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Arterial capacitance changes with starvation-realimentation in the dog, and associated vascular electrolyte changes.

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ARTERIAL CAPACITANCE CHANGES WITH STARVATION-REALIMENTATION IN THE DOG, AND ASSOCIATED VASCULAR ELECTROLYTE CHANGES

by

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INTRODUCTION

Some of the effects of starvation and realimentation have been documented in the literature. Hypertension has been one of the most frequently recorded results of starvation-realimentation. Even though possible mechanisms of the resultant hypertension have been investigated, the possibility of structural change in the arterial tree influencing hypertension has not been explored. The primary goal of this project was to determine if short term starvation-realimentation over a one month period, results in decreased arterial capacitance and decreased arterial distensibility. If such a change occurs, hypertension may result.

The second goal of this project was to evaluate the indirect method for determining arterial capacitance. Presently, an accurate index of arterial capacitance can only be obtained by removing vessel segments, which usually requires sacrificing the animal, and determining a stretch-tension relationship. Therefore, the value of the indirect method can be readily appreciated. Long term projects could be designed, with animals serving as their own controls, and changes in individual animals could be evaluated. Thus, establishing the validity of this method would offer a useful tool for research, and could possibly have clinical implications.

A third goal of this project was to compare cardiovascular parameters of Specific Pathogen Free (SPF) dogs and street dogs.

A comparison of arterial capacitance, arterial stretch-tension, and arterial vessel electrolyte concentrations was of primary interest. There has been emphasis for the utilization of standard breeds of animals for research. The theory being that standardized breeds or groups will result in better controlled experiments, and more reliable results. However, the question must be asked, "What is the response of these animals to stress conditions?"

The effect of treatment and animal type on arterial vessel sodium and potassium concentrations was of interest. Elevations of arterial sodium and potassium have been reported in hypertensive animals and man. Various theories have been expressed regarding the relationship between these electrolytes and arterial reactivity. The relationship between these electrolytes, and arterial capacitance and distensibility, has not been established.

REVIEW OF LITERATURE

The Structural and Physical Properties of Arteries

Structural properties of arteries

Buck (1963) discussed the structural properties of the tunica intima and tunica media. The tunica intima is composed of the endothelium and subendothelium, and is demarcated from the tunica media by the internal elastic lamina. The endothelial cells are characterized by an inconsistency in height throughout the arterial tree, tending to be more cuboidal in the smaller arteries and squamous in the aorta. These cells contain small invaginations of the plasma membrane known as pinocytic vesicles. It has been hypothesized that these vesicles are involved in the transport of materials into and out of the cell. The subendothelium consists of elastic fibers and smooth muscle cells. This layer is believed to arise from a "splitting" of the internal elastic lamina, and the accumulation of acid mucopolysaccharide pools between the internal elastic lamina and the endothelium. Smooth muscle cells then migrate into the forming subendothelium from the media. The subendothelial smooth muscle cells are arranged longitudinally.

The arterial tunica media consists of smooth muscle cells, elastic fibers, and collagen. In the aorta, heavy elastic lamellae alternate with interlamellar spaces which contain the smooth muscle cells. Each muscle cell extends from one

lamellae to the next. The long axes of the cells are parallel to one another, but oblique to the elastic lamellae. The media of the muscular arteries consists of closely united smooth muscle cells, and elastic fibers are present in all arteries except the smallest arterioles and arteriovenous anastomoses. Elastic tissue is found in highest proportion in the aorta where it makes up 30 to 40% of its dry weight. In muscular arteries the major elastic membranes consist of the internal and external elastic lamellae. The elastic membranes are composed of fibrous networks, and have fenestrations through which cells and materials may pass. The collagen content of the media of normal muscular arteries is very low. However, in the aorta of man the collagen content is greater, while in the rat, collagen fibrils are seemingly distributed randomly.

Pease and Molinari (1960), in an electron microscopy study of the pial vessels of the cat and monkey, demonstrated a close relationship between elastic fibers and the baserent membranes of smooth muscle cells. The elastin appeared to blend and attach with the basement membranes of smooth muscle cells to form a continuous system. On the other hand, collagen was never found to be directly associated with either elastic fibers or basement membranes, but formed a separate framework which permeated the tunica media of larger vessels. Fibrocytes and histocytes were never seen in the endothelium and media. This fact led to the conclusion that the smooth muscle

cells are responsible for organizing the connective tissue skeleton. The authors speculated that the elastin consists of two elements; a mucopolysaccaride matrix which is not specialized, but becomes elastin when a second substance is deposited within it. The matrix was considered to be a precursor material, probably from the smooth muscle cells.

Pease and Paule (1960), in a study of the thoracic aorta of the rat, demonstrated a direct attachment of muscle to elastin by a thin (200 Å) layer of "cement substance". No evidence of any direct attachment of collagen to either smooth muscle or elastin was found. The authors further demonstrated small masses of intracellular elastin within the endothelial cells. This finding was felt to be due to phagocytosis by the endothelial cells.

Haust et al. (1965) studied fetal, neonatal, and adult aortas in an attempt to determine the pattern of elastogenesis. The intima of the fetus consisted of a continuous layer of endothelial cells which rested on the internal elastic lamina. In older fetuses, smooth muscle cells were occasionally present in the intima, and associated with the smooth muscle cells were small elastic and collagen fibers. In some newborns, one to two layers of smooth muscle cells were found between the endothelium and the internal elastic lamina. The internal elastic lamina also had gaps which were frequently occupied by cellular elements. The media of the fetus and newborn consisted of smooth muscle cells which alternated regularly

with elastic lamellae, smaller elastic elements, and collagen filaments. Elastic filaments were found to have a close relationship with the basement membrane of smooth muscle cells. It was concluded that the elastic fibers originate at the level of the basement membrane of the smooth muscle cells.

Fischer and Llaurado (1966) examined, from dogs, the collagen and elastin content of different arterial beds. The ratio of collagen to elastin (C/E) was used as an index. It was noted that the composition of the arteries did not reflect the connective tissue content of the part of the aorta from which they arose. For example, the C/E ratio for the coronary artery was 3.12 ± 0.21 and for the carotid artery was 2.55 ± 0.13, while the C/E ratio for the ascending aorta was 0.49 ± 0.04. Similarly, the C/E ratio was greater for the renal artery (2.46 ± 0.27) than for the abdominal aorta (1.58 ± 0.15). The property of a high C/E ratio indicates low distensibility. Since the carotid and renal arteries are pathways to blood pressure sensors, this property would serve them well, since pressures would be transmitted without alteration to the detector. The authors concluded that the decrease in distensibility of the abdominal aorta when compared with the thoracic aorta, might reflect the effect of external environment on arterial connective tissue content since less protection is afforded the abdominal aorta.

Fischer and Llaurado (1967) demonstrated a lower C/E ratio in the renal arteries of dogs with renal hypertension.

This result was thought to be somewhat paradoxical, since an increase in collagen content would be expected to occur to lend more support to the hypertensive artery. The change in distensibility of the renal artery was felt to reflect a disruption in the function of the transmitting properties of this artery to the kidney baroreceptors.

Apter et al. (1966) suggested that the decrease in elastin, found chemically down the aorta, was due to thinning of the elastic lamellae and not due to a decrease in number. Phase-contrast microscopy revealed the same number of lamellae per unit thickness in the pulmonary artery as in the aorta, although the lamellae were much thinner in the pulmonary tree.

Physical properties of the arterial tree

Texon (1963) discussed the hemodynamics of the arterial tree with regard to laminar flow, turbulence, Poiseuille's law, and Reynold's number.

> "Laminar or streamline flow in a circular tube, is also called Poiseuille flow because Poiseuille (a physician) first studied the steady flow of liquids in cylindrical tubes. Poiseuille's law states that the pressure drop is directly proportional to the length of the tube, to the rate of flow, and to the viscosity, while it is inversely proportional to the fourth power of the radius."

When the velocity of flow increases to a critical point and laminar flow breaks down, turbulence occurs, and Poiseuille's law ceases to apply. The critical point is dependent on the velocity of flow, the density and viscosity of the fluid, and the diameter of the tube. These factors are combined in the

Reynold's number defined as:

$$Re = \frac{VDp}{u}$$

where V = velocity of flow

D = diameter of the tube

p = density of the fluid

u = viscosity of the fluid.

A Reynold's number of 2000 is usually given as the critical value for transition from laminar to turbulent flow.

Burton (1954) hypothesized the structural-functional relationship of elastin, collagen, and smooth muscle in the arterial wall. Values for the modulus of each tissue were given with collagen being the least distensible ($1x10^9$ dynes/cm^2) followed by elastin ($3x10^6$ dynes/cm^2) with smooth muscle being the most distensible ($6x10^4$ dynes/cm^2). From elastic diagrams, Burton considered the elastic fibers and collagenous fibers to be arranged parallel with each other, but with the collagen fibers initially at less than their "unstretched" length. This would mean that when the vessel is distended, the elastic fibers with a great range of distensibility before the elastic limit is reached, function to produce maintenance tension against the normal blood pressures and normal pressure fluctuations. The collagenous fibers are stretched at higher pressures and have a protective supporting role. The smooth muscle functions to provide active tension and contributes little to the maintenance tension. It was further hypothesized

that the constricted vessel is more distensible than the dilated vessel, because the elastic and collagen fibers are brought closer to their unstretched length, and thus provide less resistance to stretch. Burton concluded that the most important function of the elastic fibers in the blood vessel wall is to cooperate with the smooth muscle to provide graded contractions, and prevent all or none instability as is seen in the A-V shunts.

Peterson et al. (1960) analyzed pressure-diameter relationships to evaluate the mechanical properties of arteries in vivo. A stress (pressure)-strain (diameter displacement) relationship was made and this was considered to be the elastic modulus. The effect of varying levels of anesthesia was evaluated, and it was found that if the animal was allowed to become "light" and a large intravenous dose was given, an immediate decline in the elastic modulus (increased distensibility) of the femoral and carotid arteries and the abdominal aorta was observed. However, after three minutes the moduli returned to normal values although the level of anesthesia was still very deep. This effect was believed to be due to a direct influence on the vessel wall by the anesthetic agent. The authors also demonstrated an increase in the elastic modulus (decreased distensibility) with intravenous injection of norepinephrine. It was concluded that the smooth muscle makes a significant contribution to the elastic modulus of the arterial wall.

Patel et al. (1960), when studying the mechanical properties of the major pulmonary arteries, demonstrated similar effects (decreased distensibility) of norepinephrine on the pulmonary arteries. The authors postulated that either the smooth muscle itself increases in elastic modulus, or that norepihephrine altered the physical properties of collagenous and elastic fibers by increasing their elastic moduli. A decrease in distensibility was also noted when a vasodilating agent (Priscoline) was given intravenously. This seeming paradox was felt to be due to stretching of the elastic and collagen fibers which results in their becoming more resistant to further stretch, and thus less distensible.

Bergel (1961) studied the static elastic properties of the arterial wall, and demonstrated an increase in elastic modulus as the vessel was distended. The mean values for static elastic modulus (dynes/cm^2 x10^6) at 100 mmHg pressure were thoracic aorta 4.3, abdominal aorta 8.7, femoral artery 6.9, and carotid artery 6.4. Bergel also calculated an elastic modulus for smooth muscle of 1x10^6 dynes/cm^2 which is much higher than the value given by Burton (1954) of 6x10^4 dynes/cm^2.

Learoyd and Taylor (1966) studied the effects of age on the elastic properties of human arterial walls. An increase was noted in the elastic modulus of the thoracic aorta in the "old" group (16.6x10^6 dynes/cm^2) when compared with the "young" group (7.5x10^6 dynes/cm^2). Furthermore, a decrease in the

elastic modulus of the peripheral vessels was noted with age, and the wall of these vessels became thicker with age.

Distensibility vs capacitance

Burton (1954) described distensibility as the % increase in volume per mmHg rise in pressure:

$$D = \frac{100}{V} \times \frac{dV}{dP}$$

Capacitance, on the other hand, is described as the increase in volume caused by a given increase in pressure:

$$C = \frac{dV}{dP}$$

Roach and Burton (1957) demonstrated the function of the various components in the arterial wall by obtaining distensibility curves on human iliac arteries. Elastic tension diagrams were made with fresh vessel segments, segments treated with formic acid (to remove collagen), and segments treated with trypsin (to remove elastin). Curves recorded from fresh segments and collagen depleted segments demonstrated little change in shape at low pressures. However, at higher pressures (above 100 mmHg) the collagen depleted arteries were much more distensible. Conversely, elastin depleted vessels showed a marked decrease in distensibility at low pressures when compared with fresh vessels. The authors concluded that the elastic fibers were chiefly responsible for tension at low pressures, but play a minor role at pressures greater than 100 mmHg.

Speckmann and Ringer (1966) demonstrated, in turkeys, a greater "distensibility" at medium and high pressure ranges (100-225 and 225-500 mmHg) in the thoracic aorta than the abdominal aorta. It is interesting to note that the values of distensibility which the authors reported, had units in ml/mmHg, which is actually a measurement of capacitance.

Warner et al. (1953) evaluated, in man, the capacitance of the arterial tree indirectly by measuring the cardiac output, using an aortic and femoral artery pulse contour curve, and applied the following formula which he derived:

$$CO = kF\,(Pmd)(1 + Sa/Da)$$

where CO = cardiac output

k = capacitance (arterial)

F = heart rate

Pmd = end systolic mean distending pressure

Sa/Da = ratio of systolic drainage area to diastolic drainage area

Once the value of capacitance was found, Warner was able to calculate beat to beat changes in cardiac output.

Pulse-wave velocity

Another method used to estimate arterial distensibility is the pulse-wave velocity method. To quote Burton (1965):

> "The determination of pulse-wave velocity would remain rather academic except that it is one of the few ways that the arterial distensibility, as an index of the aging of arteries, can be measured conveniently in man. The connection between the pulse-wave velocity and volume distensibility of the arteries is based on a classic

calculation in physics for the velocity of propagation of transverse waves."

$$\text{Distensibility} = \frac{12.7}{V^2}$$

Hallock (1934), on 500 persons aged 5 to 85, demonstrated an increase in pulse-wave velocity with age. The average velocity in young persons was 4 m/sec, while in old persons the average velocity was 10 m/sec.

The Effects of Starvation and Refeeding on the Cardiovascular System

Keys et al. (1950) in the "Minnesota Experiment", in which 32 men underwent periods of semi-starvation (24 weeks) and rehabilitation, demonstrated bradycardia, decreased arterial pressure (systolic and diastolic), venous pressure, pulse rate, and cardiac output. There were decreased amplitudes of all electrocardiogram deflections, with right axis shift of the QRS and T complexes. The absolute plasma volume was increased, while the absolute blood volume was decreased during the period of semi-starvation. During the twelve week period of refeeding, the above mentioned parameters slowly returned to normal. Keys observed that the most severe deteriorating effect of starvation was on the heart, which was slow to regain normal function and was also in danger of failure, when overeating occurred during rehabilitation.

Brozek et al. (1948) reported that two years following the relief of the World War II siege at Leningrad, hypertension suddenly became a major medical problem. The increased incidence of hypertension was seen in all ages, and not just in the elderly patients. Before the war, patients with hypertension accounted for 10% of all admissions to the Theraputic Clinic of the Pavlov Fist Medical Institute. This proportion dropped during the period of semi-starvation (October 1941 to March 1942) and then increased progressively through 1943. By June 1943, 60% of the patients admitted were hypertensive. The rise in blood pressure was attributed to refeeding after the war, and the necessity for hard work during the war.

Wilhelmj et al. (1951) demonstrated a lowered blood pressure and decreased heart rate in dogs during fasting, which lasted for varying periods of time (2 to 14 days). During the first few days of the fast, the blood pressure usually fell and then always rose, often to levels above pre-fasting levels. The blood pressure would then begin an irregular descent to a stable fasting level.

Wilhelmj et al. (1956) subjected four trained dogs to six "fat episodes" during a fourteen month period. Each episode consisted of a prolonged preliminary fast followed by realimentation with a diet containing 50% or more of the calories from beef suet and butter, and fed at a level of 120 $Cal/m^2/hr/24$ hours. The blood pressure remained high

and often rose during the fasting stage. After the fat episodes the dogs were placed on a kennel diet, and the blood pressure returned to normal. Wilhelmj postulated that the homeostatic mechanisms which tend to prevent a fall in blood pressure during fasting had become hypereffective, and that if they could be stimulated for prolonged periods of time, true hypertension might result. The dogs were then placed on various diet schedules (fasting excluded) for a period of 475 days. A diastolic hypertension resembling benign essential hypertension developed in three out of four dogs.

Wilhelmj et al. (1957) studied the effects of total sympathectomy on the blood pressure of fasted and refed dogs. Following bilateral paravertebral ganglionectomy and adrenal denervation, the systolic pressure was within the normal range, while diastolic pressure tended to be at the lower limits of normal. During fasts of three to six weeks duration the blood pressure did not fall, but remained the same or rose above the control level. When these dogs were realimented with a high carbohydrate diet, the blood pressure remained at the fasting level. When fasted normal dogs were realimented with the high carbohydrate diet, systolic pressure rose significantly while diastolic pressure was normal or low.

Smith et al. (1964) demonstrated, in swine, a notable increase in blood pressure following periods of total starvation and refeeding. The initial control blood pressure was

133 ± 6/96 ± 7 mmHg, and following the fifth phase of starvation and refeeding with a diet high in glucose the pressure was 183 ± 10/139 ± 10 mmHg. A hypertensive trend was noted following the first phase of starvation and refeeding. Electrocardiograms recorded during starvation revealed arrythmia and T wave inversion.

Consolazio et al. (1966) studied, in six men, the effects of ten days of complete fasting and four days of rehabilitation. Blood pressures taken at rest decreased from 113 mmHg on the first day to 102 mmHg on day ten of fasting, and returned to 115 mmHg after four days of refeeding. Diastolic pressures decreased from 73 mmHg on day one to 68 mmHg on day ten of starvation, and returned to normal on the third day of refeeding. Consolazio recorded electrocardiogram changes which were similar to those recorded by Keys (1950).

Bernardis and Brownie (1965) demonstrated a decrease in blood pressure in adrenal enucleated rats and intact rats on a restricted food intake. Following ad libitum realimentation, a significant blood pressure rise occurred in the adrenal enucleated rats when compared with controls. Hypertension occurred without increased sodium intake. The authors concluded that the regenerating adrenal did not lose its hypertensive potential despite food and NaCl restriction.

The Electrolyte Content of Hypertensive and Normotensive Arteries

Tobian and Binion (1952) studied specimens of renal artery from cases classified as hypertensive or normotensive, from clinical and postmortem data. A significant difference was found between the arterial sodium content of hypertensive patients and normotensive patients. The respective values were 480 $\pm$ 69 meq/kg dry weight for the former and 395 $\pm$ 71 meq/kg for the latter. No significant difference was found in the arterial potassium content between hypertensive and normotensive patients. The water content was 17% higher in the arteries of hypertensive patients, and a similar increase (19%) was found in the aorta of hypertensive rats when compared with normotensive rats. It was hypothesized that the increased sodium and water content in the arteries resulted in a "waterlogging" and narrowing of the arterial lumen. This in turn would lead to increased peripheral resistance and hypertension.

Tobian and Redleaf (1958) demonstrated an increase in the sodium and potassium content of rat aortas, with adrenal regeneration hypertension. The sodium and potassium aortic concentrations were 300.5 $\pm$ 12.6 and 145 $\pm$ 3.6 meq/kg dry weight respectively in the hypertensive rats, and 273 $\pm$ 4 and 132 $\pm$ 2.5 meq/kg dry weight in the normotensive rats. These increases were significant for both sodium and potassium.

It was further demonstrated that when an ischemic kidney was removed from markedly hypertensive rats (mean pressure = 195 ± 14 mmHg), the rats remained hypertensive and aortic sodium and potassium levels were increased significantly. Sodium increased from a control level of 292.6 ± 4.2 to 343.9 ± 5.9 meq/kg dry weight in the hypertensive rats, and potassium increased from 119.5 ± 2 to 136 ± 2 meq/kg dry weight. The effect of increased sympathetic tone on the aortic electrolyte content was also examined by infusing norepinephrine for a 30 minute period. This was found to have no effect. The authors speculated that the increase in sodium and potassium, in some cases of hypertension, might alter the tone of the arterial smooth muscle. This might be obtained either through an effect on membrane potential, or through a direct effect on actomyosin.

