VASCULAR RESPONSES OF SKIN AND SKELETAL MUSCLE DURING PROSTAGLANDIN A_1 INFUSIONS

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY
JANET L. PARKER
1972

L...
Michi... 3
University

BINDING BY
HOAG & SONS'
BOOK BINDERY INC.
LIBRARY BINDERS
RINGPORT, MICHIGAN

ABSTRACT

VASCULAR RESPONSES OF SKIN AND SKELETAL MUSCLE DURING PROSTAGLANDIN A_1 INFUSIONS

By

Janet L. Parker

Collateral-free, innervated canine forelimbs were used to study blood flows, vascular resistances, and transcapillary fluid flux changes in skin and skeletal muscle vascular beds during prostaglandin A_1 infusions. Large and small artery and vein pressures were measured and total and segmental vascular resistances were calculated in both skin and muscle during natural and constant (pump-perfused) arterial inflow. Steady-state muscle (brachial) and skin (cephalic) vein outflows were measured, and limb weight was monitored continually. During natural perfusion (N=16), intra-arterial PGA_1 infusions (0.2-10.0 µg/min) decreased skin and muscle small artery pressures at each level of infusion. Initially (0.2-1.0 µg/min) skin and muscle flows increased 20%, skin, muscle, and total resistances decreased, and muscle and skin small vessels resistances decreased. Limb weight also increased. When the systemic pressure began to fall (1.0-10.0 µg/min) these values returned toward control levels. During

constant flow (N=9), intra-arterial infusions (0.2-10.0 µg/min), brachial (perfusion) and small artery pressures and total resistances decreased due to active vasodilation in small vessel segments of both skin and muscle. No redistribution of blood flow between skin and muscle vascular beds occurred. Venous resistances remained unchanged. A lower dose range of infusions (0.02-0.20) in another group of animals (N=5) produced changes qualitatively similar to those seen in the previous constant flow group over the lower infusion rates. Limb weight measurements suggest little effect upon transcapillary fluid movement. Ten minute intravenous infusions (6 µg/min) during natural arterial perfusion (N=5) showed a slight increase in flow during the first minute followed by large decreases in flow during the remainder of infusion. Total outflow decreased 50%. Initially, total and small vessel resistances were decreased, although the systemic blood pressure was well below control and tending to cause reflex vasoconstruction. The data demonstrates that PGA_1 causes active vasodilation in the skin and muscle beds of the dog forelimb, that this vasodilation is dose related, and that the major site of action is at the small vessel (arteriolar) level.

VASCULAR RESPONSES OF SKIN AND SKELETAL MUSCLE DURING PROSTAGLANDIN A_1 INFUSIONS

By

Janet L. Parker

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Physiology

1972

GTRRI

DEDICATION

to my husband

to my father

to the loving memory of my mother

ACKNOWLEDGEMENTS

The author wishes to express her sincere appreciation to her advisor, T. E. Emerson, Jr., Ph. D., for his invaluable instruction and encouragement during the course of the graduate program. The author is also indebted to Drs. J. B. Scott and R. M. Daugherty for their advice and consultation.

The author's gratitude is also extended to Mr. R. S. Underwood and Mr. W. M. Wynne for their technical assistance.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The presence of a vasodilator with smooth muscle stimulating activity was first demonstrated by von Euler, nearly forty years ago, in the seminal fluid of man and sheep. Since that time the prostaglandins have been found to be widely distributed in mammalian tissues, and shown, in many biological systems, to be among the most potent substances known (Bergstrom et al., 1968). In the past decade, they have been ascribed a myriad of biological activities and chemical purification techniques have enabled their use in many clinical situations ranging from induction of labor to bronchodilation.

The effects of the prostaglandin A (PGA) compounds, in contrast to the numerous actions of the prostaglandin E and prostaglandin F compounds, are relatively specific for the cardiovascular system. Furthermore, they are not substantially metabolized in the lungs, as are the other prostaglandins, and have therefore been postulated as humoral factors in the regulation of arterial pressure and regional blood flow (Higgins et al., 1971). In addition, the PGA compounds have been recently studied with regard to possible therapeutic

uses in circulatory shock, congestive heart failure, and hypertension (Higgins et al., 1971).

However, the intracies of the cardiovascular actions of the PGA compounds have not been completely elucidated. Although they have been shown to have potent peripheral dilatory activity, little is known about their effects upon segmental resistances and transvascular fluid fluxes. The aim of the present study was to determine the local and remote effects of PGA_1 on canine forelimb 1) skin and muscle blood flow, 2) parallel and series coupled vascular resistances, and 3) transcapillary fluid movement.

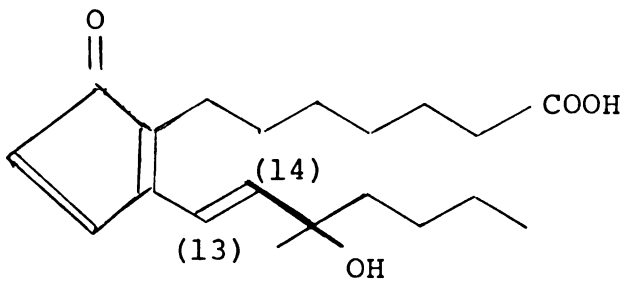
CHAPTER II

REVIEW OF LITERATURE

The prostaglandins are a unique family of unsaturated fatty acids, grouped chemically into four series, named E, F, A, and B. They are widely distributed in mammalian tissues and body fluids, and are attributed widely varying and sometimes opposing biological actions. Although they appear to have potential value in many clinical conditions, a physiological role for any of the prostaglandins remains to be demonstrated.

Chemically, the prostaglandins are all derived from the hypothetical parent compound, prostanoic acid, and consist of a five membered ring in a twenty carbon skeleton. The fourteen known prostaglandins (PGs), have common structure and differ only in the degree of unsaturation or substitution in the cyclopentane ring or aliphatic side chains (Bergstrom et al., 1968). The E group (PGE) contains characteristic 11 α-hydroxy and 9-keto groups, and is easily dehydrated by weak alkali to the 10:11 unsaturated ketone, prostaglandin A (PGA). PGA can isomerize to form the double conjugated ketone, PGB. The F prostaglandins are analogous to the E

compounds but the 9-keto group is reduced to a hydroxyl (Bergstrom et al., 1962a; Bergstrom et al., 1962b). The groups are further defined by a subscript number, referring to the number of double bonds present in the aliphatic side chain. Thus, PGA_1 has only the 13:14 trans double bond, whereas PGE_2 and PGF_3 have two and three bonds, respectively.



PGA_1

Prostaglandin research was initiated with the clinical observation that the human uterus responds to semen with contraction or relaxation (Kurzok and Lieb, 1930). Later, the presence of this biologically active substance in the seminal fluid of man and sheep was independelty demonstrated by Goldblatt (1933) and von Euler (1934). Von Euler showed that this substance caused a prolonged fall in blood pressure after intravenous injection in the rabbit and cat, and termed this active principle prostaglandin (von Euler, 1936). Due to the lack of isolation and purification techniques, little definitive work was done with prostaglandin until nearly thirty years later. In 1957, Sune Bergstrom undertook

to isolate this substance and found not one, but thirteen naturally occurring prostaglandins in sheep vescicular glands (Bergstrom et al., 1960). Bergstrom and his co-workers succeeded in elucidating the structure of the PGE and PGF compounds in 1960, and a phenomenal expansion of prostaglandin literature followed. Recently, some of the prostaglandins have been totally synthesized in the laboratory (Beal et al., 1967).

