basis of Therapeutics. New York, Macmillan, 6th ed, pp592–607, 1980.
3. Grollman A. The action of alcohol, caffeine, and tobacco on the cardiac output (and its related functions) of normal man. J Pharmacol Exp Ther **39**: 313–329, 1930.
4. Marcus ML, Skelton CL, Grauer LE, Epstein SE. Effects of theophylline on myocardial mechanics. Amer J Physiol **222**:1361–1365, 1972.
5. Izzo JL Jr, Ghosal A, Kwong T, Freeman RB, Jaenike JR. Age and prior caffeine use alter the cardiovascular and adrenomedullary responses to oral caffeine. Amer J Cardiol **52**:769–773, 1983.
6. Robertson D, Frolich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA. Effects of

caffeine on plasma renin activity, catecholamines, and blood pressure. N Engl J Med **298**:181–186, 1978.
7. Curatolo PW, Robertson D. The health consequences of caffeine. Ann Intern Med **98**:641–653, 1983.
8. Bellet S, Kershbaum A, Finck EM. Response of free fatty acids to coffee and caffeine. Metabolism **17**: 702–707, 1968.
9. Bellet S, Kershbaum A, Roman L. Effect of cola drinks on serum free fatty acids. Arch Environ Health **17**:803–806, 1968.
10. Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest **67**: 1111–1117, 1981.
11. Berlin CM Jr, Denson HM, Daniel CH, Ward RM. Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. Pediatrics **73**:59–63, 1984.
12. Horning MG, Butler CM, Nowlin J, Hill RM. Drug metabolism in the human neonate. Life Sci **16**:651–671, 1975.
13. Acheson KJ, Zahorska-Markiewicz B, Anatharamum K, Jequier E. Caffeine and coffee: Their influence on metabolic rate and substrate utilization in normal weight and obese individuals. Amer J Clin Nutr **33**: 989–997, 1980.
14. Jung RT, Shetty PS, James WPT, Barrand MA, Callingham BA. Caffeine: Its effect on catecholamines and metabolism in lean and obese humans. Clin Sci **60**:527–535, 1981.
15. Quinby GE, Nakamoto T. Theophylline effects on cellular response in protein-energy malnourished neonatal rat brain. Pediatr Res **18**:546–549, 1984.
16. Krause BR, Balzer M, Hartman AD. Adipocyte cholesterol storage: Effect of starvation. Proc Soc Exp Biol Med **167**:407–411, 1981.
17. Hartman AD, Cohen AI, Richane CJ, Hsu T. Lipolytic response and adenyl cyclase activity of rat adipocytes as related to cell size. J Lipid Res **12**: 498–505, 1971.
18. Fintel MC, Burns AH. A simplified working heart apparatus specialized for use with radioisotopes and oxygen electrodes. Ala J Med Sci **19**:129–135, 1982.
19. Neely JR, Liebermeister H, Battersby EJ, Morgan HE. Effect of pressure development on oxygen consumption by isolated rat heart. Amer J Physiol **212**: 804–814, 1967.
20. Penpargkul S, Scheuer J. The effect of physical training upon the mechanical and metabolic performance of the rat heart. J Clin Invest **49**:1859–1868, 1970.
21. Bruning JL, Kintz BL. Computational Handbook of Statistics. Philadelphia, Scott, Foresman, 1977.
22. Tallarida RJ, Murray RB. Manual of Pharmacologic Calculations with Computer Programs. New York, Springer-Verlag, 1981.
23. Graham DM. Caffeine—Its identity, dietary sources, intake and biological effects. Nutr Rev **36**:97–102, 1978.
24. Vestal RE, Eiriksson CE Jr, Musser B, Ozaki LK, Halter JB. Effect of intravenous aminophylline on plasma levels of catecholamines and related cardiovascular and metabolic responses in man. Circulation **67**:162–171, 1983.
25. Grossman W, Carabello BA, Gunther S, Fifer MA. Ventricular wall stress and the development of cardiac hypertrophy and failure. Perspect Cardiovasc Res **7**: 1–18, 1983.
26. Laks MM, Morady F, Swan HJC. Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest **64**:75–78, 1973.
27. Ostman I, Sjostund NO, Swedin G. Cardiac norepinephrine turnover and urinary catechol excretion in trained and untrained rats during rest and exercise. Acta Physiol Scand **86**:299–308, 1972.
28. Clozel M, Branchaud CL, Tannenbaum GS, Dussault JH, Aranda JV. Effect of caffeine on thyroid and pituitary function in newborn rats. Pediatr Res **17**: 592–595, 1983.
29. Goldfarb RD. Cardiac mechanical performance in circulatory shock: A critical review of methods and results. Circ Shock **9**:633–653, 1982.
30. Guyton AC. Textbook of Medical Physiology. Philadelphia, Saunders, p168, 1976.
31. Lin CI, Vassalle M. Role of calcium in the inotropic effects of caffeine in cardiac Purkinje fibers. Int J Cardiol **3**:421–434, 1983.
32. Grossman W, Lorell BH. Influence of cardiac hypertrophy on myocardial compliance. Perspect Cardiovasc Res **8**:211–217, 1983.
33. Bukowiecki LJ, Lupien J, Follea N, Jahjah L. Effects of sucrose, caffeine, and cola beverages on obesity, cold resistance, and adipose tissue cellularity. Amer J Physiol **244**:R500–R507, 1983.

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