Headings et al. (1960) demonstrated a higher relative sodium content in the pure tunica media wall than the whole arterial wall. It was also discovered that the medial sodium content was higher than the calculated value. The authors postulated that the excess sodium was associated with the mucopolysaccharides present in the interstitial spaces of the tunica media wall.

Jones et al. (1964) studied the electrolyte distribution in the arterial tree of normotensive and hypertensive dogs. It was found that the aorta, especially the ascending aorta,

had a higher potassium content than the more distal portions of the arterial tree. However, the opposite trend was observed for sodium. This finding was true for both normotensive and hypertensive dogs, and would indicate a higher cellular proportion in the upper aorta than in the distal arteries. Hypertensive arteries contained a significant elevation of sodium and water when compared with normotensive arteries. A significant elevation of arterial potassium content was not found in the hypertensive animals.

Douglas et al. (1967) demonstrated an increase in the aortic sodium content of twenty-one hypertensive rats, of which 11 were pregnant and ten were nonpregnant. When compared with twenty-one normotensive rats, aortic sodium and potassium content was significantly elevated. Pregnancy did not influence the aortic sodium content. However, hypertensive pregnant rats had a higher aortic potassium content than hypertensive nonpregnant rats.

Etiological Theories of Essential Hypertension

Essential hypertension should first be defined before the etiological theories are discussed. The cause or causes of essential hypertension are unknown, and the disease is further characterized by a diastolic pressure greater than 90 mmHg, increased pulse pressure, normal cardiac output, increased cardiac work, and normal plasma volume.

Krieger (1964) demonstrated neurogenic hypertension in the rat following bilateral sino-aortic denervation. Of 140 rats, 75% were permanently hypertensive while the balance returned to normal usually within three months following denervation. No difference was observed in the heart rates of the normotensive and hypertensive rats.

Marshall (1966), in a clinical study involving 860 cases of cerebrovascular disease, found no significant difference in the blood pressure of patients with brain-stem ischemia as compared with patients with ischemia of the cerebral hemispheres. This finding appeared to contradict the theory that brain-stem ischemia results in an increase in blood pressure while cerebral ischemia has little effect.

Horrobin (1966) hypothesized that the baroreceptors become "adapted" to a high arterial pressure, and interpret this pressure as normal; the author suggested that this adaptation could be primary rather than secondary.

Mendlowitz et al. (1964) dogmatically stated that essential hypertension is "a composite result of many factors influencing primarily catecholamine and secondarily sodium metabolism". They concluded that a basic hereditary defect results in a defective catecholamine storage mechanism, with a failure to absorb released norepinephrine and thus more is available to raise blood pressure. If tissue sodium is sufficiently increased, there is increased vascular responsiveness to circulating catecholamine levels. The tissue sodium

concentrations can be increased as a result of elevated angiotensin, which in turn stimulates aldosterone production by the adrenal cortex.

Knudsen and Dahl (1966) utilized two highly inbred strains of rats (one strain resistant and the other sensitive to sodium induced hypertension) to demonstrate the effect of sodium intake on blood pressure. The rate and degree of blood pressure increase, in sensitive rats, depended upon both the level of sodium intake and the age of initial intake. If 8% sodium chloride was fed immediately after weaning, all developed hypertension and most were dead within two months. They concluded that essential hypertension could be due to an "inborn error" of sodium metabolism.

Pickering (1965) has suggested that essential hypertension may be due to "multifactorial" inheritance. However, in his opinion, environmental factors may play a greater role than inheritance in the rate of rise of blood pressure with age. The environmental factors known to affect the rate of pressure rise in man are: family size, physical work, and obesity. Lower pressures are seen in people with large families, people who do not tend to put on weight with age, and in people who do hard physical work.

Hartroft (1966) has taken the nutritional approach in his studies of essential hypertension. By feeding rats diets deficient in choline and then refeeding normal concentrations of choline, permanent elevation of blood pressure was produced

later in life. If the rats were maintained on a diet deficient in choline, hypertension did not develop. Diets high in protein and sodium enhanced the rise in blood pressure in hypertensive rats, and low amounts of these ingredients reduced blood pressure.

Helmer (1965) discussed the role of the renin-angiotensin system in hypertension. Plasma renin activity is greater in hypertensive than normotensive patients, especially hypertensives with reduced renal perfusion or malignant hypertension. With the elevated plasma renin, more angiotensin II is ultimately formed resulting in an increased blood pressure and an increase in aldosterone levels. The elevated aldosterone results in sodium retention, which in turn may result in an excessive response by the arterial system to circulating catecholamines.

Chasis and Baldwin (1966) demonstrated a difference in sodium excretion of the two kidneys (one kidney excreting less sodium than the other) of hypertensive patients when compared with normal values established from normotensive patients. Hypertensive patients consistently reabsorbed more sodium (decreased urine osmolality) than normotensive patients. This was interpreted to be due to decreased renal perfusion which may be general or focal; thus, there is a decrease in glomerular filtration rate with resultant excessive sodium retention.

Greene et al. (1966) studied the distensibility of the brachial artery, of live normotensive and hypertensive patients, by in vivo pressure-volume measurements. Their results demonstrated a trend toward a decreased distensibility in hypertensive patients. The authors did not discuss whether the change was primary or secondary.

Feigl et al. (1963) demonstrated in dogs, serving as their own controls, a decrease in distensibility with hypertension produced by wrapping the kidneys with cellophane. The average elastic modulus increased from 1,813 to 3,650 gm/cm^2. This increase was statistically significant. It was their conclusion that this was a measurement of change in arterial wall composition during hypertension.

Schroeder (1965) demonstrated larger concentrations of renal cadmium and higher renal ratios of cadmium to zinc in most patients dying of "hypertensive complications". Human hypertensive patients were also found to excrete forty times more cadmium in the urine than normotensive controls. The source of renal cadmium is the diet, with shellfish and cereal grains containing the largest amounts. It was Schroeder's opinion that cadmium might act as a "biochemical renal lesion" in cases of hypertension which do not exhibit other organic renal disturbances.

It is thus obvious from this short review that there is probably no single cause of essential hypertension, but many factors may be involved or influence the development of the

disease in any one individual.

The Single Injection Indicator-Dilution Method for Determining Cardiac Output

History

Stewart (1897) was the first to use the indicator-dilution method to determine cardiac output. Hypertonic saline was used as an indicator, and the concentration in arterial blood was determined by measuring the change in electrical conductivity of the blood. The indicator was injected into either the superior vena cava or the left ventricle, and changes in arterial blood concentration were measured in the femoral artery with electrodes placed between the artery and a piece of insulating material. With this measuring device, Stewart was able to detect a plateau of indicator concentration. During this plateau, arterial blood samples were taken and analyzed for hypertonic saline concentration. Having taken samples prior to injection of indicator, which had zero concentration of hypertonic saline, the Fick formula was used to calculate cardiac output.

$$\text{Cardiac output} = \frac{\text{rate of indicator injection}}{\text{arterial indicator conc} - \text{venous indicator conc}}$$

The problem of recirculation of the indicator resulted in inconsistent values of cardiac output until Kinsman *et al.* (1929) developed a technique to correct for recirculation. By constructing simulated models of the heart and lungs, and

making flow measurements with the indicator-dilution method, they noted that when recirculation was prevented the downslope of the curve had a semilogarithmic plot. The problem of recirculation was accounted for by replotting the curve on semilogarithmic paper. Thus, a more accurate value of cardiac output was obtained.

Guyton (1963) described another method to correct for indicator recirculation. He determined if the curve was describing a semilogarithmic plot by taking the ratios of successive concentrations of indicator over fixed time intervals on the curve downslope. If a semilogarithmic plot was being described, the ratio remained constant, but at the point of recirculation the ratio changed. The next downslope value of the extrapolated curve was found by multiplying the ratio constant by the indicator concentration prior to recirculation. This procedure was then continued; that is, multiplying the previous concentration value by the ratio constant until the curve approached the abscissa.

Indicators used

Since the advent of the indicator-dilution method, many different substances have been investigated for use as indicators. Stewart (1897) used hypertonic saline as an indicator in his early studies. Initially methylene blue and glucose were used. However, no method was available at that time for quantitating their respective concentrations in the blood.

Hamilton et al. (1948) introduced Evans blue dye (T-1824) as an indicator for indicator-dilution studies of cardiac output. Evans blue dye combines readily with the plasma proteins and therefore leaves the circulation very slowly. It is considered nontoxic as used in small doses. However, high doses (50 mg) in man results in a blue discoloration of the skin. The main disadvantage of Evans blue dye is that the wavelength of maximum absorption occurs at 630 millimicrons. Oxygenated hemoglobin also absorbs light at this wavelength thereby making the results dependent on the oxygenated-reduced hemoglobin ratio. This in turn results in an error in the calculation of cardiac output.

Fox et al. (1957) introduced indocyanine green as an indicator with a maximum absorption at 805 millimicrons. At this wavelength the light absorption of oxyhemoglobin and reduced hemoglobin is the same. Indocyanine green is also nontoxic and leaves the bloodstream very rapidly after its first circulation, thus avoiding a prolonged circulatory concentration.

Fox and Wood (1960) demonstrated that variation in the pH of the indocyanine green diluent (distilled water) between 6.0 to 9.0 caused no change in the peak absorption of the dye. They further indicated that the rate of deterioration of the concentrated dye solution was slow enough to permit its use up to two days after the preparation of the dye solution. Fox and Wood emphasized that the same dye solution should be used

for calibration of the detecting instrument and for injection into the experimental animal.

Hunton et al. (1960) demonstrated that the largest percentage of indocyanine green is taken up from the plasma by the hepatic parenchyma and secreted entirely into the bile. One milligram of indocyanine green per kilogram of body weight was administered to seven dogs, and venous blood samples were taken at five minute intervals, for thirty minutes. The rate of removal was exponential for at least fifteen minutes. In all cases, average plasma disappearance rate was 7.6%/min. Biliary obstruction resulted in a decrease in plasma dye disappearance rate of 4.8%/min initially, and 0.8%/min 24 hours after obstruction. The dye concentration increased in the hepatic lymph until it equaled but never exceeded the plasma concentration. In two hepatectomized dogs receiving the same dosage of indocyanine green, the plasma disappearance rate for the first thirty minutes was 0.65%/min. This initial rate was thought to incorporate "distributional factors", because the disappearance rate fell to 0.16%/min for the next eight hours. Hunton therefore concluded that the hepatic parenchymal cells and not the reticulo-endothelial cells were responsible for indocyanine green extraction, since the latter system was reasonably intact in both the biliary obstructed and hepatectomized animals.

Calculation of cardiac output

Kinsman et al. (1929) introduced the following formula to calculate cardiac output.

$$\text{Cardiac output (in L/min)} = \frac{I60}{\overline{C}T}$$

where I = injected quantity of indicator

T = total duration of the dye curve in seconds

$\overline{C}$ = the average concentration of indicator in time T

The value $\overline{C}T$ is equal to the area under the indicator-dilution curve.

Kelman (1966) studied the errors in processing indicator-dilution curves utilizing the trapezoid rule and Simpson's rule of numerical analyses, and a planimeter to calculate the area under the curve. His study demonstrated that there is little difference in the areas obtained by means of the trapezoid rule and Simpson's rule. Kelman also stated that planimetry is satisfactory for clinical determinations of cardiac output, however, he felt that for research purposes it was better to use the trapezoid rule or Simpson's rule. He further demonstrated that error may arise from estimation of the decay constant of the curve. With ten investigators estimating identical curves for the decay constant, the coefficients of variation ranged from 1.2 to 7.8%.

Williams et al. (1966) derived a new method of calculating the area of indicator-dilution curves, by treating the segment of the curve before exponential decay as a sequence of three

parabolas. They treated the exponential decay as a single exponential and calculated this area without replotting. When this method was compared with planimetry, the standard deviation of the mean differences was 1.6%. When compared with the area calculated by a combination of the trapezoid rule and semilogarithmic replotting, the standard deviation was 1.4%.

Dalby et al. (1967) compared the results of planimetry and computer determinations of cardiac output in man. They demonstrated, using the planimeter figure as the "correct value", that when the cardiac output was below 7 L/min, there was a mean error of + 0.3% and a standard deviation of ± 8.9% in the computer calculations. However, above 7 L/min the mean error was + 1.9% and the standard deviation was ± 18.5% in the computer calculations. They concluded that the computer was very useful when the cardiac output was below 7 L/min, particularly when a rapid measurement of cardiac output was required.

The effect of injection and sampling sites on cardiac output values

Bassingthwaighte et al. (1962) conducted a study in which indicator-dilution curves were recorded simultaneously from two or three sites (pulmonary artery, aortic root, thoracic aorta, femoral artery) after injections of dye into the inferior vena cava, right ventricle, pulmonary artery, or

left atrium of anesthetized dogs. They demonstrated that the injection site has little effect (standard deviation of 5%) on estimates of cardiac output, except when right ventricular injection was combined with sampling from the pulmonary artery. The standard deviations of comparisons of such curves, with curves recorded simultaneously from the femoral artery and aortic root, were 13.7 and 16.1%. They concluded that there was excellent agreement on curves sampled centrally and peripherally. However, there may be variations in individual estimates, and the mean of repeated observations should be taken as the cardiac output value for each individual.

Lange and Botticelli (1963) demonstrated good correlation between cardiac output calculations following superior vena caval (SVC) and inferior vena caval (IVC) injection of dye and subsequent recording from the femoral artery. The cardiac output (IVC) equaled 2.81 L/min, and the cardiac output (SVC) equaled 2.73 L/min.

Samet et al. (1965) demonstrated that injection of indicator into the pulmonary artery and left atrium resulted in similar levels of cardiac output expressed as cardiac index, where cardiac index is equal to cardiac output/m^2. In 109 patients, sampled from a systemic artery, the mean cardiac index from the pulmonary artery injection was 2.78 L/min/m^2, while that from the left atrium injection was 2.73 L/min/m^2.

Krovetz and Benson (1965) demonstrated that, when injections of dye were made into the superior vena cava or right

atrium, nearly identical cardiac output values were obtained from the right and left iliac sampling sites. Sixteen such curve pairs were recorded with an average difference of 5.8% and were within the 10% error attributed to the indicator-dilution method. When injections were made into the aortic root and the descending aorta, the differences in the paired curves also recorded from the right and left iliac arteries were an average of 9.9% and 23.1% respectively. It was concluded that the degree of dye mixing is influenced by the distance available for mixing and not the degree of turbulence in the vessel traversed.

Opdyke (1965) demonstrated that the time of dye injection during the respiratory cycle affected the values of cardiac output as measured from the pulmonary artery and the descending aorta. When dye was injected early during the respiratory cycle, the cardiac output as measured in the pulmonary artery (840 ml/min) was less than that measured in the descending aorta (1,715 ml/min). On the other hand, when dye was injected late in the respiratory cycle, cardiac output was more in agreement when sampled from the descending aorta (1,690 ml/min) and the pulmonary artery (1,640 ml/min).

The effect of sodium pentobarbital anesthesia on cardiac output determination

Etsten and Li (1954), using sodium pentobarbital anesthesia, demonstrated satisfactory values for cardiac output in the dog. Thirty cardiac output determinations were made

comparing the Fick and indicator-dilution methods in eleven dogs. Their results showed a mean cardiac index, by the dye technique, of 4.31 ± 0.26 L/min/m^2 and 4.57 ± 0.29 L/min/m^2 by the Fick method. The mean difference between the two methods was 6.2%.

Nash et al. (1956) utilized the pulse-pressure contour method and the indicator-dilution method to study the effects of sodium pentobarbital anesthesia on cardiac output. A steady fall in cardiac output was demonstrated from a control value, measured in trained dogs which were awake, of 3 L/min to 1.7 L/min after three hours of anesthesia. The depression in cardiac output was significant.

On the other hand, Barlow and Knott (1964) made a similar study of the effects of sodium pentobarbital anesthesia on the cardiovascular system. They compared the hemodynamic responses of anesthetized and unanesthetized dogs. The average mean blood pressure was 30 mmHg higher in anesthetized dogs as compared with control animals, and the cardiac output averaged 40 ml/min kg higher in the anesthetized dogs. The pulse rate was also significantly higher in anesthetized dogs (mean of 149 beats/min) as compared with unanesthetized dogs (mean of 83 beats/min).

Validity of the indicator-dilution method

Hanson and Tabakin (1964) studied the reproducibility of cardiac output determinations by the indicator-dilution method

both at rest and during graded treadmill exercise. Recordings were made from one sampling site with densitometers in series and from two sampling sites. The absolute mean difference between the densitometers in series for all determinations at rest was 460 ml/min or 5.4% of the mean cardiac output. With the densitometers sampling from two sites, the absolute mean difference in simultaneous curves was 575 ml/min or 7.9% of the mean cardiac output. Their conclusion was that the results demonstrated excellent reproducibility of calculated cardiac output using the indicator-dilution method.

Benchimol et al. (1964) studied 245 indicator-dilution curves for the effect of rapidly repeated injections of indicator on the resulting calculations of cardiac output. Using indocyanine green as an indicator for a series of ten determinations, it was noted that the amplitude of the peak deflection was lower for the last few determinations as compared with the initial ones. Thus, higher output values were obtained for the eighth, ninth, and tenth determinations. However, there was only a 10% increase in output between the first and tenth curves and only a 5.7% increase between the second and tenth curves. They also remarked that the contour of the dye curves did not change significantly throughout the study. They concluded that the increasing background of indocyanine green dye had little effect on the calculations of cardiac output.

Hamilton et al. (1967) recorded 75 indicator-dilution curves and simultaneously recorded the cardiac output with an electromagnetic flowmeter. The mean cardiac output was 2.53 L/min with the indicator-dilution method and 2.62 L/min with the electromagnetic flowmeter method. The coefficient of variation was 20.4%. Hamilton concluded that it could not be assumed that one method of cardiac output determination was correct and all error existed in the other method. No systematic error was revealed in either method, and the two methods agreed closely between the mean values of cardiac output.

MATERIALS AND METHODS

Experimental Design

Animals

Thirty-two dogs, consisting of twelve Specific Pathogen Free (SPF) beagles[1] and twenty street dogs, were assigned three groups for the experiment.

Group one consisted of ten street dogs: nine females and one male. Group two consisted of twelve SPF dogs; six males and six females. Group three was comprised of ten street dogs: six females and four males.

Each animal was vaccinated for canine distemper and hepatitis, and placed in a separate cage. The normal kennel diet[2] was utilized throughout the experiment, for both preliminary diet stabilization and for the period of realimentation following starvation.

Treatment regimen

The first group of street dogs, consisting of five treatment and five control animals was placed on experiment on December 11, 1967. The animals were randomly selected to serve as treatment or control animals. All of the control animals were females, and four of the five treatment animals were

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[1]Obtained from dog colony at Veterinary Medical Research Institute, Ames, Iowa.

[2]Wayne Dog Food, Allied Mills Inc., Chicago, Illinois.

females. Feed was removed from each treatment dog for three days, and then each animal was refed for three days. This pattern of three days on and three days off feed continued for thirty days. Water was always available for all of the animals. After thirty days, the treatment animals were again placed on a daily feeding schedule until the time of data collection, which began March 6, 1968.

The SPF dogs were randomly selected as treatment or control animals and placed on experiment January 8, 1968. There were six control (male) and six treatment (female) animals. The same starvation-realimentation procedure was used. Data collection began on March 16, 1968.

The final group of street dogs was placed on experiment March 16, 1968. The animals were randomly selected as control (five females) and treatment (four males and one female) animals. Data collection began May 16, 1968. Table 1 summarizes the treatment regimen.

Table 1. Treatment regimen

Animal	Group	Experiment Started	Experiment Completed	Data Collection Begun
Street	1	12-11-1967	1-11-1968	3-8-1968
SPF	2	1-8-1968	2-8-1968	3-16-1968
Street	3	3-16-1968	4-16-1968	5-16-1968

Physiological Analyses

Arterial capacitance

Arterial capacitance was determined indirectly from the following relationship developed by Warner et al. (1953):

$$C = \frac{CO}{F \cdot dP(1 + Sa/Da)} \quad (1)$$

Where C = capacitance in ml/mmHg

CO = cardiac output in ml/min

F = heart rate/min

dP = Pressure change from the peak of systole to the end of diastole

Sa = systolic area of the aortic pulse-pressure contour

Da = diastolic area of the aortic pulse-pressure contour

Cardiac output Each animal was anesthetized with 6% sodium pentobarbital anesthesia to a surgical plane and placed in dorsal recumbency. Cardiac output was determined using the single injection indicator-dilution method. The right jugular vein was cannulated with medical grade teflon tubing (0.059 inches ID and 0.091 inches OD), and the cannula was advanced to the superior vena cava. One milliliter volumes of indocyanine green dye[1] (1.25 mg/ml) were injected at a velocity of 60 milliseconds/ml through the cannula into the superior vena cava with a Sage Model 067 Automatic Injection

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[1] Hynson, Westcott, and Dunning Inc., Baltimore, Md.