Soon after their identification, the prostaglandins were demonstrated in most mammalian tissues, including lung (Samuelsson, 1964), brain (Coceani and Wolfe, 1965), spinal cord (Horton and Main, 1967), and kidney (Daniels et al., 1967; Lee et al., 1966), and were found to be released from the stomach (Coceani et al., 1967), adrenals (Ramwell et al., 19660, diaphragm (Ramwell et al., 1965), and other organs (Bergstrom et al., 1968). They have been shown to possess a myriad of biological activities involving the cardiovascular system (vasodilation, constriction, cardiac effects), renal system (water and electrolyte excretion), the female and male reproductive systems (labor induction, therapeutic abortion, fertility), the pulmonary system (bronchodilation), the upper respiratory system (nasal patency), and the gastrointestinal system (antisecretory activity). Thus, due to their ability to affect many physiological functions, the prostaglandins appear to have potential value in a wide variety of clinical conditions.

The PGA compounds are particularly interesting with regard to their specificity upon the cardiovascular and renal systems. This group was first distinguished from the other prostaglandins because of its potent vasodepressor activity and lack of non-vascular smooth muscle stimulating activity (Daniels et al., 1965). In addition, the PGA compounds are not substantially metabolized in the lungs (McGiff et al., 1969) as are the other prostaglandins. These compounds have therefore been postulated as hormonal factors in the regulation of blood pressure and regional blood flow (Higgins et al., 1970), and their cardiovascular actions have been recently evaluated in basic and clinical studies. Most current studies are being carried out with PGA_1 because it is more readily available as a pure crystalline entity than PGA_2 and the biological properties of the two appear to be equivalent (Hinman, 1970).

Systemic Circulatory Effects

PGA_1, similar to PGE_1, has highly potent hypotensive properties in the dog (Nakano, 1967; Nakano and McCurdy, 1967); Nakano and McCurdy, 1968; Horton and Jones, 1969), cat (Horton and Jones, 1969), rat (Weeks et al., 1969), rabbit (Horton and Jones, 1969), and human (Carlson et al., 1970; Carr et al., 1970; Westura et al., 1970). Intravenous injections of graded doses of PGA_1 in dogs (0.25-4.0 µg/kg) significantly reduce mean blood pressure and total peripheral

resistance and increase heart rate and cardiac output essentially in proportion to the dose given (Nakano, 1967; Nakano and McCurdy, 1968). As has recently been shown for PGE_1 (Emerson et al., 1971) intravenous injections of PGA_1 transiently increase the venous return to the heart (Nakano and McCurdy, 1967). Effects of PGA_1 on systemic hemodynamics have been studied in intact conscious dogs after implantation of Doppler ultrasonic flow probes (Higgins et al., 1971). Intravenous influsions of 1.0 µg/min reduce arterial blood pressure and systemic resistance by averages of 30% and 51% respectively, and increase heart rate and cardiac output 64% and 47%, respectively. Since blood pressure falls while cardiac output rises, the primary mechanism of the blood pressure fall with PGA_1 is decreased peripheral resistance. Weeks et al. (1967) determined that the depressor activity of the two PGA forms is about 2.5 times as great as the PGE forms in dogs. However, studies indicate that PGA is less effective than PGE in lowering blood pressure in rats and man (Carlson, 1970; Weeks, et al., 1969).

Recently, studies have been completed on the antihypertensive effects of PGA_1 in patients with essential hypertension. Intravenous infusions of rates from 0.3 to 1.2 µg/kg/min for 30-60 min lowered blood pressure, but the magnitude of the response varied with the individual (Christlieb, 1969). Carr (1970) reported that similar infusions of PGA_1

increased cardiac output, reduced blood pressure, and decreased peripheral resistance in five patients. In addition, the renal fraction of the cardiac output increased dramatically. Lee et al. (1971) infused PGA_1 i.v. for one hour into six patients and noted a decrease in blood pressure from 200/112 mm Hg to 140/85 mm Hg at infusion rates of 2.1-11.2 µg/kg/min. In addition, none of the side effects reported to occur during PGE_1 administration (headache, facial flushing, visual symptoms, abdominal cramps)(Bergstrom et al., 1965) were found to occur during PGA_1 infusion, and these authors suggested that PGA_1 may function as an "ideal" antihypertensive agent. Westura (1970) also infused PGA_1 at two dose levels in patients. At the first level (1.0 µg/kg/min) he found a progressive fall in systemic blood pressure, a rise in stroke volume and cardiac index, and an increase in heart rate. At the higher dose (2.0 µg/kg/min) a further small decrease in systolic blood pressure was recorded, but no further lowering of diastolic blood pressure occurred. Heart rate continued to increase while the cardiac index decreased slightly. He concluded that the antihypertensive action of PGA_1 is direct peripheral dilation leading to a fall in peripheral resistance and a decline in blood pressure accompanied by a compensatory increase in heart rate which is almost entirely reflex in nature. However, the study did not permit the authors to rule out the possibility that PGA_1 had a direct stimulatory effect on the heart to increase rate.

In this regard, Carlson et al. (1970) infused lower doses of PGA_1 into three healthy subjects and noted that the heart rate tended to increase without significant change in blood pressure.

Recently, Higgins et al. (1971) demonstrated total prevention of cardiac acceleration with PGA_1 after combined beta receptor and cholinergic nerve fiber blockade in the conscious dog. These data are consistent with findings in the isolated heart (Lee et al., 1965) and anesthetized dog (Carlson and Oro, 1966; Nakano and McCurdy, 1968) which suggest that prostaglandins are devoid of direct positive chronotropic activity.

Effect Upon Myocardial Contractility

It is still unclear if PGA_1 has a direct effect upon myocardial contractility. Intravenous injections of PGA_1 in vagotomized, propanolol treated dogs decreased left ventricular end diastolic pressure and increased dp/dt, accompanied by a fall in systemic blood pressure (Nakano and McCurdy, 1968). Also, the df/dt and peak tension values of myocardial contractile force (measured with a Walton-Brodie strain gauge) increased 44%. In this study, another determinant of dp/dt, heart rate, was changing during this period and may have contributed to the increased dp/dt and force. However, when injected into the left coronary artery during perfusion at constant flow, PGA_1 augmented left ventricular

contractile force, without increasing heart rate (Nutter and Crumly, 1970).

On the other hand, in a more complete study, Higgins et al. (1971) found PGA_1 to be devoid of significant inotropic activity when alterations in heart rate and reflex sympathetic tone were controlled by atrial pacing and beta adrenergic blockade, and left ventricular pressure was held constant. In a recent publication (1972), he uses three parameters to characterize the contractile state of the left ventricle (LV):LV isolength velocity, maximum dp/dt, and the quotient of dp/dt/developed LV pressure. These parameters increased 29, 24, and 25%, respectively, during PGA_1 infusion in conscious dogs. Following beta blockade, the increases were 10, 10, and 12%, and when changes in afterload (via intra-aortic balloon) and heart rate were prevented in addition, minimal changes of 4, 8, and 6% occurred. Thus, a direct inotropic action of PGA_1 appears unlikely, and augmentation of the contractile state which results from PGA_1 infusion is apparently due to indirect reflex effects. In this regard, studies on the isolated, perfused, rabbit heart have shown no direct effect of PGA_1 on heart rate or contractility (Lee and Covino, 1965).