Pump.[1] The left common carotid artery was cannulated with tubing identical to that used for dye injection. Through this tubing, blood was withdrawn through a Gilford Model 103 (IR) Cuvette Densitometer-Oximeter[2] by a Gilford Model 105-S Constant Flow System,[3] which resulted in a constant flow through the densitometer and produced a steady base line. A series of three-way valves allowed blood withdrawn during the cardiac output recording to be returned to the animal. Thus, blood volume did not change during the series of recorded cardiac output curves. The cuvette densitometer measured optical density changes of the dye in the blood. The electrical output of the densitometer was connected by a cable to the input of the Grass Model 7 Polygraph[4] which recorded the dye curve. Each animal was heparinized with 1% heparin, and blood was withdrawn to be utilized later for dye curve calibration. A total of three dye curves were recorded from each animal.

Cardiac output computer For the third group of dogs, a Gilford Model 104 Dye Curve Computer[5] was used to calculate the area under the dye-dilution curves. The dye curves were

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[1] Sage Instruments Inc., White Plains, N.Y.

[2] Gilford Instrument Laboratories Inc., Oberlin, Ohio.

[3] Gilford Instrument Laboratories Inc., Oberlin, Ohio.

[4] Grass Instrument Company, Quincy, Mass.

[5] Gilford Instrument Laboratories Inc., Oberlin, Ohio.

simultaneously recorded by the Grass Polygraph. A comparison was made between values of cardiac output calculated manually and those calculated with the cardiac output computer.

Dye curve calibration Three blood samples of 5 ml each were mixed with different known concentrations of dye. These samples, plus a blank sample, were drawn through the densitometer, and a linear calibration was obtained. This procedure was carried out for each animal.

Packed cell volume Packed cell volume was determined to insure consistency in blood viscosity; as abnormally high or low values will affect cardiac output. Heparinized blood was drawn into microhematocrit tubes and centrifuged for five minutes. The packed cell volume was determined by direct reading from a microhematocrit reader.

Pulse-pressure contours The right femoral and right common carotid arteries were cannulated with medical grade polyvinyl tubing (0.028 inches ID and 0.046 inches OD). The carotid cannula was passed to the root of the aorta. Each cannula with a matched Statham P23Dc[1] pressure transducer had been previously calibrated for a dampening ratio of 0.64, with critical dampening being 1.0. Each transducer was plugged into a Grass Polygraph DC Preamplifier[2] for recording

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[1] Statham Laboratories Inc., Hato Rey, Puerto Rico.

[2] Grass Instrument Company, Quincy, Mass.

the pulse contours. The complete equipment for recording cardiac output and the pulse contours is shown in Figure 1. Figure 2 demonstrates a recorded cardiac output curve, femoral pulse contour, and an aortic pulse contour.

Cardiac output and pulse contour calculation The cardiac output curves and aortic pulse-pressure contours were optically enlarged (Figures 3 and 4) and traced on graph paper. This eased the burden of calculation and increased the accuracy of calculation by allowing more points to be taken from the curves. The optical system was checked for distortion, and none was found. The areas of the curves were calculated by adding the ordinates around the curve and determining the average.

Mean blood pressure Mean blood pressure was calculated by adding one-third pulse pressure to the diastolic pressure.

Pulse-wave velocity Following the cardiac output and pulse-pressure contour recordings, the animals were killed with an injection of a saturated solution of magnesium sulfate. Pulse-wave velocity can be another index to evaluate arterial distensibility. Pulse-wave velocity could be calculated by knowing distance and time. Distance was obtained by tying a cotton ligature around the femoral artery at the distal end of the femoral cannula and extending the long end of the ligature to the distal end of the aortic cannula. The length of the ligature was then measured as the distance from cannula

Figure 1. Equipment for recording cardiac output and pulse-pressure contours

A - Statham P23Dc pressure transducer for femoral artery pulse-pressure contour

B - Statham P23Dc pressure transducer for aortic pulse-pressure contour

C - Sage Model 067 Automatic Injection Pump

D - Gilford Model 103 (IR) Cuvette Densitometer-Oximeter

E - Gilford Model 105-S Constant Flow System

F - Gilford Densitometer-Oximeter power supply

G - Gilford Model 104 Dye-Curve Computer

H - Grass Model 7 Polygraph

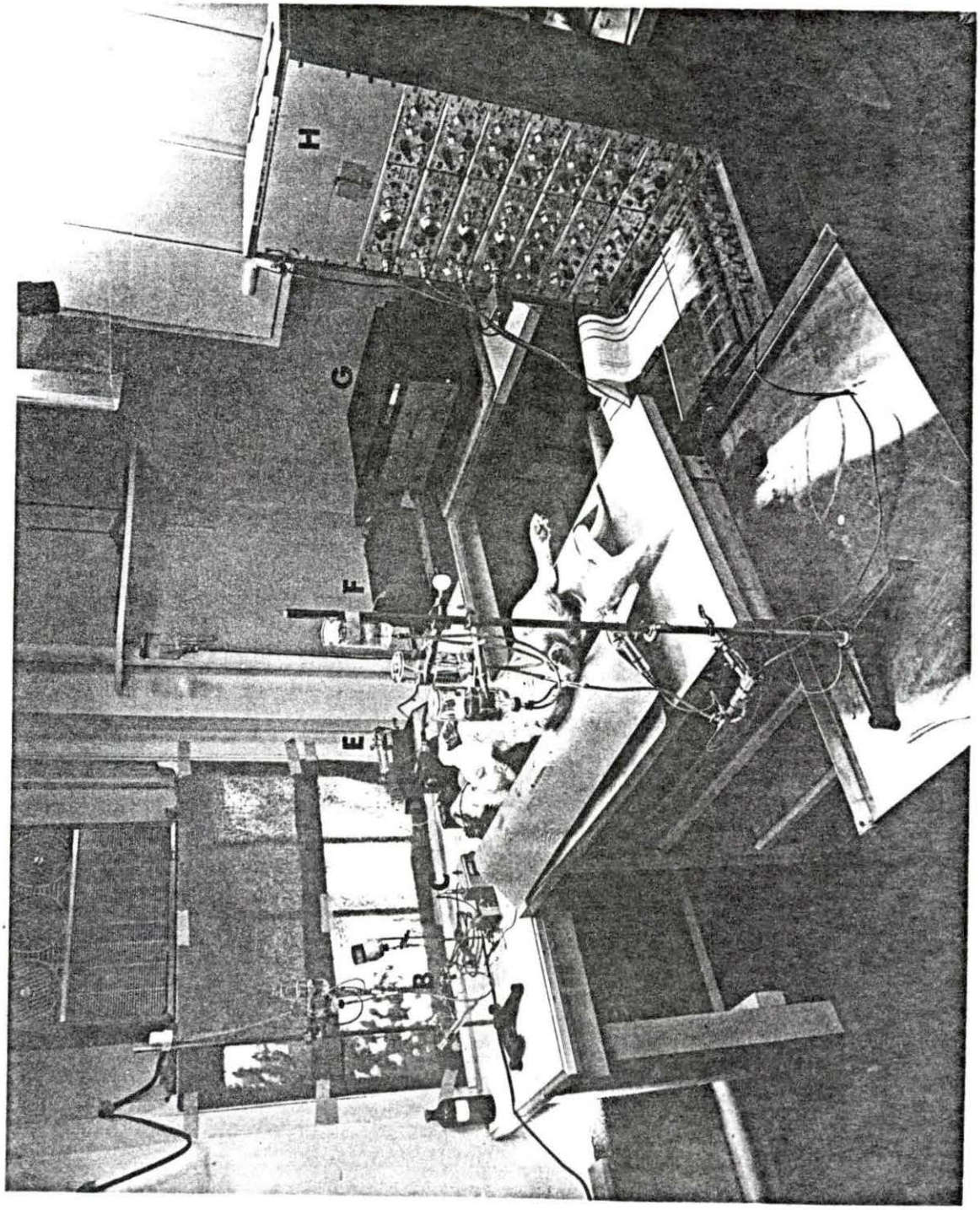
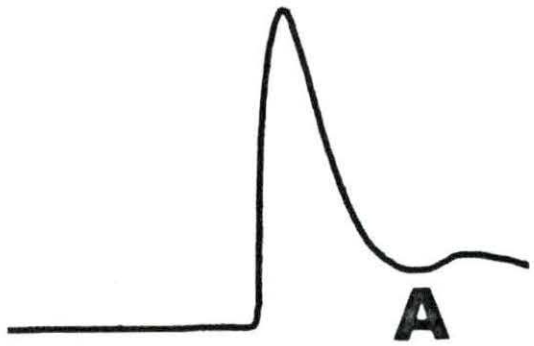

H
G
F
E
B

Figure 2. Recorded cardiac output curve, femoral artery pulse-pressure contour, and aortic pulse-pressure contour

A - Cardiac output curve

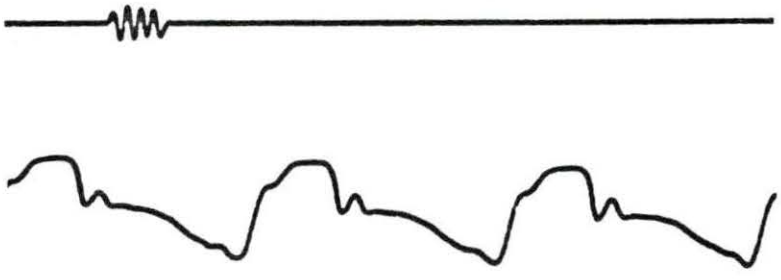
B - Femoral artery pulse-pressure contour

C - Aortic pulse-pressure contour



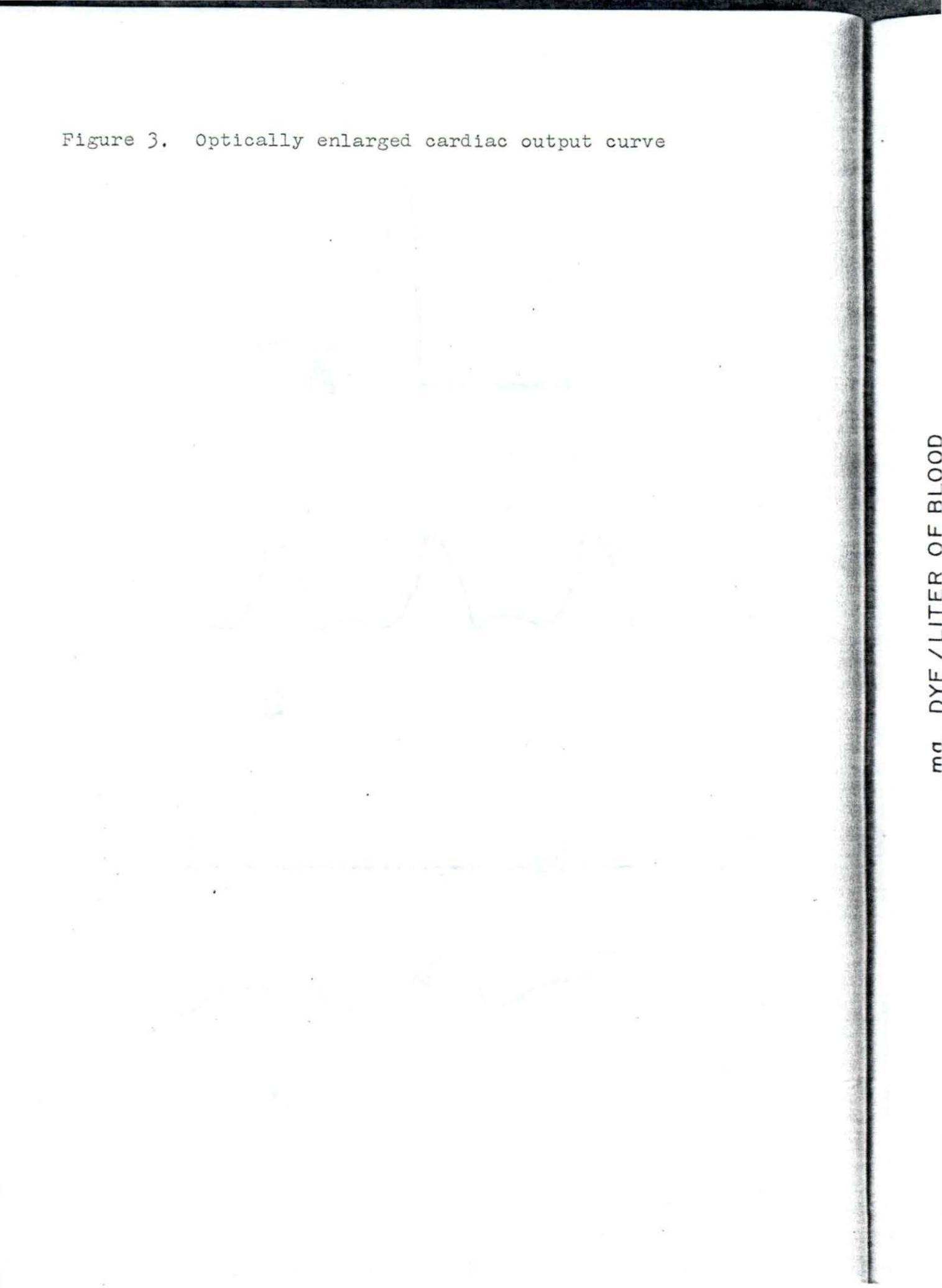
A

B



C

Figure 3. Optically enlarged cardiac output curve



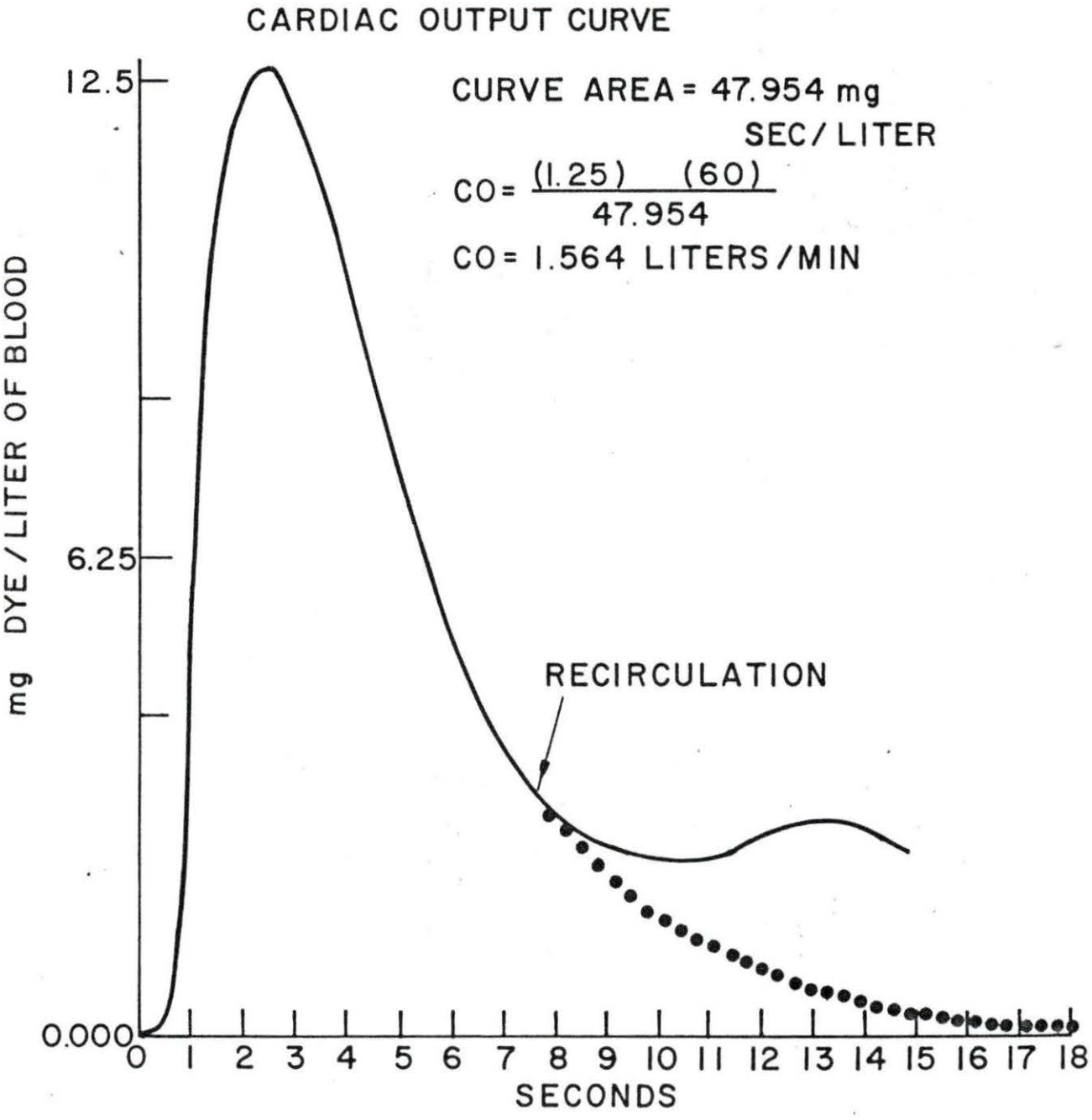
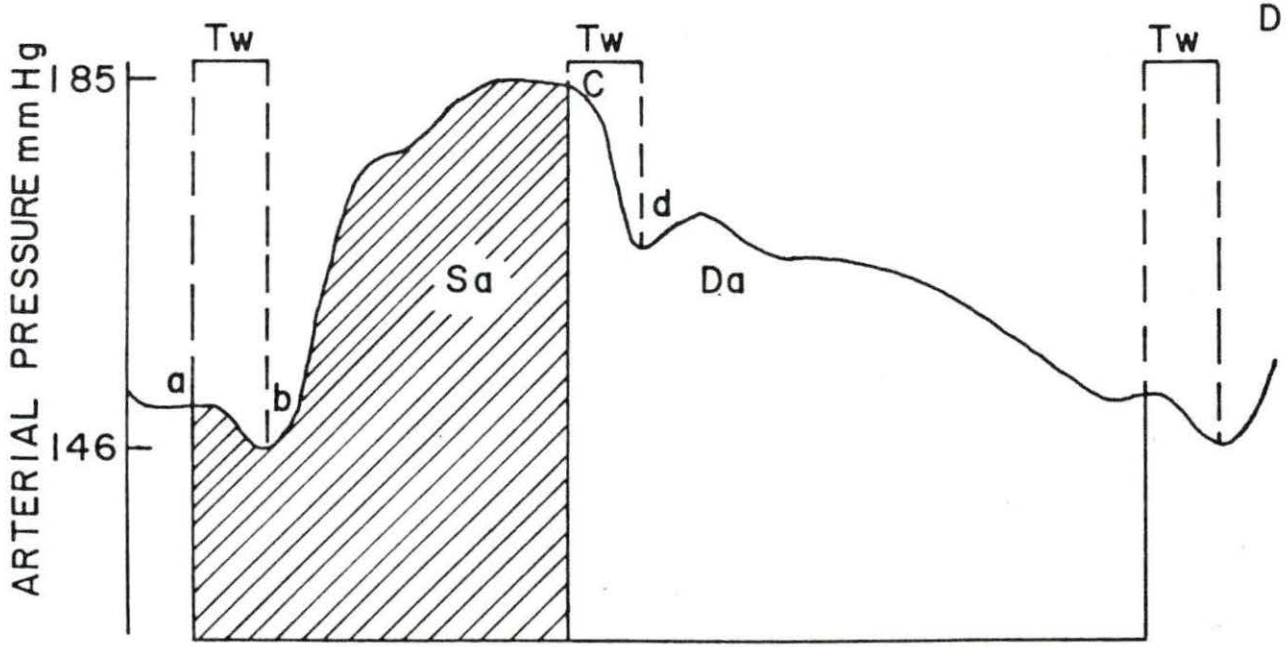

CARDIAC OUTPUT CURVE
CURVE AREA = 47.954 mg SEC/ LITER
CO = (1.25) (60) / 47.954
CO = 1.564 LITERS/MIN
12.5
6.25
0.000
mg DYE / LITER OF BLOOD
RECIRCULATION
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
SECONDS

Figure 4. Optically enlarged aortic pulse-pressure contour

AORTIC PULSE CONTOUR

Tw = TRANSMISSION TIME
Pcd = 176.6 mmHg
Pab = 148.1 mmHg
ΔP = Pcd − Pab = 28.5 mmHg
Sa = 167 mmHg
Da = 164.1 mmHg
$\frac{Sa}{Da}$ = 1.02
C = CAPACITANCE ml/mmHg
F = HEART RATE/MIN
CO = CARDIAC OUTPUT LITERS/MIN

$$C = \frac{CO}{F \ \Delta P \ (1 + \frac{Sa}{Da})} = 0.141 \text{ ml/mmHg}$$



end to cannula end. Time was obtained directly from the recorded pulse-pressure contours.

$$\text{Pulse-wave velocity} = \frac{\text{distance}}{\text{transmission time}} \qquad (2)$$

Ventricular weight

Ventricular weight was obtained after removing the atria and great vessels and carefully trimming away the fat from the ventricles.