Peripheral Vascular Effects

The local effect of a substance on specific vascular beds is frequently evaluated through changes in blood flow or resistance after close i.a. injection or infusion. In such

experiments, i.a. administration of PGA_1 increased blood flow and decreased vascular resistance in the iliac (Higgins et al., 1970), superior mesenteric (Nakano et al., 1968), mesenteric (Higgins et al., 1970), subclavian and popliteal (Barner et al., 1971), brachial and carotid (Nakano, 1968; Nakano et al., 1968), femoral (Nakano, 1968; Barner et al., 1971), renal (Nakano, 1968) and coronary (Nakano, 1968; Christlieb et al., 1969; Barner et al., 1971; Higgins et al., 1971) arteries. This effect is not blocked by atropine, propanolol, methysergide, or diphenhydramine (Nakano, 1968; Smith et al., 1967). When regional blood flows were measured by a Doppler flowmeter, i.v. injections (1 μg/kg) decreased mean aortic pressure while increasing flows and decreasing resistances in the coronary, mesenteric, renal, and iliac arteries (Bloor and Sobel, 1970). In addition, studies from isolated vascular smooth muscle have shown that partially contracted helical strips from small renal, skeletal muscle, and mesenteric arteries are contracted further by high concentrations and relaxed by low concentrations of PGA_1, demonstrating a biphasic response (Strong and Bohr, 1967).

Effect Upon Coronary Vasculature

I.a. injections of PGA_1 into the coronary circulation have been shown to increase coronary blood flow and decrease coronary resistance in the dog (Nakano, 1968). Barner et al. (1971) reported that 25 μg i.v. injections in dogs decreased

mean aortic pressure, and decreased flow in the internal carotid and popliteal arteries, concommitant with an increase and then a decrease to 12.5% below control in coronary blood flow. To ascertain a possible direct dilatory effect upon the coronary bed, Bloor et al. (1970) infused PGA_1 via an intracoronary tube and noted a 74% increase in coronary blood flow prior to any change in arterial pressure or heart rate. In addition, myocardial reactive hypermia following a 10 to 30 second occlusion of the left circumflex artery was diminished or abolished during PGA infusion. When heart rate was maintained constant by atrial overdrive (Higgins, 1970) PGA_1 still caused a marked decrease in coronary resistance which was not diminished by beta blockade. However, in contrast to the above, isolated coronary smooth muscle has been shown to contract in response to the prostaglandins (Strong and Bohr, 1967).

Renal Vascular Effects

The renal vascular bed has been shown in animal studies to be particularly sensitive to PGA infusion (Lee, 1968; Lee et al., 1971), the typical response being an increase in renal blood flow, GFR, and sodium and water excretion. Lee et al. reported that very low infusion rates of PGA_1 into patients with essential hypertension were not associated with a change in blood pressure but resulted in a significant increase in effective renal plasma flow (ERPF), GFR, and urinary flow.

At the higher infusion rates, blood pressure fell, and ERPF, GFR, and urinary flow fell towards preinfusion control levels. Thus, decreased renal perfusion pressure secondary to a reduction in systemic arterial pressure and increase in sympathetic activity offsets the direct renal vasodilating and natriuretic action of PGA_1. PGA_1 also apparently causes a shift of renal blood flow to cortical regions, as a result of decreased afferent glomerular resistance (Schoones et al., 1970).

Pulmonary Vascular Effects

Pulmonary arterial pressure (PAP) increases (Nakano and McCurdy, 1967, 1968) and pulmonary vascular resistance decreases (Nakano, 1968) following i.v. injection of PGA_1 in dogs. However, when right cardiac input was held constant PGA_1 injection did not change or decrease pulmonary arterial pressure. Thus, the mechanism of the increased PAP appears to be via increased pulmonary blood flow rather than a direct effect upon the pulmonary vessels.

Skin and Skeletal Muscle Circulation

Locally, PGA_1 is a potent dilator of the resistance vessels in the hindlimb and forelimb of the dog, although PGE_1's effect is apparently greater and more prolonged (Nakano et al., 1968). PGA_2 causes a significant decrease in total peripheral resistance and increase in femoral arterial blood flow in the dog (Lee et al., 1965). In contrast to the

above, Covino et al. (1968) found no significant change in femoral arterial blood flow during i.v. infusion in dogs, although the local effects were not separated from compensatory effects due to decreased systemic pressure. In the isolated canine hindlimb, i.a. infusions of PGA_1 caused a decreased vascular resistance and increased vascular capacity (Greenburg and Sparks, 1969). In addition, these authors reported a dilatory effect of PGA_1 upon the venous segment of the hindlimb vasculature when perfused at constant flow. They also reported that PGA_1 causes relaxation of isolated veins, although supportive data was presented only for PGE_1.

Femoral arterial blood flow is distributed mainly to skin, subcutaneous tissues, and skeletal muscle. Little work has been done to separate the effects of PGA_1 on these vascular beds. The effects of i.a. PGA_1 upon the isolated denervated hindpaw, primarily a cutaneous vascular bed, have demonstrated decreased vascular resistance in the face of decreased systemic pressure (Kadowitz et al., 1971). Daugherty et al. (1968) used the method of Haddy et al. (1961) to separate skin and muscle blood flow in the forelimb during i.a. and i.v. infusion of PGE_1, a dilator similar to PGA_1. These authors found PGE_1 to produce proportional increases in flows and decreases in resistance in skin and muscle. In addition, they reported a tendency for reduction in venous resistance.

Horton et al. (1969) report decreases in both systemic arterial blood pressure and perfusion pressure of a constant flow perfused hindlimb with i.v. infusions of PGA_1 in the cat and dog. The mechanism of the hindlimb vasodilation was further investigated using a cross-perfusion technique. The innervated hindlimb of a cat (recipient) was perfused at constant flow with blood from a donor cat. Intravenous infusions of PGA_1 into the recipient cat caused a fall in systemic pressure and a rise in perfusion pressure, although close i.a. injections into the limb resulted in a fall in perfusion pressure.

Thus, although it is clear that PGA_1 decreases total resistance in the hindlimb, the effect on the parallel and series coupled resistances in skin and muscle vascular beds has not been shown. The effect of PGA_1 upon peripheral veins also needs further attention.

Microcirculatory Effects

Few studies have been done on the effects of PGA_1 on capillary flow and pressure, and possible effects upon capillary permeability. Kaley and Weiner (1967) observed the microcirculation of the rat mesocecal bed under the microscope and noted that the similar compound, PGE_1, increased capillary flow by dilating metarterioles and venules and by opening precapillary sphincters. They also reported an increase in vascular permeability with PGE comparable to that produced

by bradykinin. However, Daugherty et al. were not able to demonstrate changes in fluid filtration or capillary permeability in the isolated forelimb during PGE_1 infusion. Using both PGE_1 and PGA_1 in the isolated hindlimb, Greenburg and Sparks (1969) found an increased K_f, capillary filtration coefficient, which they attributed solely to decreased precapillary sphincter tone.

CHAPTER III

MATERIALS AND METHODS

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg) and artificially ventilated via a cuffed endotracheal tube. The skin of the right forelimb was circumferentially sectioned 3-5 cm above the elbow. The right brachial artery, forelimb nerves, and brachial and cephalic veins were isolated and the muscles and remaining connective tissue were sectioned by electrocautery. The humerus was cut and the ends of the marrow cavity were packed with bone wax. Thus, all blood entered limb only through the brachial artery and left via the brachial and cephalic veins. The forelimb nerves (median, ulnar, radial, and musculocutaneous) were left intact and were coated with an inert silicone spray to prevent drying. Heparin was administered in a dose of approximately 10 mg/kg.