Serum analyses

Blood samples were withdrawn from the treatment and control animals at the beginning of the period of treatment, and again at the time of data collection. The blood was allowed to clot, centrifuged, and the serum was drawn off and placed in labeled tubes. The tubes were placed in a freezer until all samples were accumulated, at which time total serum cholesterol and serum sodium and potassium were analyzed with the Auto Analyzer (two channel).[1]

Arterial vessel electrolyte analyses

Sections of thoracic aorta, abdominal aorta, and femoral artery were removed at the time of post-mortem for electrolyte analyses. Each segment was blotted free of blood and non-vascular tissue was trimmed away. Each segment was then

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[1] Technicon Corporation, Ardsley, N.Y.

weighed with an electronic balance, placed in a clean glass crucible, and oven dried for 24 hours at 70°C. The segments were then weighed again to obtain the sample dry weight. Each dry segment was wet ashed in a solution containing 10 ml water, 10 ml sulfuric acid, and 10 ml nitric acid. The ashed samples were diluted to 50 ml, placed in polyethylene bottles, and submitted for analyses. Each vessel segment was analyzed for sodium and potassium with the Auto Analyzer (two channel).[1]

Arterial stretch-tension analyses

One centimeter segments of thoracic aorta, abdominal aorta, and femoral artery were removed from the SPF dogs and the first group of street dogs. The segments were placed in a plastic bag containing a 0.1% solution of p-chloro-phenyl-diguanide[2] in isotonic saline. The bags were heat sealed, marked, and stored in a refrigerator until segments had been collected from all animals, at which time the analyses were performed. Stretch-tension analysis was done immediately after death in the second group of street dogs to check the effect of storage on the vessels.

Stretch-tension procedures Vessel segments were placed in a constant temperature isotonic saline bath (37°C).

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[1]Technicon Corporation, Ardsley, N.Y.

[2]Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

Two stainless steel couplings were placed in the lumen of the vessel segment. Stainless steel wire extended from one coupling to a micromanipulator and from the other coupling to a Grass FT .03C Force Displacement Transducer.[1] The output of the transducer was recorded by the Grass Model 7 Polygraph.[2] The micro-manipulator was moved two or three times to initially stretch the vessel and decrease hysteresis. An initial tension of 10 grams was used as a starting point. The vessels were then stretched by even increments of tension. At each increment, a reading of vessel stretch in millimeters was made, and a movement of 0.002 mm/gm tension was recorded. Thus, a corrected value of vessel stretch was obtained.

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[1] Grass Instrument Company, Quincy, Mass.

[2] Grass Instrument Company, Quincy, Mass.

RESULTS AND DISCUSSION

Data Analyses

Data from this project were analyzed statistically with a computer.[1] An analysis of variance program was used to analyze arterial stretch-tension data, and the F-test was conducted on the results. A correlation matrix was used to analyze 23 variables at the 5 and 1% levels. A Student's t-test was conducted on all variables (5 and 1% levels) to examine the effect of treatment, sex, and the difference between SPF and street animals.

Many of the statistically significant correlations of this experiment are unexplainable at this time. These correlations are included in the appendix, tables 16 and 17, and may prove useful to workers in the future.

Physiological Analyses

Arterial capacitance

Arterial capacitance, as determined by the method of Warner et al. (1953), was not affected by treatment or sex. However, as illustrated in Figure 5, arterial capacitance was significantly (1% level) greater for street dogs than SPF dogs. The mean value for the street dogs was 0.247

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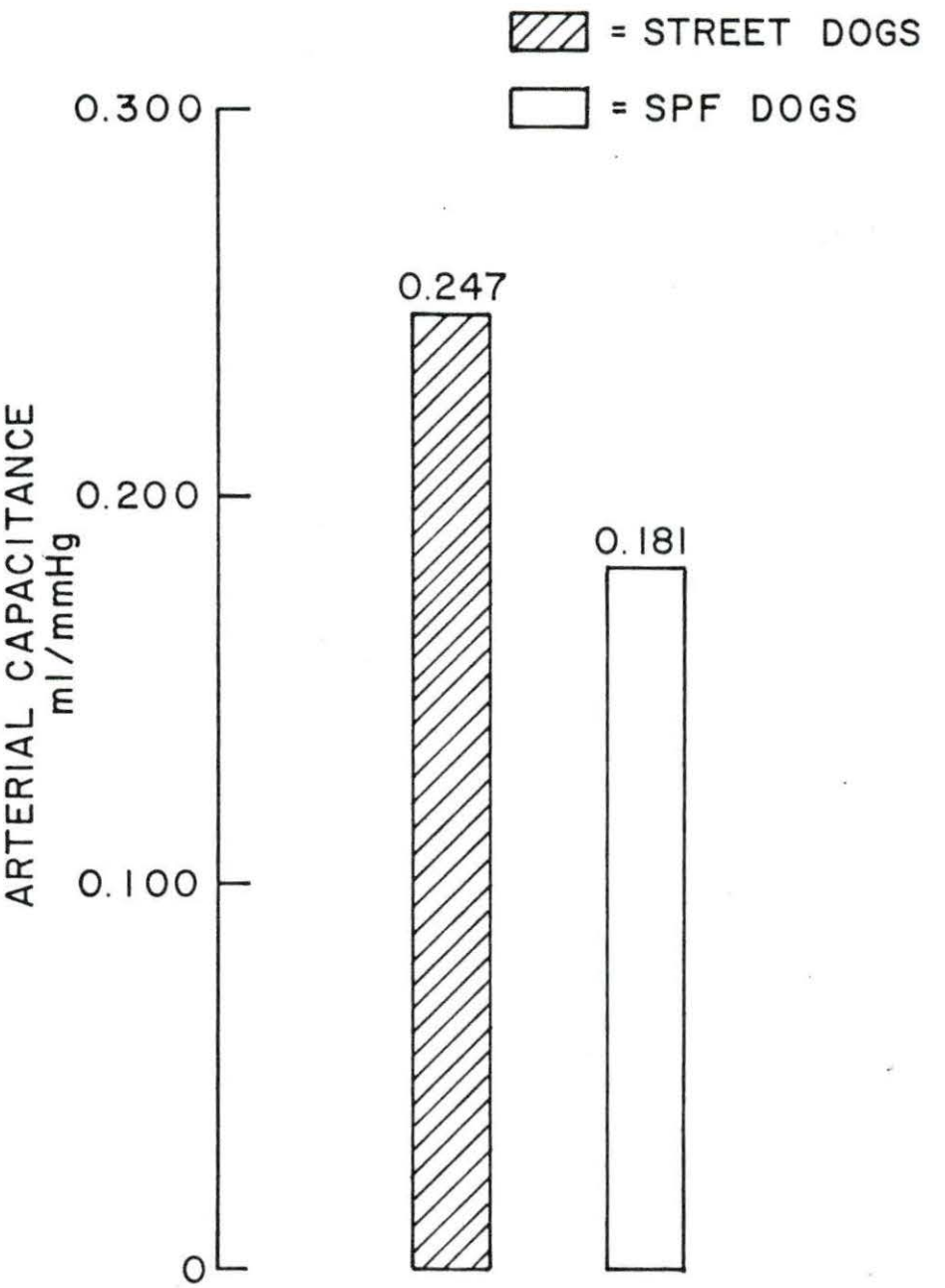
[1]Computer Center, Iowa State University, Ames, Iowa.

Figure 5. Arterial capacitance of SPF and street dogs


= STREET DOGS
= SPF DOGS
0.300
0.200
0.100
0
ARTERIAL CAPACITANCE
ml/mmHg
0.247
0.181

ml/mmHg, and for the SPF dogs was 0.181 ml/mmHg. The SPF dogs also exhibited a trend, although not statistically significant, toward increases in systolic, diastolic, and mean blood pressure (Figures 6, 7, and 8).

The explanations for the lower arterial capacitance in the SPF dogs must be considered speculative. Hereditary and environmental factors must be considered. Environmental changes, which might be considered minor or negligible to street dogs, may be extremely stressful to SPF dogs since they are raised in reportedly ideal conditions. Such a standardized life, without frequent stresses, may lead to an inability to cope with situations as they arise.

If the SPF dogs have been highly inbred, many physiological differences from street dogs may be present. The results indicate that cardiovascular differences are present (decreased arterial capacitance and possible hypertension). Another possibility could be selection of a hypertensive group of animals to initiate the SPF colony. The question of hereditary and environmental influence has not been answered but should be investigated.

Arterial capacitance was positively correlated (1% level) with cardiac output and body weight and at the 5% level with ventricular weight. The correlation with body weight is extremely valuable and has clinical implications. A mean value of arterial capacitance/kg body weight was calculated from recorded values for both street dogs and SPF dogs. The

Figure 6. Systolic blood pressure of SPF and street dogs

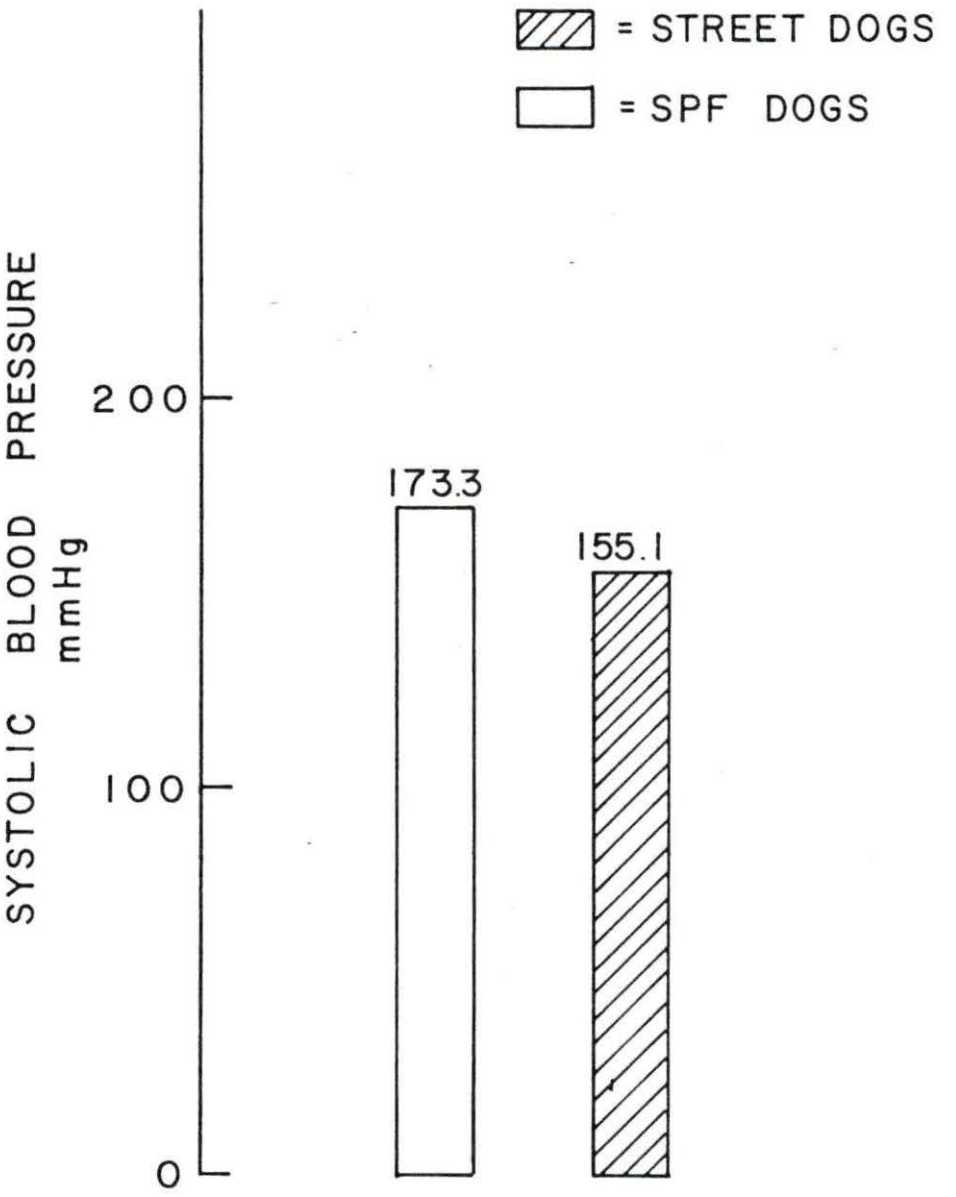

= STREET DOGS
= SPF DOGS
SYSTOLIC BLOOD PRESSURE
mmHg
200
100
0
173.3
155.1

Figure 7. Diastolic blood pressure of SPF and street dogs

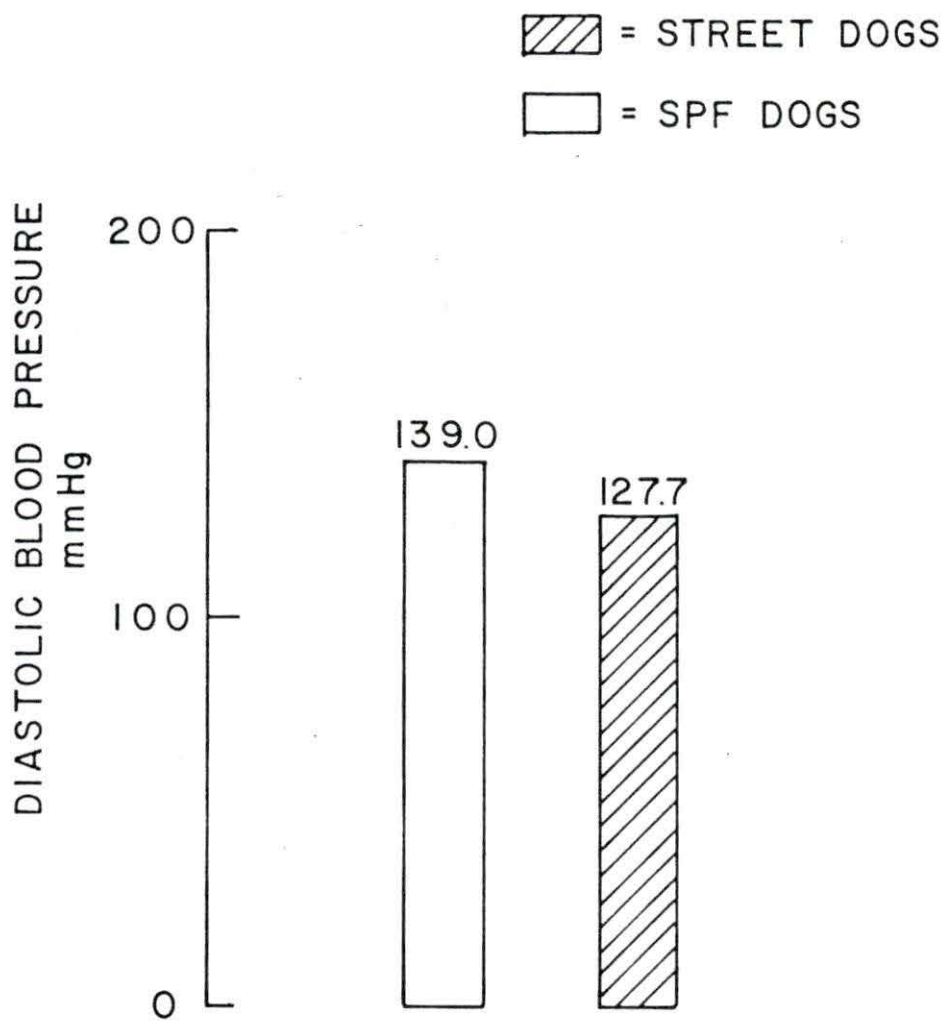
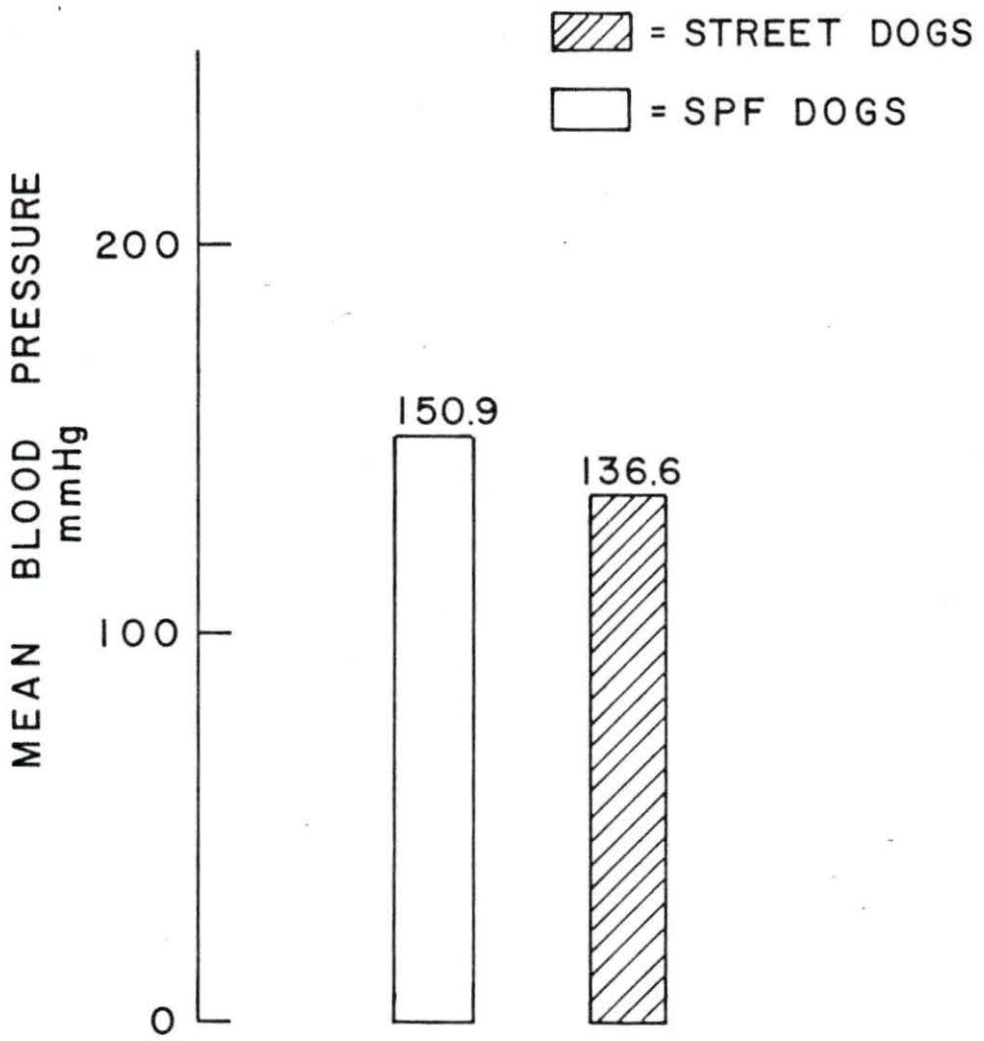

= STREET DOGS
= SPF DOGS
DIASTOLIC BLOOD PRESSURE
mmHg
200
100
0
139.0
127.7

Figure 8. Mean blood pressure of SPF and street dogs


= STREET DOGS
= SPF DOGS
MEAN BLOOD PRESSURE mmHg
200
100
0
150.9
136.6

mean value for street dogs was 0.019 ml/mmHg kg, with a range of 0.010 to 0.037 ml/mmHg kg. The mean value for the SPF dogs was 0.015 ml/mmHg kg, with the range being 0.008 to 0.024 ml/mmHg kg. Thus, knowing body weight, one can calculate an approximate arterial capacitance for a dog.