Small bore polyethylene tubing was used to measure intravascular pressures as previously described by Daugherty et al. (1968) at the following sites: 1) brachial artery via a side branch (PE 60), 2) skin small artery from the third superficial volar metacarpal artery on the undersurface of the paw (PE 60), 30 muscle small artery from a vessel supplying a

flexor muscle in the middle portion of the forelimb (PE 50), 4) skin small vein from the second superficial dorsal metacarpal vein on the upper surface of the paw (PE 60), 5) muscle small vein from a deep vessel draining a flexor muscle in the middle portion of the forelimb (PE 10), 6) skin large vein from the cephalic vein via a side branch (PE 60), 7) muscle large vein from the brachial vein via a side branch (PE 60). The systemic pressure of the animal was monitored by placing a catheter (PE 240) into the aorta via a femoral artery. Pressures were measured with low-volume displacement transducers (Statham Laboratories, Model P23Gb, Hato Rey, Puerto Rico) and recorded on a direct writing oscillograph (Sanborn Co., Model 60-1300, Boston, Mass.). The brachial and cephalic veins were partially transected 3-5 cm downstream from the sites of the large vein pressure measurement and the vessels cannulated with a short section of large bore polyethylene tubing, usually PE320 or PE380. Outflow from both veins flowed by gravity into a graduated cylinder blood reservoir maintained at constant volume by a Sigmamotor pump (Sigmamotor, Model T-6SH, Middleport, N. Y.) connected to a cannulated jugular vein. Blood flows were determined by timed collections of the two outflows with a graduated cylinder and stopwatch. The median cubital vein represents the major connection between the skin and muscle vascular beds in this preparation. Following ligation of this vessel, the brachial

venous outflow is predominately from muscle, and the cephalic venous outflow is predomnately from the skin vascular bed. This preparation thus presents fairly complete separation of the two parallel coupled vascular beds, and has been shown to accurately represent them in previous studies (Daugherty et al., 1967; Abboud, 1968; Daugherty et al., 1968). After cannulation, the forelimb was placed on a wire mesh platform attached to a strain gauge torsion balance. In each experiment, the balance was calibrated by the addition of a 2g weight which produced a deflection of 8-15 mm pen deflection on the oscilloscope. Limb weight was monitored continually during all of the experiments.

In 21 animals, limbs were perfused naturally through the uninterrupted brachial artery. PGA_1 was infused intra-arterially (Harvard Apparatus, Model 901, Dover, Mass.) via a side branch of the brachial artery, whereas the intravenous infusions were made into the cannulated jugular vein. In the remaining fourteen animals, a finger type blood pump (Sigma-motor, Inc., Model T,10, Middleport, N. Y.) was interposed between the femoral and brachial arteries, and the limbs perfused at constant flow. PGA_1 was then infused into the tubing upstream to the pump.

PGA_1 was stored at 0°C in stock solutions containing 0.1 ml of 95% ethanol for each milligram PGA_1 and diluted to the appropriate concentrations with normal saline at the start of each experiment. In all intra-arterial infusions, PGA_1 was

infused at sequentially increasing rates, and steady state values of each parameter were obtained at each infusion level. When perfused naturally (N=16), the rates of infusion employed were from 0.2-10 μg/min, and in the constant flow preparations, PGA_1 was infused at two dose ranges, 0.2-10 μg/min (N=9) and 0.02-2.0 μg/min (N=5). The intravenous infusions were all made at a single infusion rate of 6.0 μg/min for ten minutes in five animals, and all of the forelimbs were perfused naturally. Normal saline was infused intra-arterially at the rates listed above to serve as the corresponding control series for each of the groups.

Total forelimb resistance was calculated by dividing the pressure gradient across the limb (mean venous pressure subtracted from arterial pressure) by the total venous outflow. Total skin and muscle resistances were calculated by dividing the appropriate pressure gradients by the cephalic and brachial venous outflows, respectively. Skin and muscle arterial, small vessel, and venous resistances were calculated by dividing their respective arterial, small vessel, and venous pressure gradients by the appropriate cephalic or brachial venous outflow.

Statistical analysis was completed using the student t test modified for paired replicates. A P value less than 0.05 was considered significant.

CHAPTER IV

RESULTS

I. Intra-arterial Infusion-Natural Brachial Artery Inflow

The effect of intra-arterial administration of PGA_1 on forelimb weight, blood flows, and aortic, arterial, and venous pressures are shown in Figure 1. Note that total venous outflow increased progressively over the lower dose range due to a rise in both cephalic ($P < 0.05$) and brachial ($P < 0.05$) vein outflows. At the infusion rate of 1.0 µg/min the flows began to progressively decrease to levels below control. Forelimb weight increased to 7.2 grams above control ($P < 0.05$) and then began to decrease to a level not significantly different than control. The change in weight appears to reflect the increases in flows and venous pressures. Aortic pressure remained constant at the low infusion rates and began to decline at 1.0 µg/min ($P < 0.05$). Throughout all infusion rates muscle and skin small artery pressures decreased, the decrease becoming significant ($P < 0.05$) in both muscle and skin at 0.5 µg/min. Skin small vein pressure rose and began to fall again at 1.0 µg/min ($P < 0.05$); muscle small vein pressure rose slightly ($P < 0.05$) before decreasing. Both large vein

pressures rose ($P < 0.05$ at 0.5 µg/min) and fell ($P < 0.05$ at 10 µg/min) proportionately throughout infusion. All parameters were monitored for several minutes after stopping the infusion. During this period arterial pressures tended to return to preinfusion values. Saline control infusions were without significant effect upon any of these parameters. Figure 2 illustrates total resistances in the natural flow preparation calculated from the data shown in Figure 1. Total forelimb resistance during infusion of PGA_1 fell from 1.6 to 1.3, the decrease becoming significant at 2.0 µg/min. Total skin resistance fell to 2.7 ($P < 0.05$) before rising again, and total muscle resistance fell from 4.1 to 3.2 ($P < 0.05$) before increasing. After stopping the infusion, the resistances increased to or above control levels. Figure 3 shows the segmental resistance components of Figure 2. Resistance decreased significantly in muscle and skin small vessel segments at the lower doses of infusion, becoming significant at 0.5 µg/min. At the higher doses, resistance increased to control levels in muscle small vessels and near control levels in skin small vessels. When PGA_1 infusion was stopped, both resistances increased. On the average, skin arterial and skin venous resistances both fell, although neither of these changed significantly. Muscle arterial resistance remained unchanged at the lower doses of infusion, and rose as the infusion rate was increased ($P < 0.05$ at 10 µg/min); muscle venous resistance remained unchanged throughout infusion.

Figure 1. Average responses of forelimb blood flows, pressures, and weight to progressively increasing rates of intrabrachial infusion of prostaglandin A_1 at natural arterial inflow.

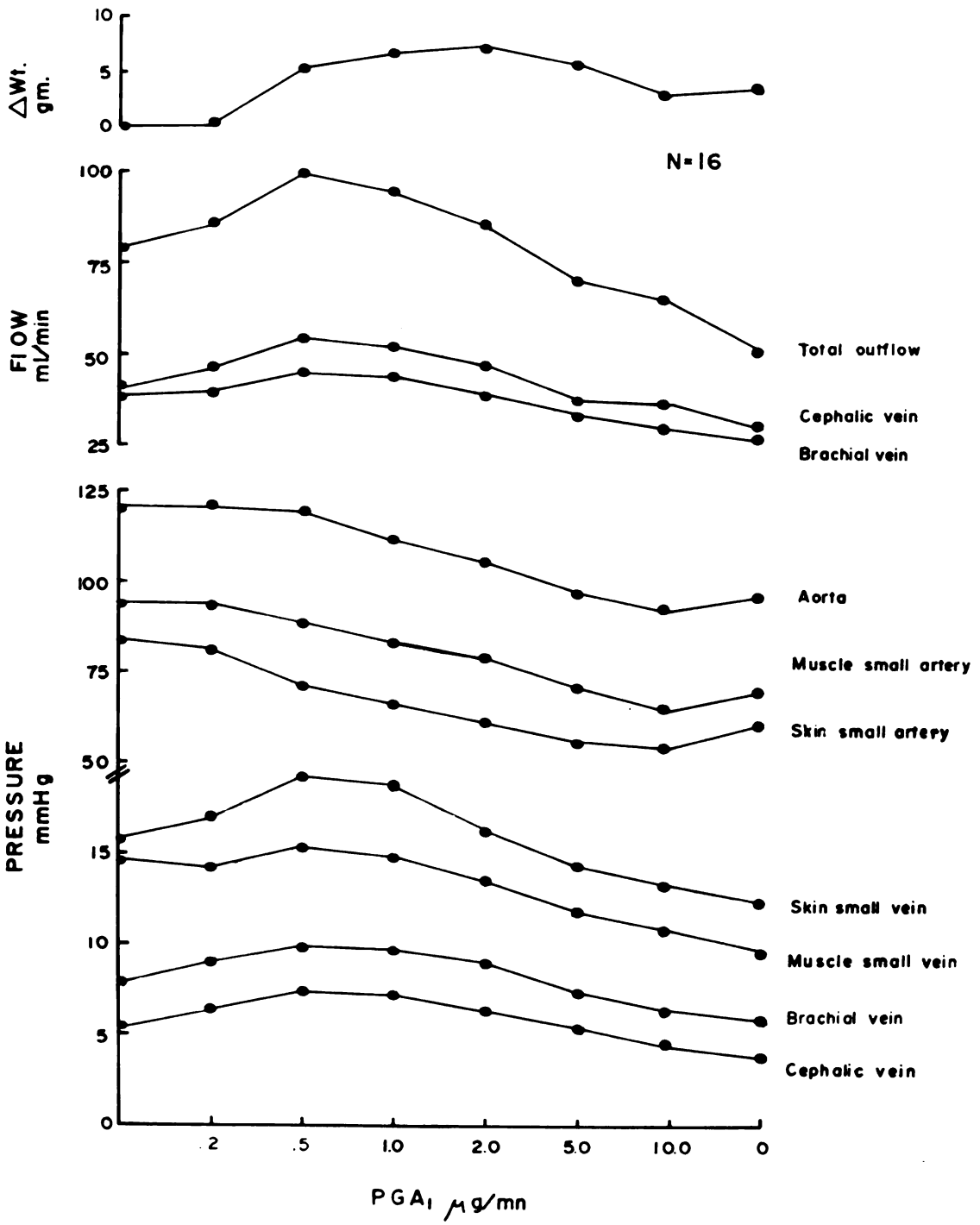

ΔWt. gm.
10
5
0
N=16
FLOW ml/min
100
75
50
25
Total outflow
Cephalic vein
Brachial vein
PRESSURE mmHg
125
100
75
50
15
10
5
0
Aorta
Muscle small artery
Skin small artery
Skin small vein
Muscle small vein
Brachial vein
Cephalic vein
.2
.5
1.0
2.0
5.0
10.0
0
PGA1 μg/mn

Figure 1

Figure 2. Total forelimb, total muscle and total skin resistance responses to progressively increasing rates of intrabrachial infusion of PGA_1. Data from experiments illustrated in Figure 1.

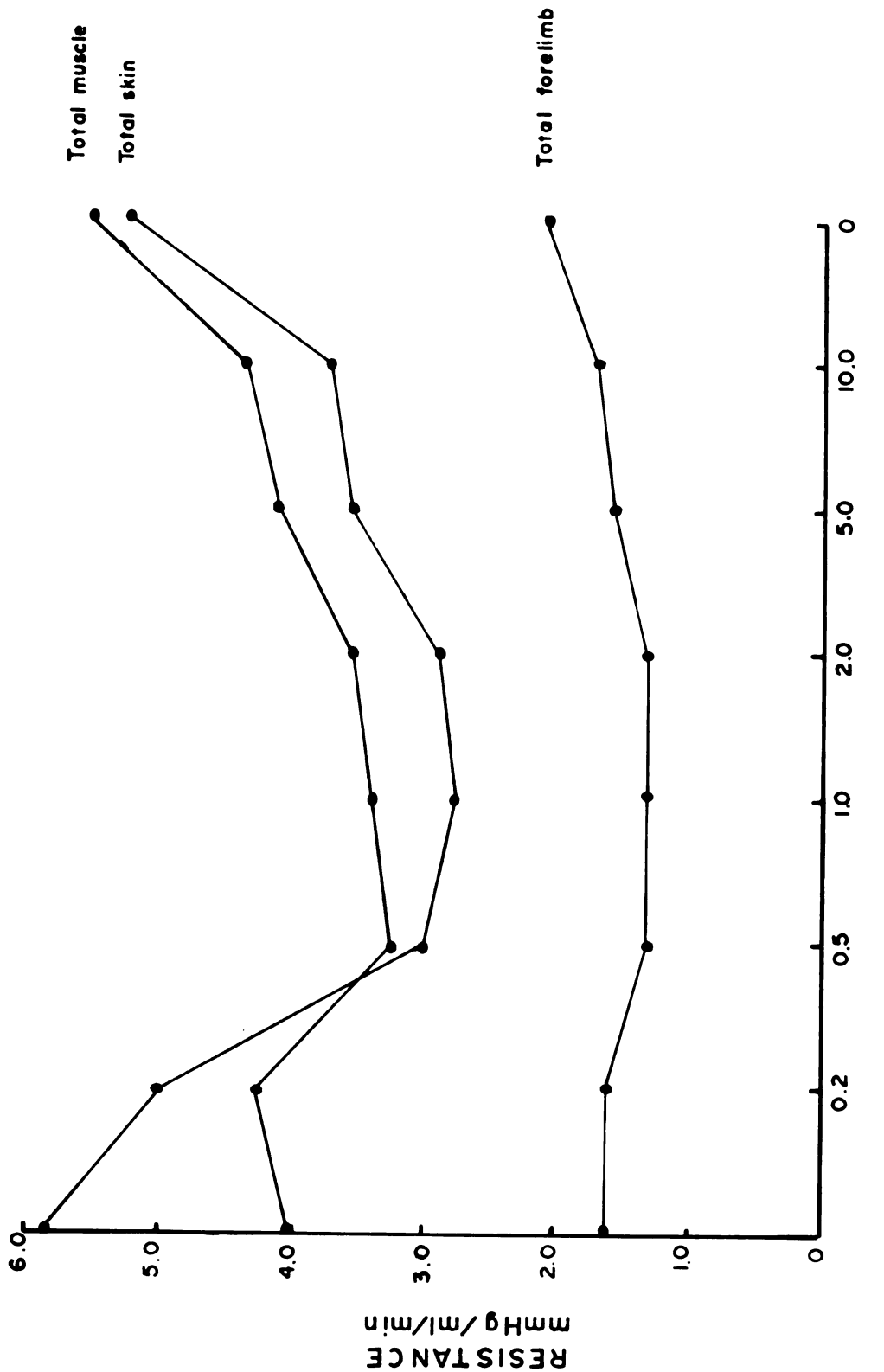

Total muscle
Total skin
Total forelimb
RESISTANCE
mmHg/ml/min
6.0
5.0
4.0
3.0
2.0
1.0
0
0.2
0.5
1.0
2.0
5.0
10.0
0
PGA, μg/mn

Figure 2

Figure 3. Segmental resistance responses to progressively increasing rates of intrabrachial infusion of PGA_1. Data taken from the experiments illustrated in Figure 1.