Using the method of Warner et al. (1953), equation 1 of the Materials and Methods, it would be possible to calculate stroke volume or cardiac output. This method would require two pressure transducers and a recording instrument, would be less expensive, and values of cardiac output would be determined more quickly than with the indicator-dilution method. Recorded values of cardiac output would not be as accurate as those recorded by the indicator-dilution method, because of an assumed arterial capacitance. However, the values would be comparative and useful for emergency or prolonged surgical procedures.

Cardiac output

The period of starvation-realimentation (treatment) had no significant effect on cardiac output. There was no significant difference in the cardiac output of the SPF and street dogs. However, males had a significantly (5% level) greater cardiac output than females. Systolic, diastolic, mean blood pressure, and ventricular weight were significantly correlated (1% level). Heart rate was significantly correlated at the 5% level. All of these results are logical and need no discussion.

However, as Figure 9 illustrates, SPF males had a significantly greater (1% level) cardiac output than street males. The mean cardiac output for the SPF males was 2059 ml/min, while that for the street males was 1275 ml/min. There was no significant difference between SPF females and street females. This finding, along with the decreased arterial capacitance in the SPF dogs, indicates possible cardiovascular differences in the SPF dogs.

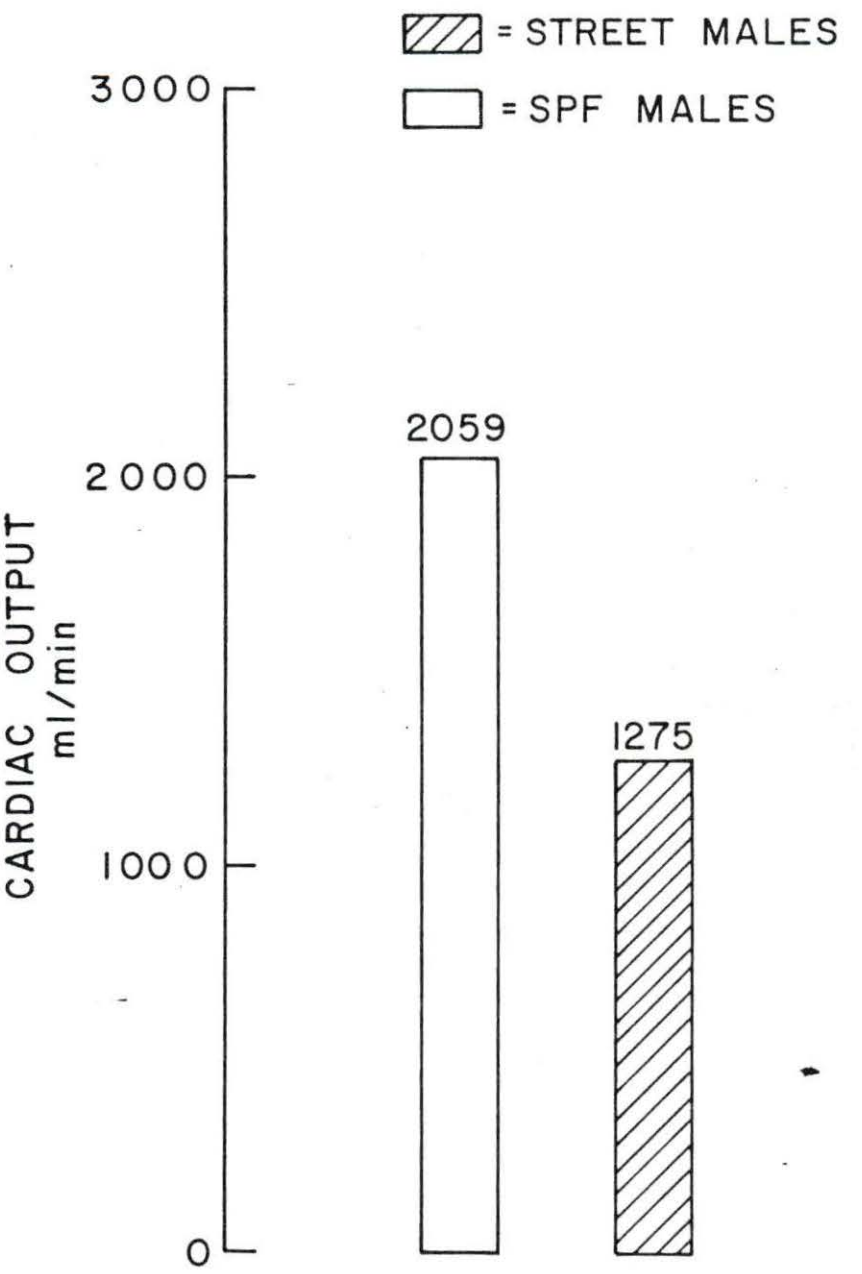
A comparison was made between values of cardiac output calculated manually and with the Gilford Model 104 Dye-Curve Computer.[1] Table 2 demonstrates greater reproducibility between the manual and computer methods of calculation than reported by Dalby and Sloman (1967).

Table 2. Comparison of cardiac output values calculated manually and with a cardiac output computer

Manual Cardiac Output ml/min	Computer Cardiac Output ml/min	Absolute Difference ml/min	% Difference
931	949	18	1.9
1390	1354	36	2.6
1564	1603	39	2.5
873	881	3	0.9
1507	1486	21	1.3

[1]Gilford Instrument Laboratories Inc., Oberlin, Ohio.

Figure 9. Cardiac output of SPF males and street males


= STREET MALES
= SPF MALES
3000
2000
1000
0
CARDIAC OUTPUT
ml/min
2059
1275

Packed cell volume

No significant changes in packed cell volume were recorded.

Ventricular weight

Ventricular weight was not affected significantly by treatment or by animal type (SPF or street). Ventricular weight was significantly greater (5% level) in males than females. The mean value for the males was 98.2 gm and for the females was 77.8 gm. Ventricular weight was correlated with arterial capacitance (5% level) and with body weight (1% level). These are accepted results and require no discussion.

Pulse-wave velocity

No significant changes were recorded for pulse-wave velocity by the intercannula distance method, nor was there any correlation with arterial capacitance. Correlation was expected, since pulse-wave velocity has been considered, according to Hallock (1934) and Burton (1965), a valid method for determining relative arterial capacitance. It is possible that extremely severe changes must occur in the capacitance of the arterial tree for changes in pulse-wave velocity to be recorded.

Serum analyses

No significant data were recorded from serum samples, except for unexplainable or possible nonsense correlations.

Arterial vessel electrolyte analyses

Neither treatment nor sex had any influence on arterial vessel sodium and potassium concentrations. However, differences were noted between the SPF and street dogs. Thoracic aorta potassium (1% level) and femoral artery potassium (5% level) concentrations were significantly higher in the SPF dogs. The SPF mean thoracic aorta potassium concentration was 6.744 mg/gm dry artery, while the street dog mean was 5.286 mg/gm dry artery. The SPF mean femoral artery potassium concentration was 5.839 mg/gm dry artery, and the street dog mean was 4.173 mg/gm dry artery.

Abdominal aorta and femoral artery sodium were significantly higher (5% level) in street dogs. The street dog mean abdominal aorta sodium concentration was 8.230 mg/gm dry artery, while the SPF mean was 7.014 mg/gm dry artery. The street dog mean femoral artery sodium concentration was 7.213 mg/gm dry artery, while the SPF mean was 5.342 mg/gm dry artery.

These results seem to indicate an inverse relationship between the SPF and street dogs with respect to their vessel sodium and potassium concentrations. Furthermore, there was a trend toward a higher thoracic aorta sodium content in

street dogs and higher abdominal aorta potassium content in SPF dogs. According to Tobian and Binion (1952) and Tobian and Redleaf (1958), sodium and potassium are increased significantly in hypertensive animals. Although the SPF dogs demonstrated a trend toward hypertension, relative to the street dogs, the arterial sodium and potassium concentrations did not reflect this.

Figure 10 illustrates the mean concentration and distribution of sodium and potassium in the thoracic aorta, abdominal aorta, and femoral artery. Jones et al. (1964) demonstrated higher concentrations of potassium in the thoracic aorta than in the more distal portions of the arterial tree. Figure 10 verifies this report. However, Jones et al. also noted increased sodium concentrations in the distal portions of the arterial tree relative to the thoracic aorta. The reverse was found to be true in this project, except for an increase in abdominal aorta sodium in street dogs.

Arterial stretch-tension analyses

The analysis of variance and F-test were conducted on the thoracic aorta, abdominal aorta, and femoral artery stretch-tension data. Figure 11 demonstrates the highly significant (0.01% level) difference in the distensibility of the thoracic aorta of street dogs and SPF dogs, with more stretch in the street dogs. The femoral artery demonstrated an identical pattern, Figure 12, and at the same level of

Figure 10. The mean concentration and distribution of sodium and potassium in the thoracic aorta, abdominal aorta, and femoral artery of SPF and street dogs

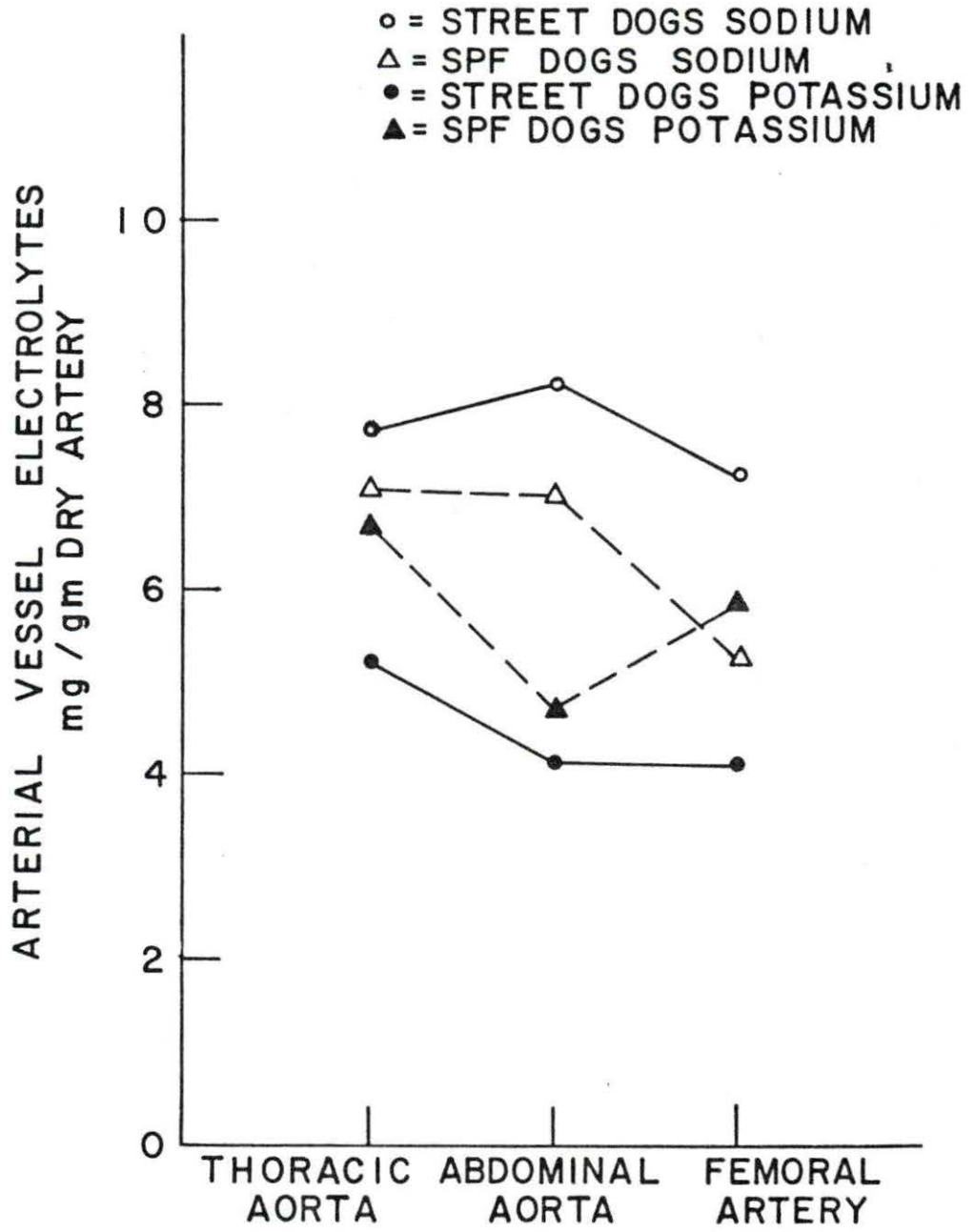

o = STREET DOGS SODIUM
Δ = SPF DOGS SODIUM
• = STREET DOGS POTASSIUM
▲ = SPF DOGS POTASSIUM
ARTERIAL VESSEL ELECTROLYTES
mg / gm DRY ARTERY
10
8
6
4
2
0
THORACIC AORTA
ABDOMINAL AORTA
FEMORAL ARTERY

Figure 11. Distensibility difference in the thoracic aorta of street and SPF dogs

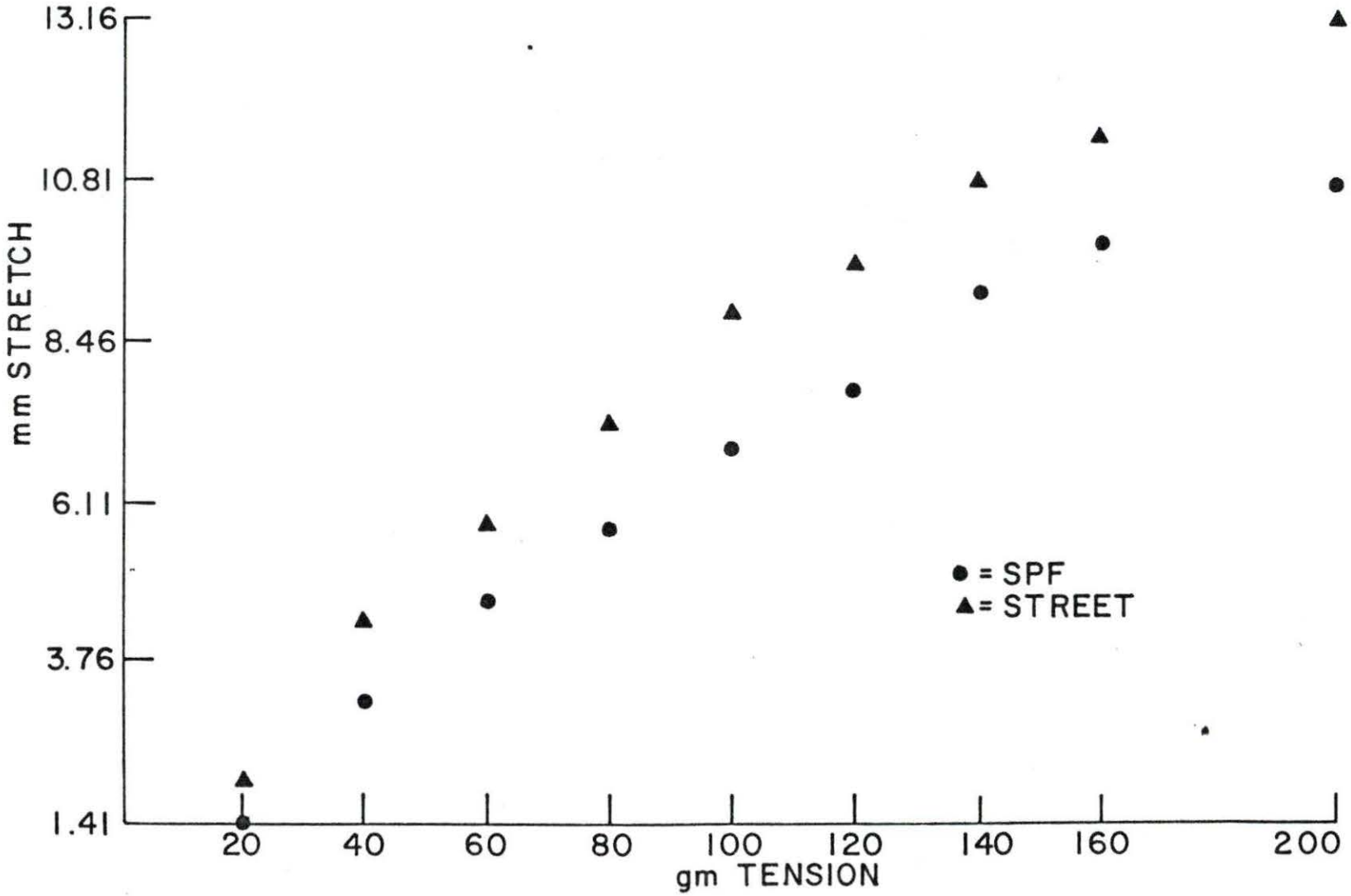
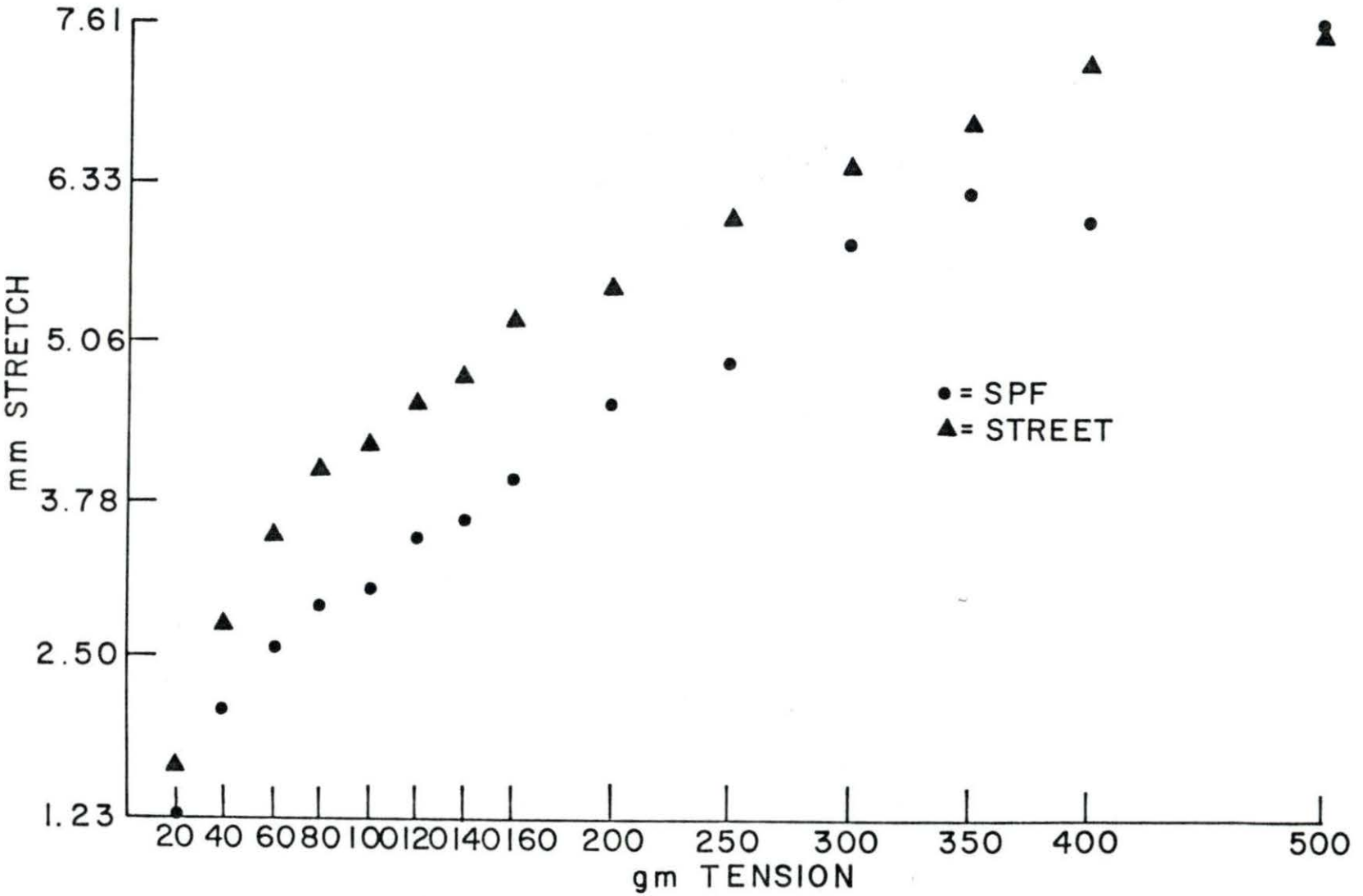

13.16
10.81
8.46
6.11
3.76
1.41
mm STRETCH
20
40
60
80
100
120
140
160
200
gm TENSION
● = SPF
▲ = STREET

Figure 12. Distensibility difference in the femoral artery of street and SPF dogs


7.61
6.33
5.06
3.78
2.50
1.23
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
● = SPF
▲ = STREET

significance (0.01% level). The same results were obtained for the abdominal aorta, Figure 13, although the level of significance was less (5% level). Thus, the results of the indirect measurement of arterial capacitance, which demonstrated decreased arterial capacitance in the SPF dogs, were verified.

The reason for the decreased distensibility in SPF dogs is unknown. It is possible that either the street dogs contain more elastic tissue in their vessels, or that the SPF vessels are more collagenous. Fischer and Llaurado (1966) studied the collagen-elastin ratio of various arteries. A similar study, comparing various samples of SPF and street dogs, would perhaps provide some enlightenment of the question of collagen and elastic distribution in the two types of animals.

One might further speculate on the influence of vessel potassium on arterial distensibility, since potassium was significantly elevated in the thoracic aorta (1% level) and femoral artery (5% level) of SPF dogs.

Figures 14, 15, and 16 illustrate the influence of sex on arterial distensibility. Males demonstrated significantly greater distensibility in the thoracic aorta (1% level), abdominal aorta (0.5% level), and the femoral artery (0.01% level). The indirect method of determining arterial capacitance did not indicate this sex difference. It can be recognized, from qualitative examination of the stretch-tension

Figure 13. Distensibility difference in the abdominal aorta of street and SPF dogs

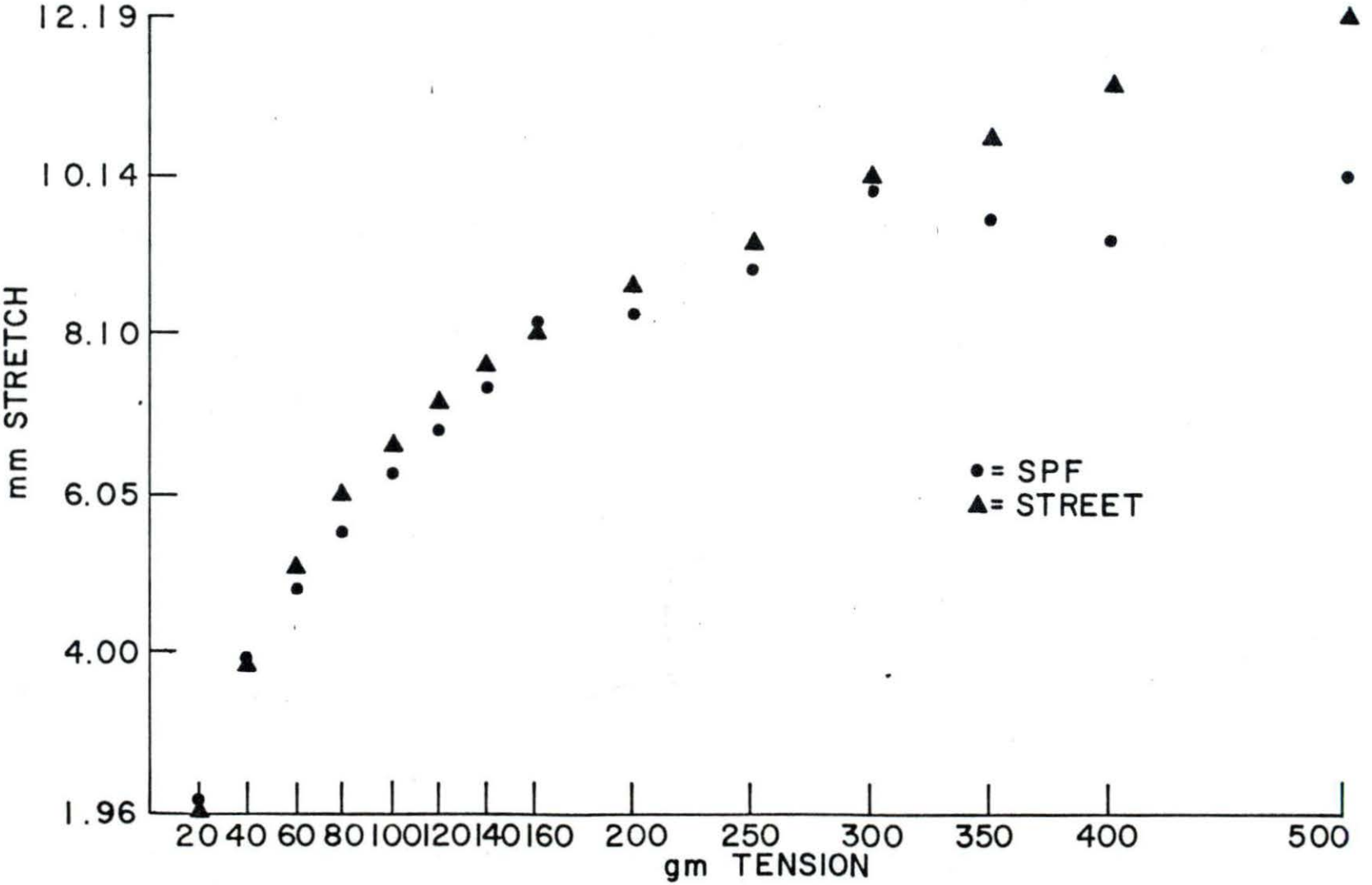

12.19
10.14
8.10
6.05
4.00
1.96
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
●= SPF
▲= STREET

Figure 14. Influence of sex on thoracic aorta distensibility

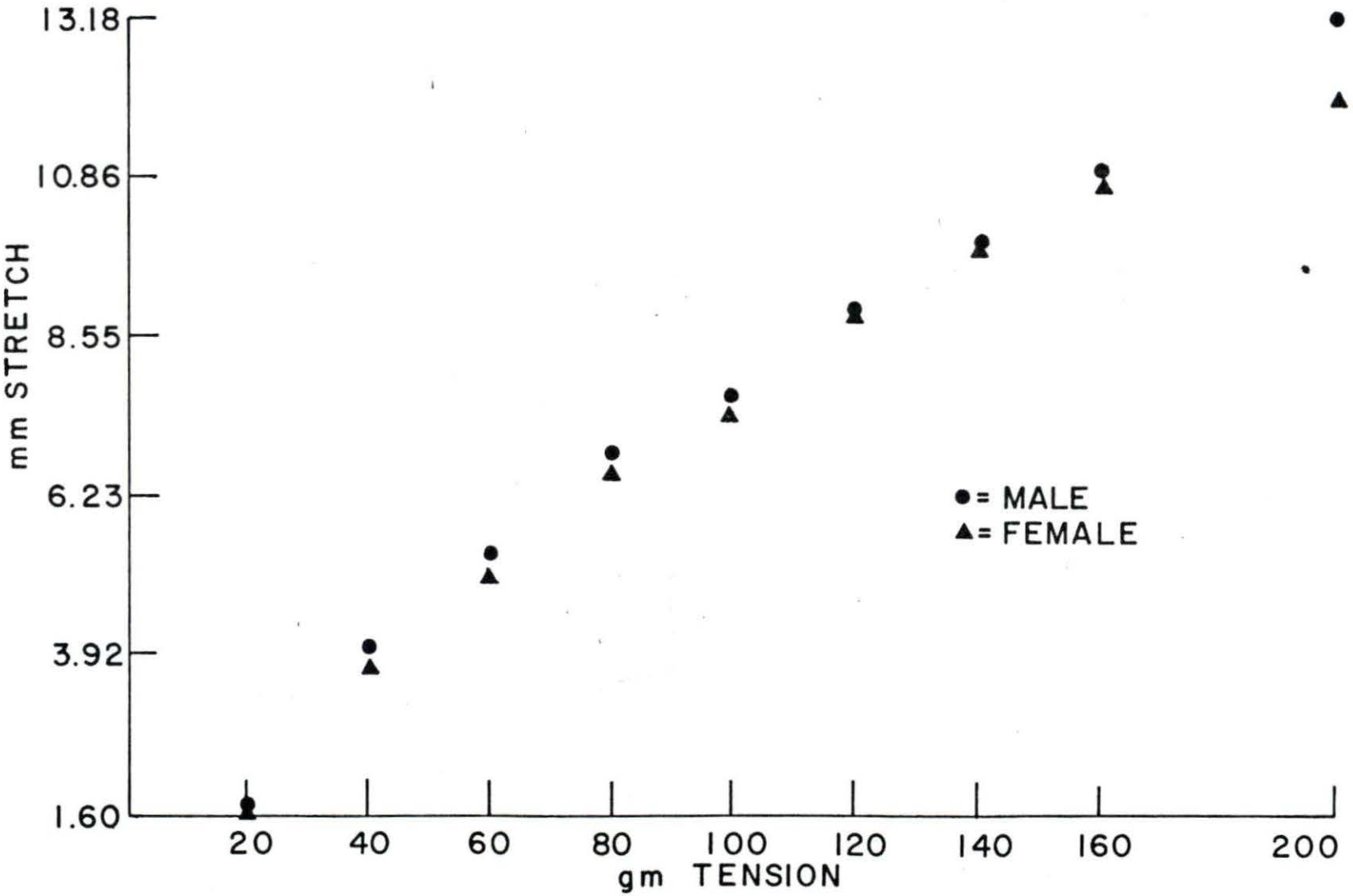

13.18
10.86
8.55
6.23
3.92
1.60
mm STRETCH
20
40
60
80
100
120
140
160
200
gm TENSION
●= MALE
▲= FEMALE

Figure 15. Influence of sex on abdominal aorta distensibility

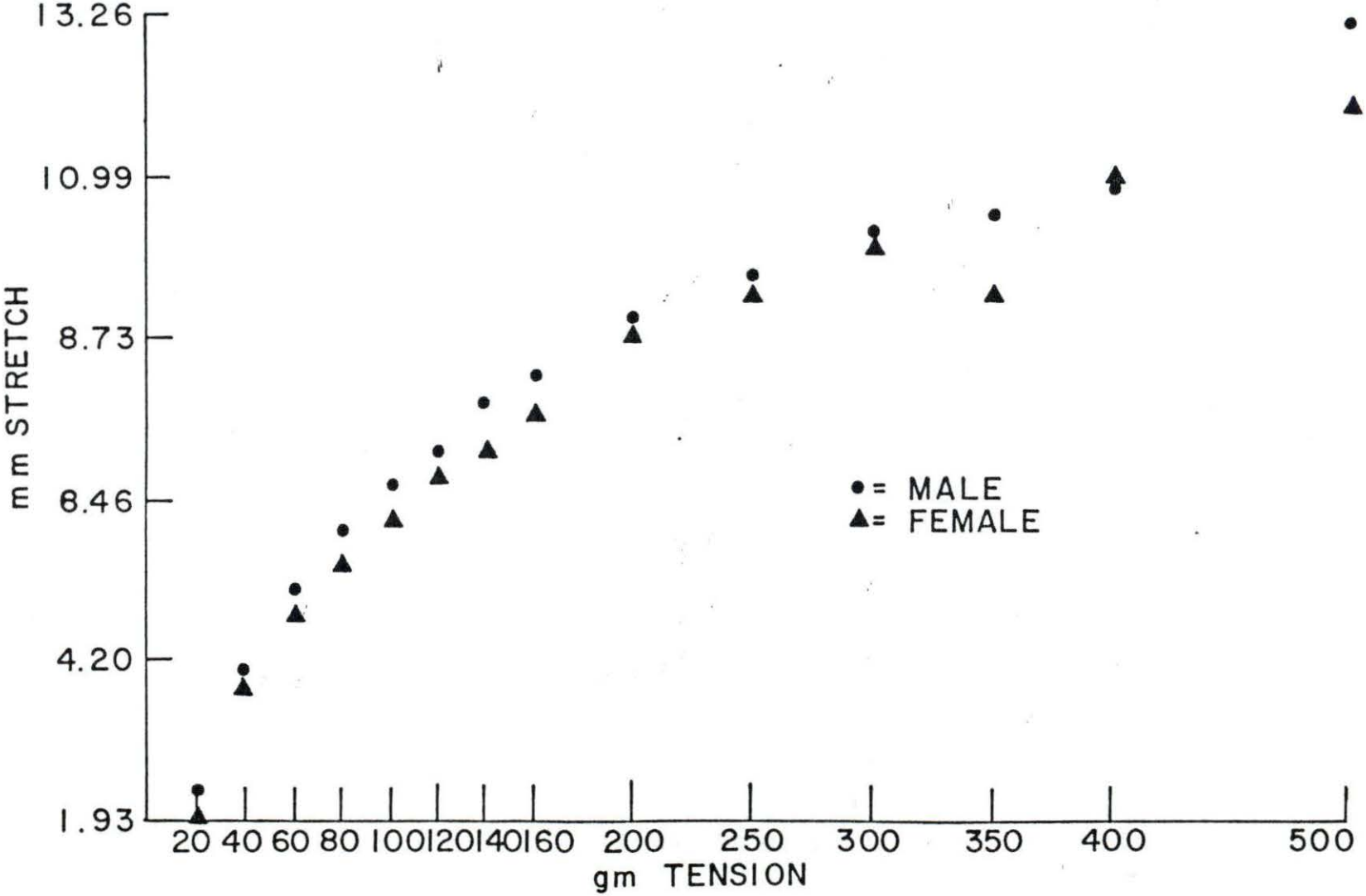
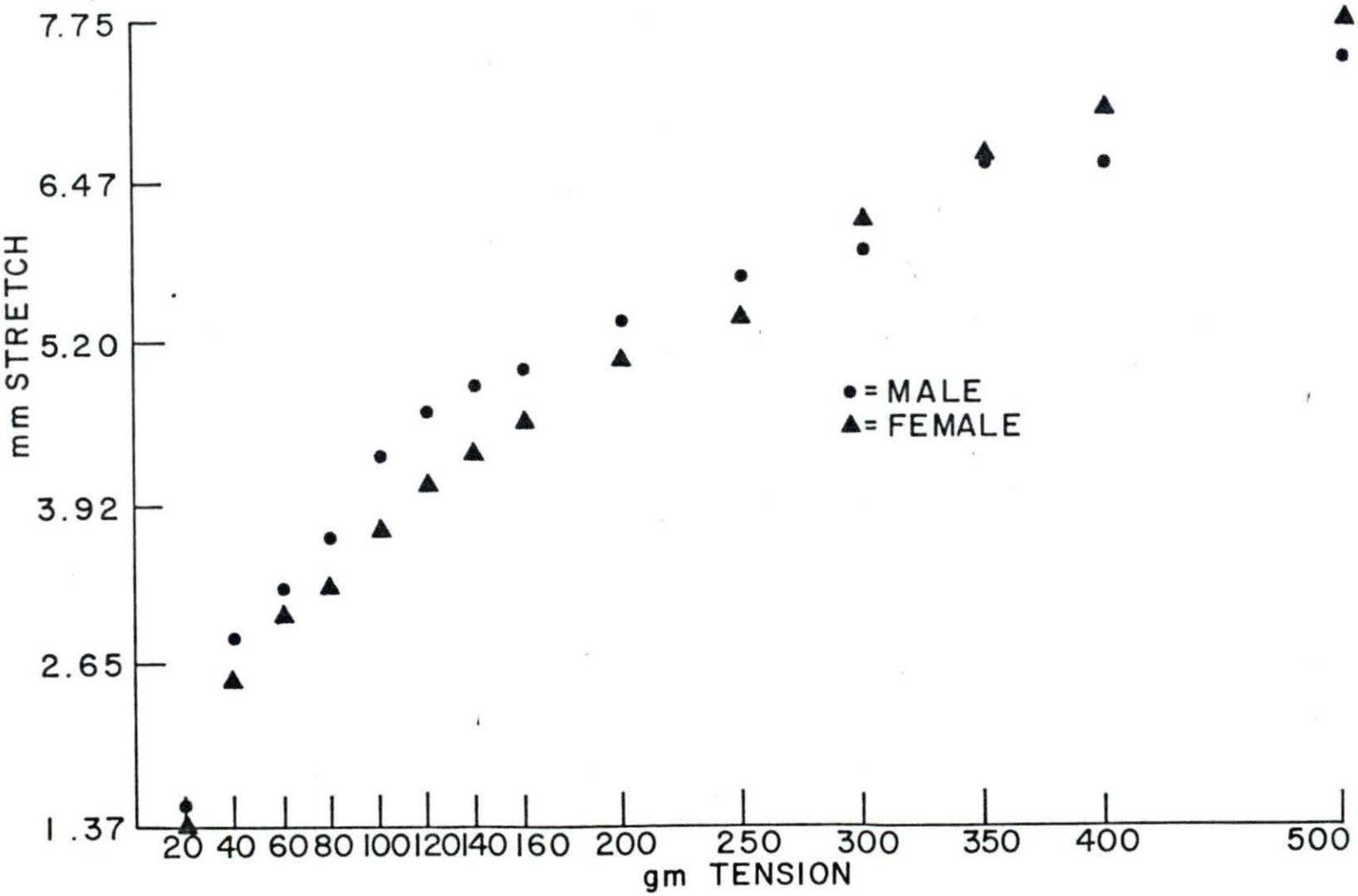

13.26
10.99
8.73
8.46
4.20
1.93
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
● = MALE
▲ = FEMALE

Figure 16. Influence of sex on femoral artery distensibility


7.75
6.47
5.20
3.92
2.65
1.37
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
● = MALE
▲ = FEMALE

curves, that the sex difference is not as great as the type difference (SPF vs. street). Therefore, the indirect method of evaluating arterial capacitance may not be able to detect subtle changes in capacitance, but only severe changes. Furthermore, the body may be able to compensate for and mask early changes in vascular structure.

Figure 17 illustrates the effect of treatment on thoracic aorta distensibility. Treatment animals had significantly greater (5% level) distensibility of the thoracic aorta than control animals.

Figure 18 indicates the nonsignificant difference in distensibility of the abdominal aorta of treatment and control animals. It is interesting to note that the control animals demonstrate more stretch early in the curve, and the treatment animals demonstrate more stretch late in the curve. It is possible that the crossover indicates tearing of fibers, and therefore more stretch/increment of tension for the treatment dogs.