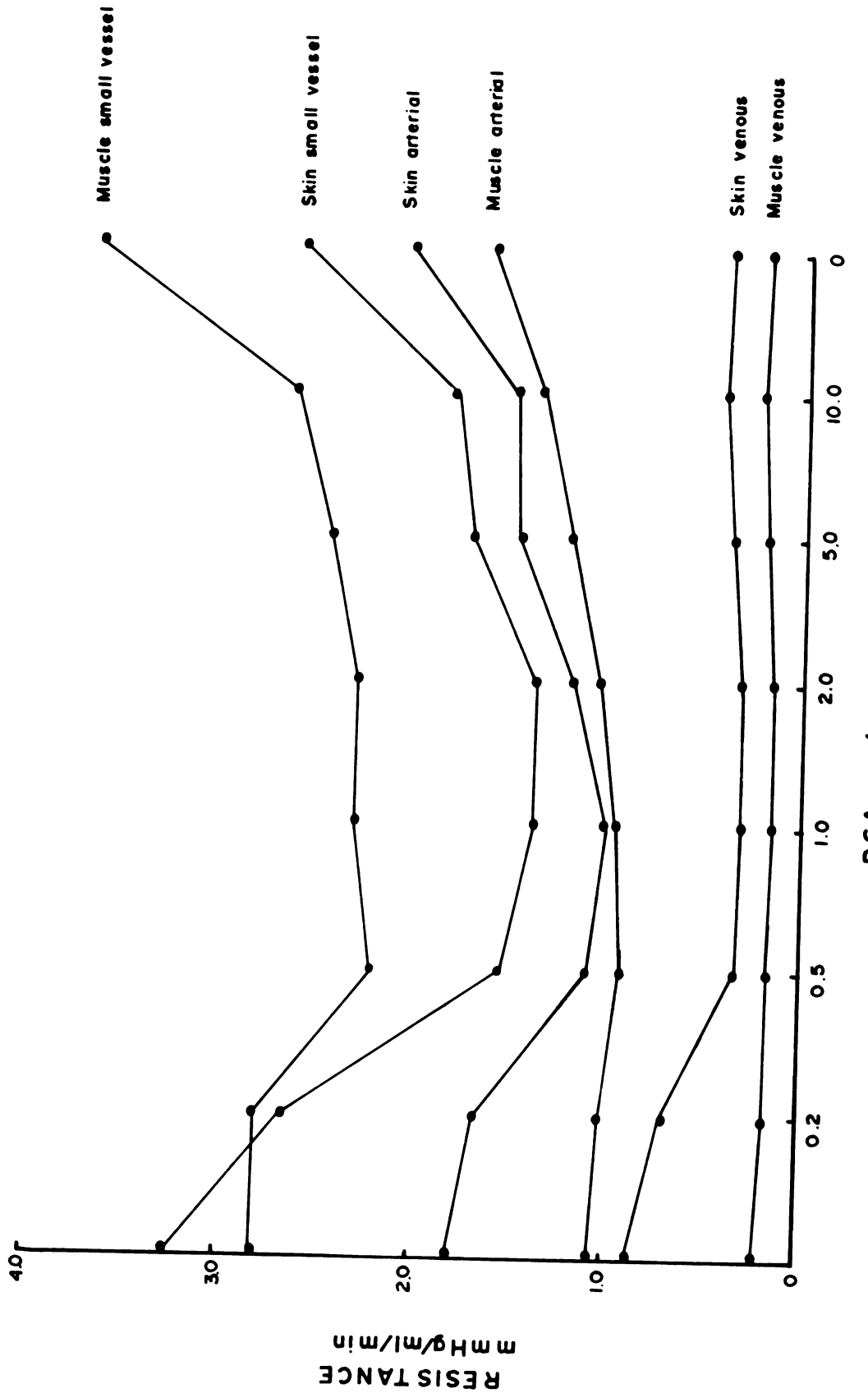

Muscle small vessel
Skin small vessel
Skin arterial
Muscle arterial
Skin venous
Muscle venous
RESISTANCE
mmHg/ml/min
4.0
3.0
2.0
1.0
0
0.2
0.5
1.0
2.0
5.0
10.0
0
PGA, μg/mn

Figure 3

II. Intra-arterial Infusion-Constant Brachial Artery Flow

Figure 4 illustrates the pressure, flow, and weight changes in the forelimbs perfused at constant arterial inflow and receiving the same dose of PGA_1 as the limbs perfused at natural flow. During the control period, the limbs gained an average of 0.9 gram, apparently due to the dependent position of the limb relative to the right atrium. At 0.2 and 0.5 µg/min rates the steady state weight gain was 3.8 and 5.6 grams, respectively ($P < 0.05$). Weight then stabilized at a level significantly above control as the rate was further increased. The significant changes in the pressure parameters of these limbs occurred in 1) the decreasing aortic pressure, and 2) the proportionate decrease and then increase in the brachial artery, muscle small artery, and skin small artery pressures. The increase in pressure of large and small arteries occurring from 1.0 to 10 µg/min coincides with the decrease in aortic pressure. All pressures rose during the post infusion period. As skin and muscle blood flows remained unchanged in this series, the decreases in pressure reflect decreases in resistances. Calculated resistances show decreases in total skin and muscle resistances which are due to decreases in the small vessel segment of both vascular beds. Neither muscle or skin arterial resistances changed significantly, although skin arterial resistances decreased on the average ($P > 0.05$).

Figure 4. Average responses of forelimb blood flows, pressures and weight to progressively increasing rates of intrabrachial infusion of prostaglandin A_1 at constant arterial inflow.