A highly significant (0.01% level) decrease in femoral artery distensibility was recorded in the treatment animals. Figure 19 illustrates this finding, which was reversal of the thoracic aorta results. This paradox is difficult to explain, however, the femoral artery, being a more collagenous vessel, may reflect distensibility changes earlier than the thoracic aorta. If, due to treatment, elastic fiber

Figure 17. Effect of treatment on thoracic aorta distensibility

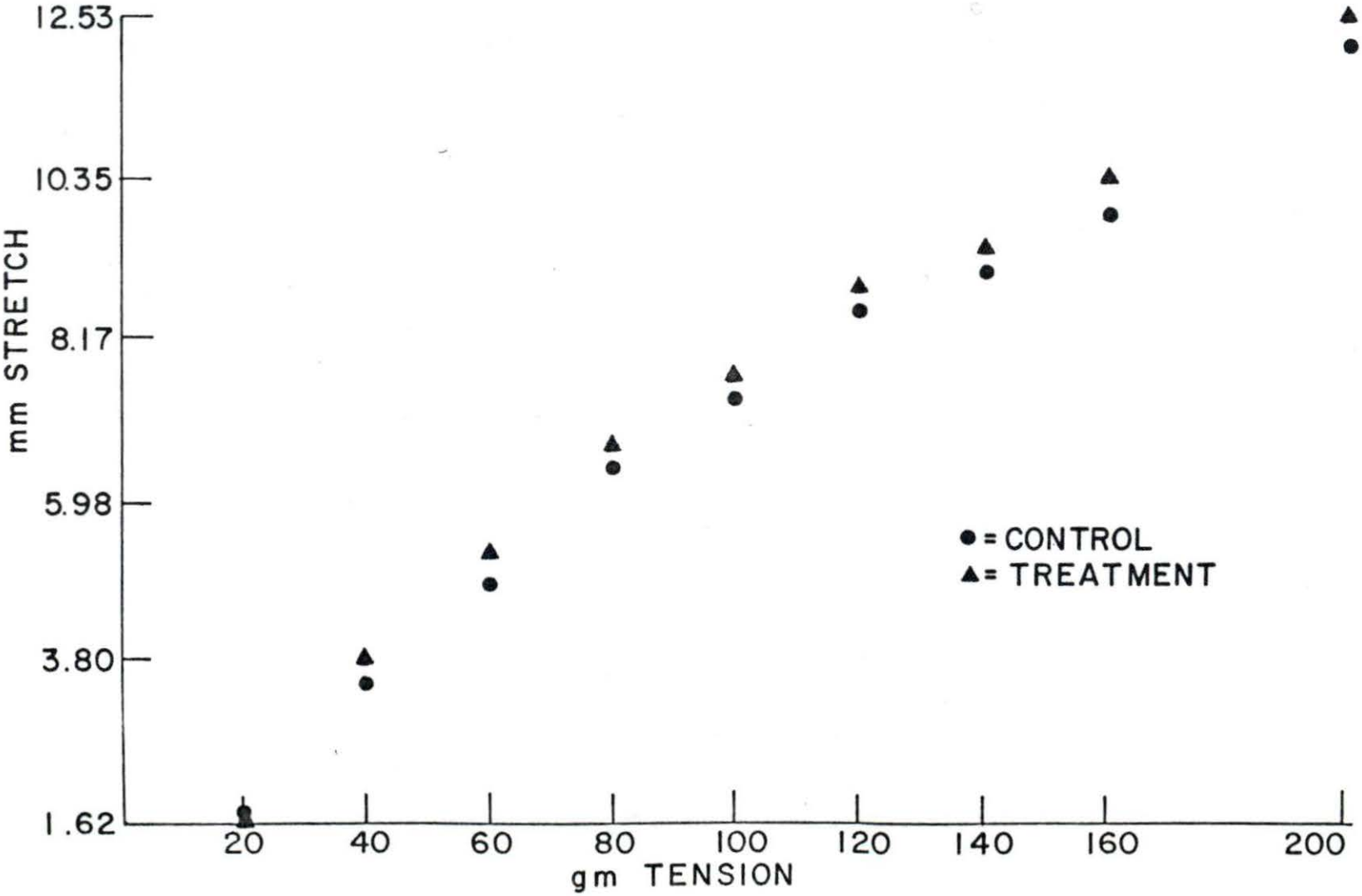

12.53
10.35
8.17
5.98
3.80
1.62
mm STRETCH
20
40
60
80
100
120
140
160
200
gm TENSION
● = CONTROL
▲ = TREATMENT

Figure 18. Effect of treatment on abdominal aorta distensibility

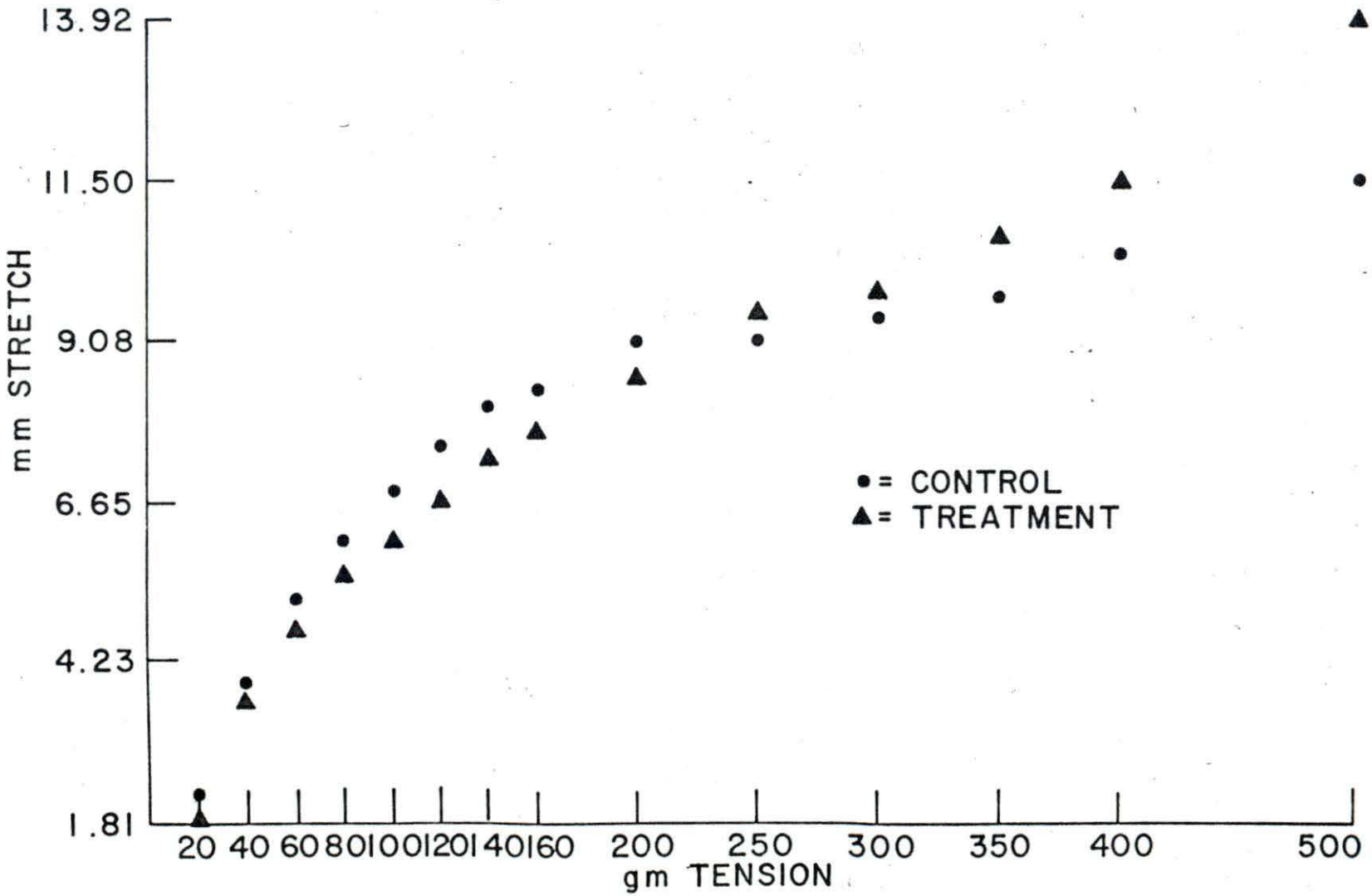
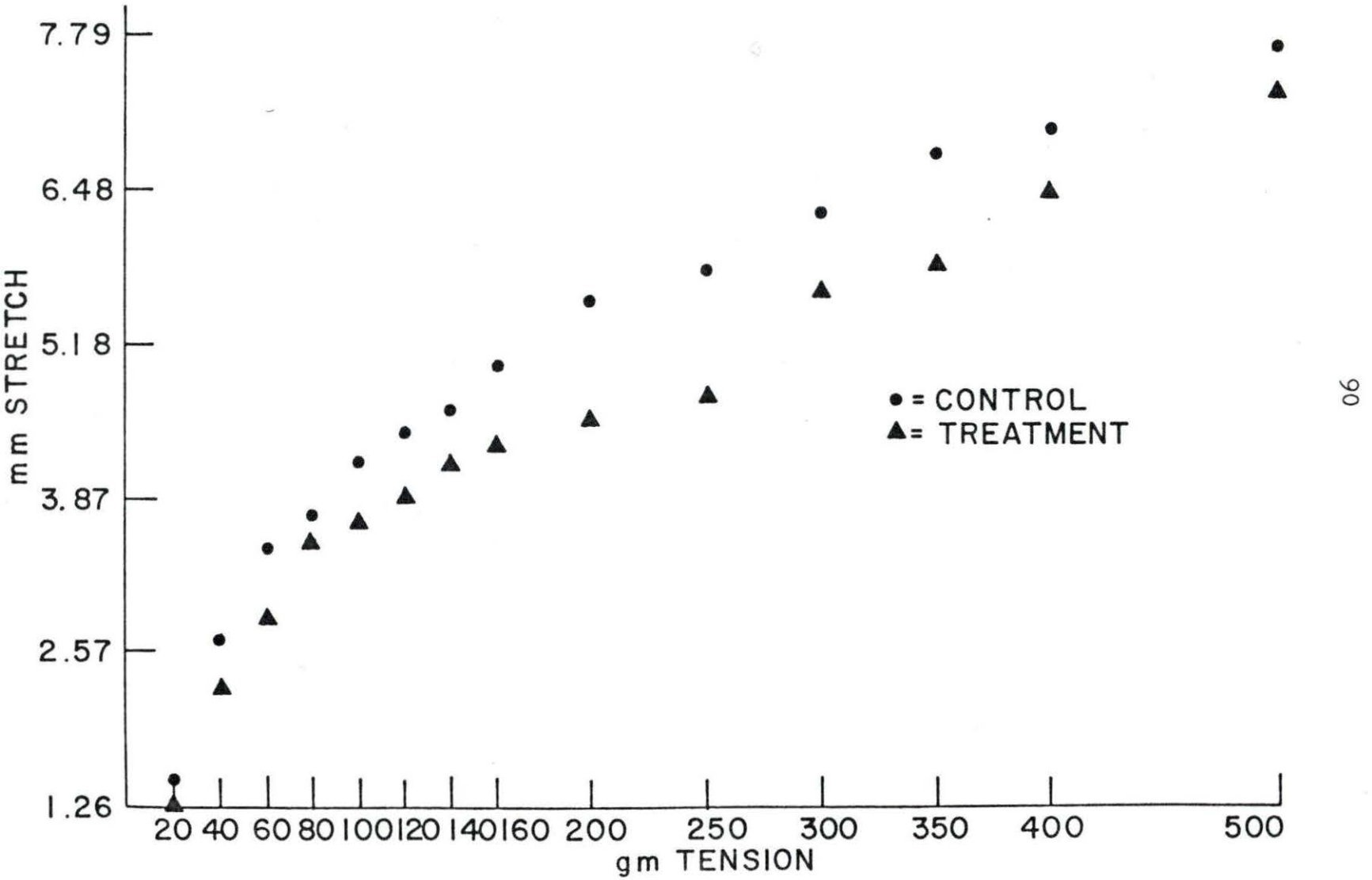

13.92
11.50
9.08
6.65
4.23
1.81
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
● = CONTROL
▲ = TREATMENT

Figure 19. Effect of treatment on femoral artery distensibility


7.79
6.48
5.18
3.87
2.57
1.26
mm STRETCH
20 40 60 80 100 120 140 160 200 250 300 350 400 500
gm TENSION
● = CONTROL
▲ = TREATMENT

breakdown occurs in the thoracic aorta, the vessel would be initially more distensible until collagenous repair occurs. Again C/E ratio studies might possibly answer this question. The reason the abdominal aorta demonstrates less change is unexplainable at this time.

From the relation $P = T/r$ and the conversion factor, 980, for grams into dynes and the factor, 7.5×10^{-4}, for dynes into mmHg, the tension could be converted into mmHg as:

$$P = \frac{T \times 980 \times 7.5 \times 10^{-4}}{r} \qquad (1)$$

where P = pressure in mmHg

T = total tension

r = initial radius + radius increase with tension.

Since the dimensions of pressure are gm/cm^2, T is expressed in gm/cm.

In order to apply this equation, the original value of r must be known. The original value of r was not measured in this project. However, the following is a sample calculation using an assumed initial r value of 1.0 cm for the thoracic aorta of a dog. At a tension of 160 grams, dr = 0.3 cm. Therefore r + dr = 1.3 cm. Applying equation (1):

$$P = \frac{160 \times 980 \times 7.5 \times 10^{-4}}{1.3}$$

$$= \frac{117.6}{1.3}$$

$$P = 90.5 \text{ mmHg}$$

This value of pressure is in close agreement with Burton (1965), who gives a value of 100 mmHg for a r of 1.3 cm and T of 170 grams.

SUMMARY AND CONCLUSIONS

The effect of short term starvation-realimentation (treatment) on arterial capacitance, arterial vessel sodium and potassium concentrations, and arterial distensiblity was evaluated. Treatment had no effect on arterial capacitance as determined by the indirect method. However, arterial stretch-tension analyses demonstrated a highly significant (0.01% level) decrease in femoral artery distensibility due to treatment. A reverse effect of treatment was recorded for the thoracic aorta (5% level). The abdominal aorta initially demonstrated a trend toward more distensibility in control animals. However, there was a crossover of the curves with resultant overall nonsignificance. The crossover perhaps represented tearing of fibers of the vessel in the treatment animals. The reversal between the thoracic aorta and femoral artery can probably be explained by a slower rate of repair in the thoracic aorta. That is, initial destruction of fibers with increased distensibility followed by collagenous repair, and decreased distensibility.

From the recorded results, it seems quite possible that the experimental period was too short since a tissue destruction and repair process is probably involved. Rather than a project of two months duration between initiation and data collection, any future experiments of this design, should have a duration of at least one year. Furthermore the

duration of starvation periods should also be considered, if the dog is used as an experimental animal. Perhaps the short periods of starvation (three days) are not as stressful to the dog, especially street animals, which may do without food for several days in their natural habitat. Therefore, longer periods of starvation (7-10 days or longer) could be utilized. Longer periods of starvation might enable one to critically examine the theory of total starvation being beneficial to obese humans. Controlled supplementation with vitamins and minerals during starvation could indicate the effect of vitamin and mineral deficiency states on arterial capacitance. Such an approach could be extremely fruitful.

If a prolonged experiment were designed (one year or longer), and the animals served as their own controls, the indirect method of evaluating arterial capacitance could be quite useful. With this method, data could be collected initially and every three months until termination of the experiment. Thus, comparative changes for each animal, from initiation to termination of the experiment, could be recorded.

Arterial capacitance was positively correlated (1% level) with body weight. A mean value of arterial capacitance/kg body weight was calculated from recorded values for both SPF and street dogs. The mean value for the street dog was 0.019 ml/mmHg kg and for SPF dogs 0.015 ml/mmHg kg. Knowing body weight and using the method of Warner *et al.* (1953), beat to

beat changes in stroke volume or cardiac output can be calculated.

Sex effects were statistically significant for cardiac output, ventricular weight, and arterial stretch-tension analyses. Cardiac output and ventricular weight were significantly greater (5% level) for males. Males demonstrated significantly greater distensibility in the thoracic aorta (1% level), abdominal aorta (0.5% level), and the femoral artery (0.01% level). The indirect method of determining arterial capacitance did not reflect a sex difference. Thus, it would appear that the indirect method is not as sensitive to smaller differences in arterial capacitance.

The differences between SPF dogs and street dogs were evaluated. The arterial capacitance, as measured indirectly, was significantly greater (1% level) for street dogs. SPF males had a significantly greater (1% level) cardiac output than street males, although there was no significant difference between type females. Stretch-tension analyses demonstrated greater distensiblity in the street dogs vessels. The levels of significance were, thoracic aorta (0.01%), abdominal aorta (5%), and femoral artery (0.01%). SPF dogs had significantly higher concentrations of potassium in the thoracic aorta (1% level) and femoral artery (5% level). Conversely, street dogs had significantly higher (5% level) concentrations of sodium in the abdominal aorta and femoral artery.

There is a possibility that a relationship exists between arterial distensibility and the concentrations of sodium and potassium. It is interesting to note that the high levels of potassium in the thoracic aorta and femoral artery of the SPF dogs seem to coincide with the low distensibility in these two yessels. Furthermore, a trend was noticed toward a higher potassium concentration in the abdominal aorta of the SPF dogs.

From these results, it is evident that differences are present between street and SPF dogs. A question which immediately arises is, "What is the cause of the physiological differences present in these two types of dogs?" This question cannot be answered at this time. However, environmental causes should be investigated. This SPF type should not be condemned because of the results of this project. For certain projects, these animals could serve very well, and if animals were needed with a trend toward hypertension, they would apparently be useful.

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APPENDIX

Table 3. Treatment animals (recorded data)[a]

Animal		Sex	Bd Wt kg	Vent Wt gm	AC ml/mmHg	CO ml/min	SBP mmHg	DBP mmHg	MBP mmHg	PWV m/sec	PCV	HR
Street	1	F	20.45	95.7	0.425	2353	162.5	126.5	138.5	8.3	44	210
Street	2	F	13.41	79.2	0.271	1152	140.0	120.0	126.6	5.4	41	150
Street	3	M	12.95	93.2	0.342	1504	122.5	104.5	110.5	5.4	43	150
Street	4	F	12.73	66.2	0.218	1250	163.5	141.5	146.8	5.7	44	180
Street	5	F	11.14	84.5	0.196	1681	203.5	177.0	185.7	5.1	45	210
Street	11	M	14.77	93.5	0.187	971	130.5	107.5	115.1	8.7	40	162
Street	12	M	20.45	133.7	0.254	1382	150.0	125.0	133.3	6.4	41	138
Street	13	M	12.86	89.3	0.244	903	117.5	104.0	108.5	8.4	41	180
Street	14	M	9.09	67.5	0.335	1616	175.0	145.0	155.0	6.9	44	216
Street	15	F	20.23	95.3	0.318	1507	143.5	120.5	123.2	7.4	41	132
SPF	7	F	10.50	69.2	0.178	1160	147.5	116.5	127.3	6.7	43	123
SPF	8	F	10.50	70.2	0.146	1005	143.5	118.5	126.8	6.0	40	174
SPF	9	F	11.10	62.0	0.163	682	136.0	117.5	123.7	5.8	43	132
SPF	10	F	11.10	72.9	0.141	1470	179.5	144.0	155.9	8.6	41	153
SPF	11	F	11.10	72.3	0.084	670	194.0	150.5	168.1	8.0	43	156
SPF	12	F	10.90	73.6	0.193	1620	162.0	133.0	142.7	6.5	40	172

[a]Bd Wt = Body Weight; Vent Wt = Ventricular Weight; AC = Arterial Capacitance; CO = Cardiac Output; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MBP = Mean Blood Pressure; PWV = Pulse-Wave Velocity; PCV = Packed Cell Volume; HR = Heart Rate/min.

Table 4. Control animals (recorded data)[a]

Animal	Sex	Bd Wt kg	Vent Wt gm	AC ml/mmHg	CO ml/min	SBP mmHg	DBP mmHg	MBP mmHg	PWV m/sec	PCV	HR
Street 6	F	8.18	56.4	0.169	887	154.0	135.0	141.4	6.7	40	180
Street 7	F	9.09	65.9	0.196	1038	140.0	115.0	123.4	5.7	41	138
Street 8	F	12.50	67.2	0.148	2157	247.5	158.5	188.2	6.4	46	180
Street 9	F	10.90	55.7	0.105	637	149.5	129.0	135.8	5.0	46	183
Street 10	F	9.77	67.4	0.188	765	85.0	61.5	70.0	4.2	45	126
Street 16	F	13.64	87.3	0.132	1121	166.5	130.0	142.3	10.8	42	150
Street 17	F	16.13	107.4	0.163	1514	179.5	143.0	155.2	9.0	40	174
Street 18	F	14.09	100.0	0.462	2019	156.0	137.5	145.3	6.3	45	198
Street 19	F	16.82	89.5	0.344	1935	162.0	137.0	145.3	8.6	38	174
Street 20	F	14.32	95.6	0.246	929	153.0	134.0	140.4	6.7	40	123
SPF 1	M	17.70	105.6	0.222	2405	193.0	157.5	169.4	5.8	40	200
SPF 2	M	11.36	100.1	0.273	2027	162.5	133.5	143.2	5.1	41	180
SPF 3	M	14.50	119.1	0.213	2439	186.0	141.5	156.4	8.5	47	156
SPF 4	M	13.20	98.1	0.144	1437	185.0	149.0	161.4	14.1	44	200
SPF 5	M	12.30	86.1	0.176	1944	209.5	162.5	178.2	8.7	40	140
SPF 6	M	15.50	94.0	0.242	2104	180.5	144.5	156.5	7.6	45	160

[a]Bd Wt = Body Weight; Vent Wt = Ventricular Weight; AC = Arterial Capacitance; CO = Cardiac Output; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MBP = Mean Blood Pressure; PWV = Pulse-Wave Velocity; PCV = Packed Cell Volume; HR = Heart Rate/min.