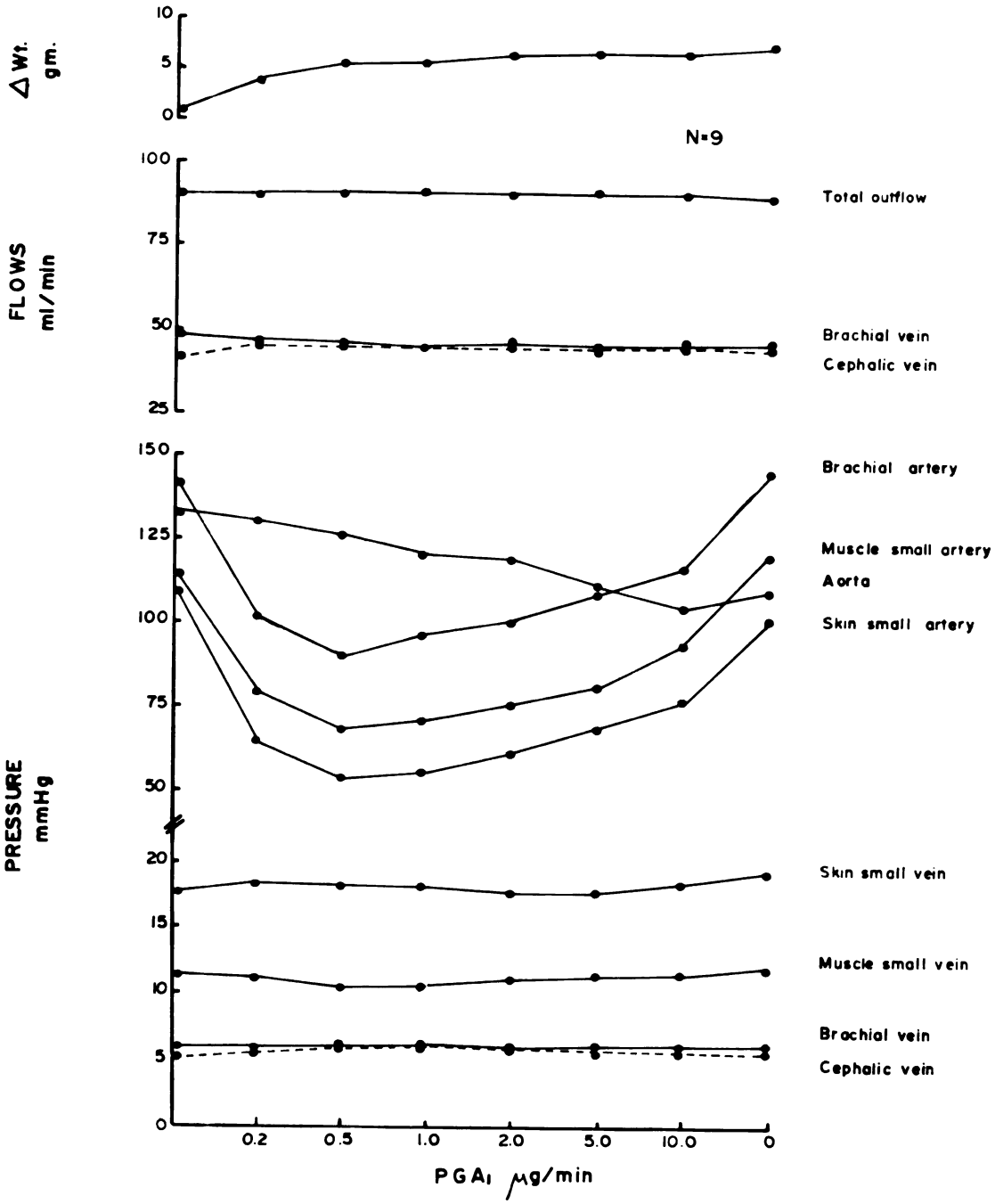

Δ Wt. gm.
10
5
0
N=9
FLOWS ml/min
100
75
50
25
Total outflow
Brachial vein
Cephalic vein
PRESSURE mmHg
150
125
100
75
50
20
15
10
5
0
Brachial artery
Muscle small artery
Aorta
Skin small artery
Skin small vein
Muscle small vein
Brachial vein
Cephalic vein
0.2
0.5
1.0
2.0
5.0
10.0
0
PGA1 μg/min

Figure 4

Because of the extreme potency demonstrated in the previous two studies, another series of constant flow perfused limbs was performed while exploring a lower dose range. This series demonstrates purely local effects of PGA_1 and is illustrated in Figure 5. Forelimb weight did not change significantly during the entire infusion of PGA_1. There was no shift of blood flow between the muscle and skin vascular beds, as indicated by the brachial and cephalic vein outflows. Brachial artery pressure decreased progressively during the entire infusion, indicating a corresponding decrease in total forelimb resistance. The proportionate decreases in the muscle and skin small artery pressures indicate similar changes in their respective resistances. Calculated resistances show that the only significant changes in the segmental resistances occurred in the small vessel segment. All venous pressures remained constant throughout the entire infusion period, indicating a constant resistance to blood flow through this segment.

III. Intravenous Infusion-Natural Brachial Artery Flow

Limb weight, pressure, and flow changes during intravenous infusion of PGA_1 are shown in Figure 6. Forelimb weight gained 3 grams during the first minute of infusion ($P < 0.02$) and then fell progressively to below control levels at minute 10 ($P > 0.05$). At twenty minutes post-infusion,

Figure 5. Average responses of forelimb blood flows, pressures and weight to progressively increasing rates of a low dose of intrabrachial infusion of prostaglandin A_1 at constant arterial inflow.