Table 5. Thoracic aorta electrolytes (mg/gm dry artery)

Animal	Treatment or Control	Sodium	Potassium
Street 1	T	4.727	4.609
Street 2	T	8.052	5.784
Street 3	T	8.626	5.847
Street 4	T	8.134	7.375
Street 5	T	7.086	6.377
Street 6	C	8.435	5.258
Street 7	C	7.558	6.067
Street 8	C	8.950	4.123
Street 9	C	8.292	5.194
Street 10	C	7.409	4.915
Street 11	T	7.674	6.289
Street 12	T	8.105	6.034
Street 13	T	7.341	5.661
Street 14	T	6.237	5.839
Street 15	T	7.317	6.105
Street 16	C	8.327	5.543
Street 17	C	8.015	6.145
Street 18	C	7.808	4.643
Street 19	C	8.183	5.067
Street 20	C	8.006	4.321
SPF 1	C	6.757	6.224
SPF 2	C	8.096	6.519
SPF 3	C	7.339	5.550
SPF 4	C	7.208	6.467
SPF 5	C	6.814	7.847
SPF 6	C	7.087	7.028
SPF 7	T	7.728	4.609
SPF 8	T	7.390	6.765
SPF 9	T	7.534	5.946
SPF 10	T	6.403	6.638
SPF 11	T	6.410	8.072
SPF 12	T	7.278	5.987

Table 6. Abdominal aorta electrolytes (mg/gm dry artery)

Animal	Treatment or Control	Sodium	Potassium
Street 1	T	8.184	3.047
Street 2	T	7.413	3.938
Street 3	T	9.119	4.657
Street 4	T	10.433	6.821
Street 5	T	7.145	3.573
Street 6	C	7.682	3.014
Street 7	C	7.402	4.540
Street 8	C	8.584	3.998
Street 9	C	9.367	3.538
Street 10	C	7.131	4.466
Street 11	T	8.557	4.576
Street 12	T	8.151	3.994
Street 13	T	7.849	4.741
Street 14	T	8.942	4.255
Street 15	T	8.191	4.463
Street 16	C	7.845	4.178
Street 17	C	7.613	3.885
Street 18	C	8.841	4.008
Street 19	C	8.158	3.973
Street 20	C	7.987	3.899
SPF 1	C	7.351	3.804
SPF 2	C	7.261	4.702
SPF 3	C	6.015	3.067
SPF 4	C	7.441	4.919
SPF 5	C	6.273	5.332
SPF 6	C	7.305	4.435
SPF 7	T	7.194	3.754
SPF 8	T	6.524	5.176
SPF 9	T	7.325	5.337
SPF 10	T	7.977	5.650
SPF 11	T	6.347	5.035
SPF 12	T	7.156	5.213

Table 7. Femoral artery electrolytes (mg/gm dry artery)

Animal	Treatment or Control	Sodium	Potassium
Street 1	T	9.065	4.403
Street 2	T	7.809	3.319
Street 3	T	9.293	3.949
Street 4	T	7.742	4.443
Street 5	T	6.479	2.754
Street 6	C	6.647	2.825
Street 7	C	6.126	4.463
Street 8	C	8.807	4.278
Street 9	C	5.731	3.248
Street 10	C	4.637	7.883
Street 11	T	8.134	2.861
Street 12	T	8.021	3.861
Street 13	T	7.584	4.605
Street 14	T	8.632	4.109
Street 15	T	8.111	3.459
Street 16	C	6.658	5.543
Street 17	C	6.010	5.206
Street 18	C	6.285	4.135
Street 19	C	5.988	3.897
Street 20	C	6.527	4.212
SPF 1	C	6.389	8.689
SPF 2	C	5,832	5.948
SPF 3	C	4.675	5.298
SPF 4	C	7.012	4.768
SPF 5	C	5.965	4.056
SPF 6	C	5.125	2.901
SPF 7	T	4.177	7.100
SPF 8	T	5.808	3.949
SPF 9	T	4.259	7.241
SPF 10	T	4.389	7.462
SPF 11	T	4.887	5.538
SPF 12	T	5.583	7.117

Table 8. Treatment animals (thoracic aorta mm stretch/gm tension)

Animal	Grams Tension (initial tension = 10 gm)								
	20	40	60	80	100	120	140	160	200
Street 1	--	--	--	--	--	--	--	--	--
Street 2	--	--	--	--	--	--	--	--	--
Street 3	--	--	--	--	--	--	--	--	--
Street 4	--	--	--	--	--	--	--	--	--
Street 5	--	--	--	--	--	--	--	--	--
Street 11	1.71	4.25	6.04	7.59	8.63	9.92	10.88	11.84	13.43
Street 12	3.54	7.25	9.13	10.59	11.86	13.01	14.03	15.43	17.26
Street 13	1.79	3.83	5.54	7.25	8.55	9.76	10.88	11.93	13.85
Street 14	1.29	3.25	4.71	6.09	7.05	7.97	8.65	9.31	10.26
Street 15	1.62	3.92	5.54	7.00	8.55	9.67	10.97	12.09	13.63
SPF 7	1.27	2.92	4.13	5.28	6.30	7.20	8.03	8.74	10.60
SPF 8	1.15	2.80	4.32	5.40	6.30	7.07	8.47	9.43	10.85
SPF 9	1.52	3.48	5.32	6.84	8.11	9.07	10.10	11.18	--
SPF 10	1.40	3.17	4.57	5.72	6.68	7.64	8.41	9.12	10.35
SPF 11	1.65	3.48	4.88	6.28	7.49	8.64	9.72	10.62	--
SPF 12	1.34	2.86	4.32	5.53	6.61	7.76	8.78	9.56	--

Table 9. Control animals (thoracic aorta mm stretch/gm tension)

Animal	Grams Tension (initial tension = 10 gm)								
	20	40	60	80	100	120	140	160	200
Street 6	--	--	--	--	--	--	--	--	--
Street 7	--	--	--	--	--	--	--	--	--
Street 8	--	--	--	--	--	--	--	--	--
Street 9	--	--	--	--	--	--	--	--	--
Street 10	--	--	--	--	--	--	--	--	--
Street 16	1.79	3.92	5.55	6.84	8.05	9.09	9.87	10.84	12.10
Street 17	1.46	3.34	4.78	5.96	7.08	8.13	8.97	9.93	11.18
Street 18	1.84	4.08	5.76	7.22	8.58	9.89	10.95	11.93	13.47
Street 19	1.88	4.47	6.24	7.70	8.95	10.01	10.95	11.78	12.93
Street 20	2.22	4.37	6.08	7.42	8.66	9.84	10.80	11.88	13.46
SPF 1	1.40	3.30	4.57	5.84	6.99	7.89	8.85	10.24	--
SPF 2	1.55	3.42	4.38	5.84	6.80	7.89	8.72	9.62	--
SPF 3	1.34	2.98	4.32	5.53	6.55	7.32	8.16	8.93	--
SPF 4	1.46	3.17	4.57	5.84	6.80	7.95	9.03	9.93	11.10
SPF 5	1.37	3.42	4.88	6.22	7.49	8.26	9.35	10.12	--
SPF 6	1.52	3.42	4.88	6.47	7.55	8.64	9.35	10.18	--

Table 10. Treatment animals (abdominal aorta mm stretch/gm tension)

Animal	Grams Tension (initial tension = 10 gm)													
	20	40	60	80	100	120	140	160	200	250	300	350	400	500
Street 1	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 2	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 3	1.46	2.87	3.69	4.28	4.86	5.27	6.10	6.83	--	--	--	--	--	--
Street 4	1.71	3.15	3.78	4.16	4.60	5.17	5.40	5.84	6.02	--	--	--	--	--
Street 5	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 11	1.79	3.75	5.04	6.09	6.80	7.34	7.88	8.35	9.35	10.25	10.82	11.28	--	--
Street 12	2.96	6.08	7.88	9.17	10.21	10.96	11.63	12.21	13.06	13.86	14.40	15.00	15.53	16.33
Street 13	2.04	4.17	5.54	6.42	7.30	7.76	8.30	8.76	9.35	10.16	10.65	11.21	11.78	--
Street 14	1.32	2.83	3.71	4.34	4.63	4.92	5.22	5.56	5.83	6.36	6.81	7.20	7.60	--
Street 15	1.91	4.08	5.24	6.04	6.71	7.21	7.63	8.01	8.60	9.25	9.81	10.25	10.78	11.50
SPF 7	1.59	3.17	4.01	4.74	5.08	6.01	6.66	7.31	8.98	9.88	10.90	--	--	--
SPF 8	1.57	3.32	4.38	5.09	5.85	6.26	6.97	7.74	8.35	9.88	10.60	--	--	--
SPF 9	1.65	3.42	4.38	5.22	5.86	6.34	6.84	7.21	8.23	8.94	10.15	--	--	--
SPF 10	2.02	3.42	4.32	5.09	5.61	6.09	6.60	7.06	7.73	8.63	10.15	--	--	--
SPF 11	1.63	3.07	3.86	4.69	5.44	6.16	6.85	7.28	8.83	9.26	10.51	--	--	--
SPF 12	1.82	3.11	4.64	5.35	6.20	6.59	7.06	7.51	8.23	8.94	9.59	10.48	--	--

Table 11. Control animals (abdominal aorta mm stretch/gm tension)

		Grams Tension (initial tension = 10 gm)													
Animal		20	40	60	80	100	120	140	160	200	250	300	350	400	500
Street	6	2.14	4.10	6.16	7.30	8.15	8.93	9.22	9.80	11.10	--	--	--	--	--
Street	7	2.08	3.85	4.79	5.56	6.15	6.54	6.97	7.30	8.21	8.98	9.63	10.18	--	--
Street	8	3.42	5.41	6.48	7.40	8.34	8.91	9.34	9.92	10.36	--	--	--	--	--
Street	9	2.04	3.88	5.17	6.13	6.76	7.25	7.72	8.20	8.99	9.62	10.29	--	--	--
Street	10	1.40	2.48	3.11	4.32	5.01	5.36	5.80	6.16	6.79	7.41	8.03	8.51	9.04	9.70
Street	16	1.79	3.75	4.88	5.62	6.08	6.68	6.94	7.31	7.73	8.25	9.00	9.60	10.08	10.66
Street	17	1.59	3.65	5.05	6.14	7.02	7.51	7.92	8.30	8.90	9.52	9.96	10.35	11.56	12.10
Street	18	1.46	3.32	4.55	5.51	6.13	7.01	7.47	7.84	8.50	9.08	9.56	10.05	10.53	11.36
Street	19	2.79	4.42	5.78	6.60	7.25	7.76	8.10	8.51	9.08	9.83	10.50	11.22	11.58	12.16
Street	20	2.11	4.28	5.88	6.82	7.70	8.44	8.97	9.74	10.50	11.48	11.90	12.45	12.92	13.73
SPF	1	1.67	3.75	4.91	5.85	6.53	7.21	7.75	8.28	9.00	--	--	--	--	--
SPF	2	1.84	3.80	5.01	5.72	6.30	6.76	7.22	7.74	8.68	9.63	10.28	--	--	--
SPF	3	1.46	2.92	4.01	4.78	5.36	5.95	6.35	6.74	7.34	8.00	8.40	8.80	9.18	10.19
SPF	4	2.15	4.30	5.57	6.57	7.93	8.39	8.95	9.56	--	--	--	--	--	--
SPF	5	2.86	4.92	6.32	6.97	7.95	8.77	9.06	9.53	--	--	--	--	--	--
SPF	6	3.29	5.51	6.53	7.53	8.26	9.56	10.27	11.10	--	--	--	--	--	--

Table 12. Treatment animals (femoral artery mm stretch/gm tension)

	Grams Tension (initial tension = 10 gm)													
Animal	20	40	60	80	100	120	140	160	200	250	300	350	400	500
Street 1	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 2	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 3	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 4	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 5	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Street 11	1.54	3.00	3.88	4.42	4.80	5.04	5.27	5.45	5.76	6.08	6.40	6.73	6.95	7.67
Street 12	1.96	3.75	4.71	5.22	5.55	5.69	5.88	6.06	6.38	6.73	6.95	7.23	7.48	8.25
Street 13	1.04	2.42	3.21	3.67	4.13	4.34	4.63	4.96	5.18	5.50	5.81	6.13	6.36	6.83
Street 14	1.46	2.92	3.61	3.92	4.13	4.34	4.43	4.68	5.00	5.25	5.51	5.80	6.10	6.58
Street 15	1.51	2.75	3.38	3.94	4.16	4.39	4.63	4.83	5.21	5.58	5.81	6.13	6.51	6.90
SPF 7	--	--	--	--	--	--	--	--	--	--	--	--	--	--
SPF 8	--	--	--	--	--	--	--	--	--	--	--	--	--	--
SPF 9	0.84	1.42	1.73	2.07	2.30	2.49	2.66	2.93	3.43	3.90	--	--	--	--
SPF 10	0.90	1.36	1.82	2.15	2.30	2.57	2.85	3.12	3.48	3.88	4.28	4.68	5.45	--
SPF 11	0.94	1.45	1.76	2.13	2.30	2.50	2.73	2.93	3.81	3.99	--	--	--	--
SPF 12	1.12	1.78	2.22	2.47	2.66	2.89	3.11	3.39	4.10	4.88	5.55	6.05	--	--

Table 13. Control animals (femoral artery mm stretch/gm tension)

Animal		Grams Tension (initial tension = 10 gm)													
		20	40	60	80	100	120	140	160	200	250	300	350	400	500
Street	6	1.38	2.77	3.28	3.74	4.00	4.26	4.52	4.90	5.45	--	--	--	--	--
Street	7	1.96	3.48	4.19	4.79	5.19	5.61	6.04	6.20	6.61	7.10	7.49	7.89	8.25	9.00
Street	8	2.02	3.36	4.06	4.63	5.02	5.40	5.87	6.19	6.71	7.24	7.66	8.25	8.63	9.38
Street	9	1.08	2.30	3.03	3.32	3.71	4.02	4.37	4.67	5.24	5.56	6.10	6.55	6.89	7.46
Street	10	1.37	2.23	2.67	2.97	3.18	3.35	3.65	3.73	3.96	4.26	4.58	4.92	5.20	5.85
Street	16	1.29	2.54	2.96	3.51	3.92	4.12	4.32	4.63	--	--	--	--	--	--
Street	17	0.88	1.92	2.44	2.84	3.22	3.52	3.68	--	--	--	--	--	--	--
Street	18	1.29	2.42	3.01	3.40	3.80	4.01	4.22	4.78	5.18	5.58	5.95	6.20	6.45	6.62
Street	19	1.68	3.30	4.04	4.40	4.72	4.91	5.12	5.40	5.70	6.12	6.42	6.73	6.96	7.43
Street	20	2.22	4.25	5.03	5.47	5.86	6.21	6.47	6.73	7.05	7.78	8.13	8.46	8.76	9.33
SPF	1	1.21	1.96	2.36	2.70	3.00	3.22	3.47	3.67	4.08	4.44	5.05	5.55	6.10	7.23
SPF	2	1.15	2.15	2.58	3.00	3.25	3.49	3.68	3.91	4.35	4.75	5.28	5.70	6.45	7.65
SPF	3	1.40	2.73	3.38	3.69	4.00	4.24	4.47	4.68	5.10	5.63	6.03	6.40	6.89	7.94
SPF	4	1.64	2.76	3.01	3.22	3.43	3.64	3.85	4.06	4.41	4.75	5.21	5.68	6.14	--
SPF	5	--	--	--	--	--	--	--	--	--	--	--	--	--	--
SPF	6	1.84	3.32	3.91	4.68	5.26	5.75	6.26	6.61	7.29	8.35	9.11	10.03	--	--

Table 14. Treatment animals (serum sodium, potassium, and total cholesterol)

Animal	Sodium[a] meq/L	Sodium[b] meq/L	Potassium[a] meq/L	Potassium[b] meq/L	Total Cholesterol[a] mg%	Total Cholesterol[b] mg%
Street 1	149	158	5.0	5.2	340	254
Street 2	149	150	5.0	4.8	176	250
Street 3	150	149	5.3	5.1	128	154
Street 4	146	148	5.3	5.0	162	181
Street 5	152	151	4.8	4.5	90	122
Street 11	148	156	4.6	4.3	116	116
Street 12	147	146	4.7	4.4	104	126
Street 13	150	149	4.1	3.9	154	184
Street 14	148	146	5.4	4.7	162	200
Street 15	146	147	4.4	4.3	182	204
SPF 7	149	148	4.3	5.1	134	140
SPF 8	147	148	4.3	4.5	188	152
SPF 9	151	151	4.6	4.1	200	150
SPF 10	149	147	5.0	4.3	184	162
SPF 11	147	150	4.7	3.8	148	160
SPF 12	151	150	4.5	3.7	196	173
Street mean	149	150	4.9	4.6	161	179
SPF mean	149	149	4.6	4.3	175	156
Overall mean	149	150	4.8	4.5	167	171

[a]Before treatment.

[b]At the time of data collection.

Table 15. Control animals (serum sodium, potassium, and total cholesterol)

Animal	Sodium[a] meq/L	Sodium[b] meq/L	Potassium[a] meq/L	Potassium[b] meq/L	Total Cholesterol[a] mg%	Total Cholesterol[b] mg %
Street 6	148	160	5.5	5.1	142	129
Street 7	151	153	4.8	3.5	128	96
Street 8	147	159	5.3	4.0	174	190
Street 9	148	147	4.7	4.2	168	150
Street 10	147	149	4.7	3.9	180	130
Street 16	150	150	5.2	4.0	190	180
Street 17	149	150	4.6	4.4	172	234
Street 18	151	151	5.2	4.0	178	212
Street 19	147	145	5.2	4.5	132	162
Street 20	147	148	5.2	4.2	166	182
SPF 1	148	149	4.6	4.5	164	182
SPF 2	146	148	5.2	4.1	96	128
SPF 3	147	150	5.0	4.3	152	115
SPF 4	148	152	4.3	3.8	158	170
SPF 5	147	150	4.6	4.2	194	185
SPF 6	149	151	4.3	4.2	182	175
Street mean	149	151	5.0	4.2	163	167
SPF mean	148	150	4.7	4.2	158	159
Overall mean	148	151	4.9	4.2	161	164

[a]Before treatment.

[b]At the time of data collection.

Table 16. Correlations, positive(+) and negative(-), not included in the results (1 % level)

Variables[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1 Bd Wt																							
2 Vent Wt	+																						
3 AC																							
4 CO	+																						
5 SBP																							
6 DBP					+																		
7 MBP					+	+																	
8 PWV																							
9 PCV																							
10 SSBE																							
11 SSAE																							
12 SPBE																							
13 SPAE																							
14 SCBE																							
15 SCAE														+									
16 TAS	-	-									+												
17 TAP	-															+							
18 AAS													+										
19 AAP																							
20 FAS																							
21 FAP																				-			
22 HR					+	+																	
23 AC/kg																							

[a]1 = Body Weight; 2 = Ventricular Weight; 3 = Arterial Capacitance; 4 = Cardiac output; 5 = Systolic Blood Pressure; 6 = Diastolic Blood Pressure; 7 = Mean Blood Pressure; 8 = Pulse-Wave Velocity; 9 = Packed Cell Volume; 10 = Serum Sodium Before Experiment; 11 = Serum Sodium After Experiment; 12 = Serum Potassium Before Experiment; 13 = Serum Potassium After Experiment; 14 = Serum Cholesterol Before Experiment; 15 = Serum Cholesterol After Experiment; 16 = Thoracic Aorta Sodium; 17 = Thoracic Aorta Potassium; 18 = Abdominal Aorta Sodium; 19 = Abdominal Aorta Potassium; 20 = Femoral Artery Sodium; 21 = Femoral Artery Potassium; 22 = Heart Rate; 23 = Arterial Capacitance/ kilogram.

Table 17. Correlations, positive(+) and negative(-), not included in the results (5 % level)

Variables[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1 Bd Wt																							
2 Vent Wt																							
3 AC																							
4 CO																							
5 SBP																							
6 DBP																							
7 MBP																							
8 PWV																							
9 PCV																							
10 SSBE																							
11 SSAE																							
12 SPBE																							
13 SPAE																							
14 SCBE																							
15 SCAE		+		+																			
16 TAS								-															
17 TAP																							
18 AAS																							
19 AAP																							
20 FAS																	-						
21 FAP																							
22 HR					+																		
23 AC/kg												+											

[a]1 = Body Weight; 2 = Ventricular Weight; 3 = Arterial Capacitance; 4 = Cardiac Output; 5 = Systolic Blood Pressure; 6 = Diastolic Blood Pressure; 7 = Mean Blood Pressure; 8 = Pulse-Wave Velocity; 9 = Packed Cell Volume; 10 = Serum Sodium Before Experiment; 11 = Serum Sodium After Experiment; 12 = Serum Potassium Before Experiment; 13 = Serum Potassium After Experiment; 14 = Serum Cholesterol Before Experiment; 15 = Serum Cholesterol After Experiment; 16 = Thoracic Aorta Sodium; 17 = Thoracic Aorta Potassium; 18 = Abdominal Aorta Sodium; 19 = Abdominal Aorta Potassium; 20 = Femoral Artery Sodium; 21 = Femoral Artery Potassium; 22 = Heart Rate; 23 = Arterial Capacitance/kilogram.