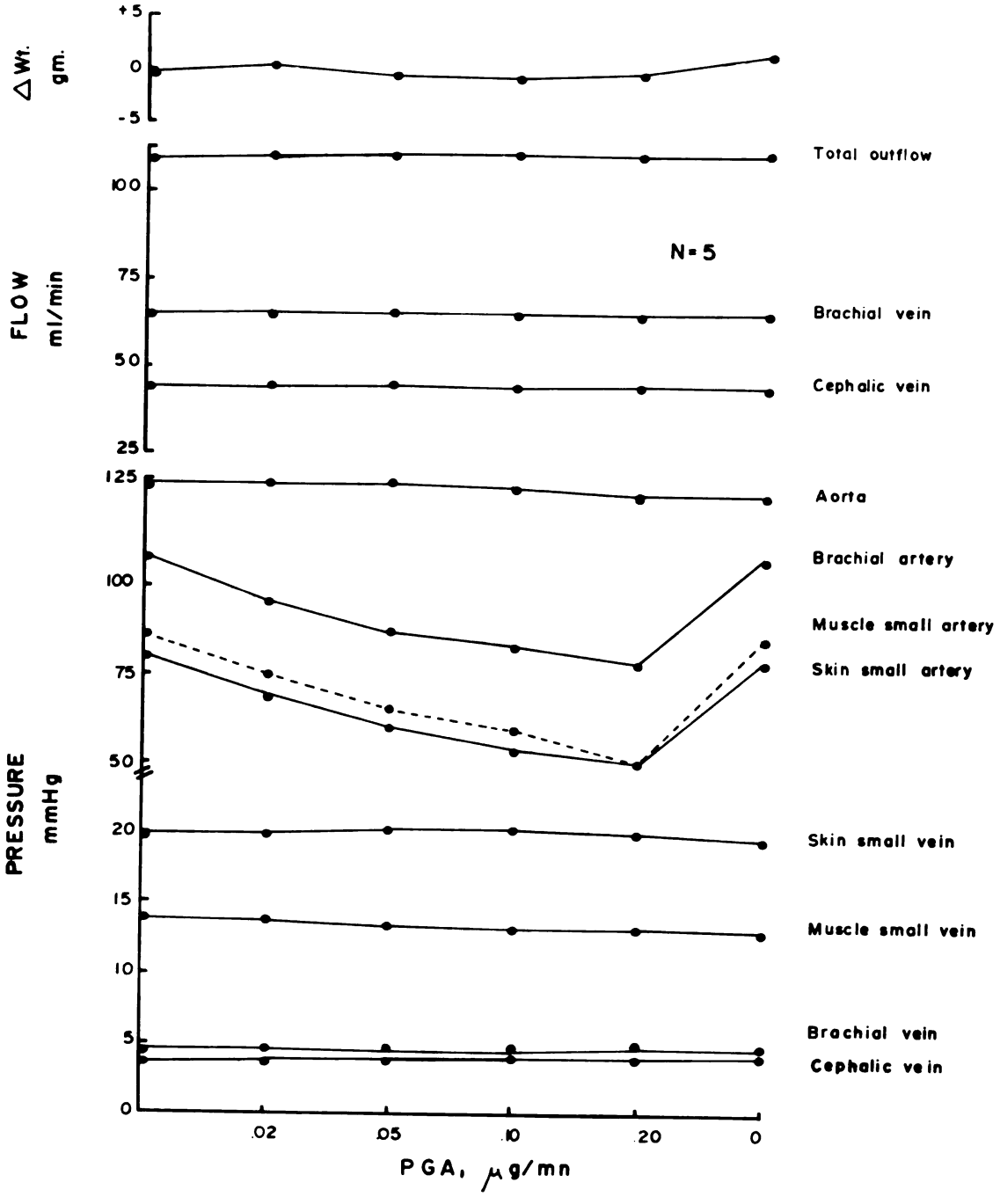

ΔWt. gm.
+5
0
-5
FLOW ml/min
100
75
50
25
N=5
Total outflow
Brachial vein
Cephalic vein
PRESSURE mmHg
125
100
75
50
20
15
10
5
0
Aorta
Brachial artery
Muscle small artery
Skin small artery
Skin small vein
Muscle small vein
Brachial vein
Cephalic vein
.02
.05
.10
.20
0
PGA, μg/mn

Figure 5

Figure 6. Average responses of forelimb blood flows, pressures and weight to intravenous infusion (6 μg/min) of prostaglandin A_1 at natural forelimb arterial inflow.

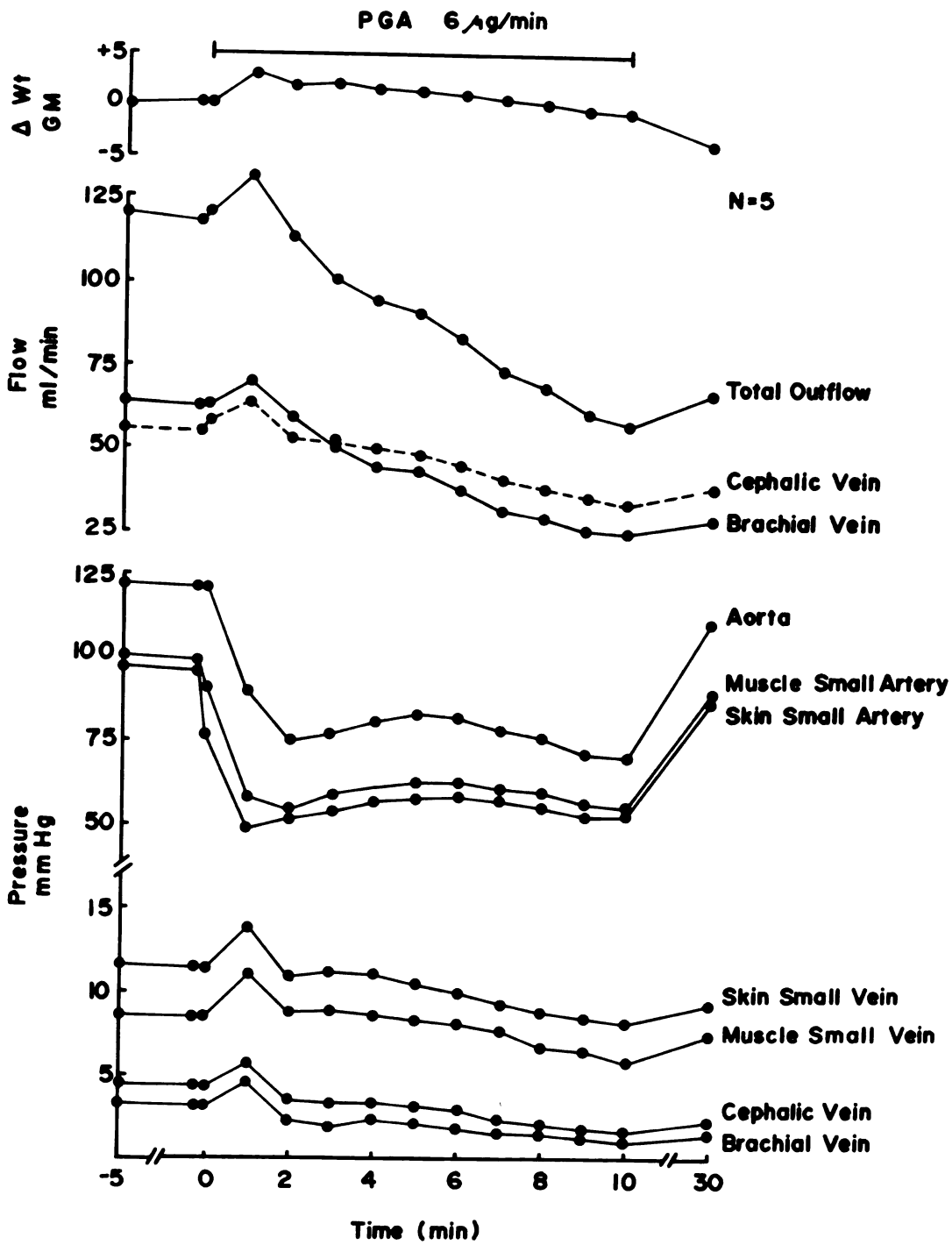

PGA 6 µg/min
+5
0
-5
Δ Wt GM
N=5
125
100
75
50
25
Flow ml/min
Total Outflow
Cephalic Vein
Brachial Vein
125
100
75
50
Pressure mm Hg
Aorta
Muscle Small Artery
Skin Small Artery
15
10
5
Skin Small Vein
Muscle Small Vein
Cephalic Vein
Brachial Vein
-5
0
2
4
6
8
10
30
Time (min)

Figure 6

limb weight had continued to fall and was 4 grams below the control value ($P < 0.05$). On the average, total outflow increased during the first minute ($P > 0.05$) due to increases in both the cephalic and brachial vein outflows; both flows decreased during the rest of the infusion period to levels well below control. Although outflows remained below control levels at 20 min. post-infusion ($P < 0.005$), they had begun to return to control values. All arterial pressures were well below control during the entire infusion period of PGA_1. Skin and muscle small vein pressures transiently rose ($P < 0.05$) and then decreased to below control values by min. 10 ($P < 0.025$). On the average, large vein pressures rose at min. 1 ($P > 0.05$) and both skin ($P < 0.01$) and muscle ($P < 0.005$) large vein pressures were reduced to levels below control by minute 10. Total resistances of these limbs are illustrated in Figure 7. Total forelimb resistance fell initially ($P < 0.005$), due to decreases in skin ($P < 0.05$) and muscle ($P < 0.025$) total resistances. At min. 2, all resistances began to steadily increase toward control levels, and total muscle resistance exceeded control levels by minute 10 ($P < 0.05$). These increases correspond with the period of decreased flow illustrated in Figure 6. The segmental resistances, shown in Figure 8, indicate that the greatest initial fall in resistance is located in the small vessel segments of both muscle ($P < 0.005$) and skin ($P < 0.025$). Following infusion, both small vessel resistances rose to values well above control.

Figure 7. Total forelimb, total muscle and total skin resistance responses to intravenous infusion (6 µg/min) of prostaglandin A_1. Data from experiments illustrated in Figure 6.

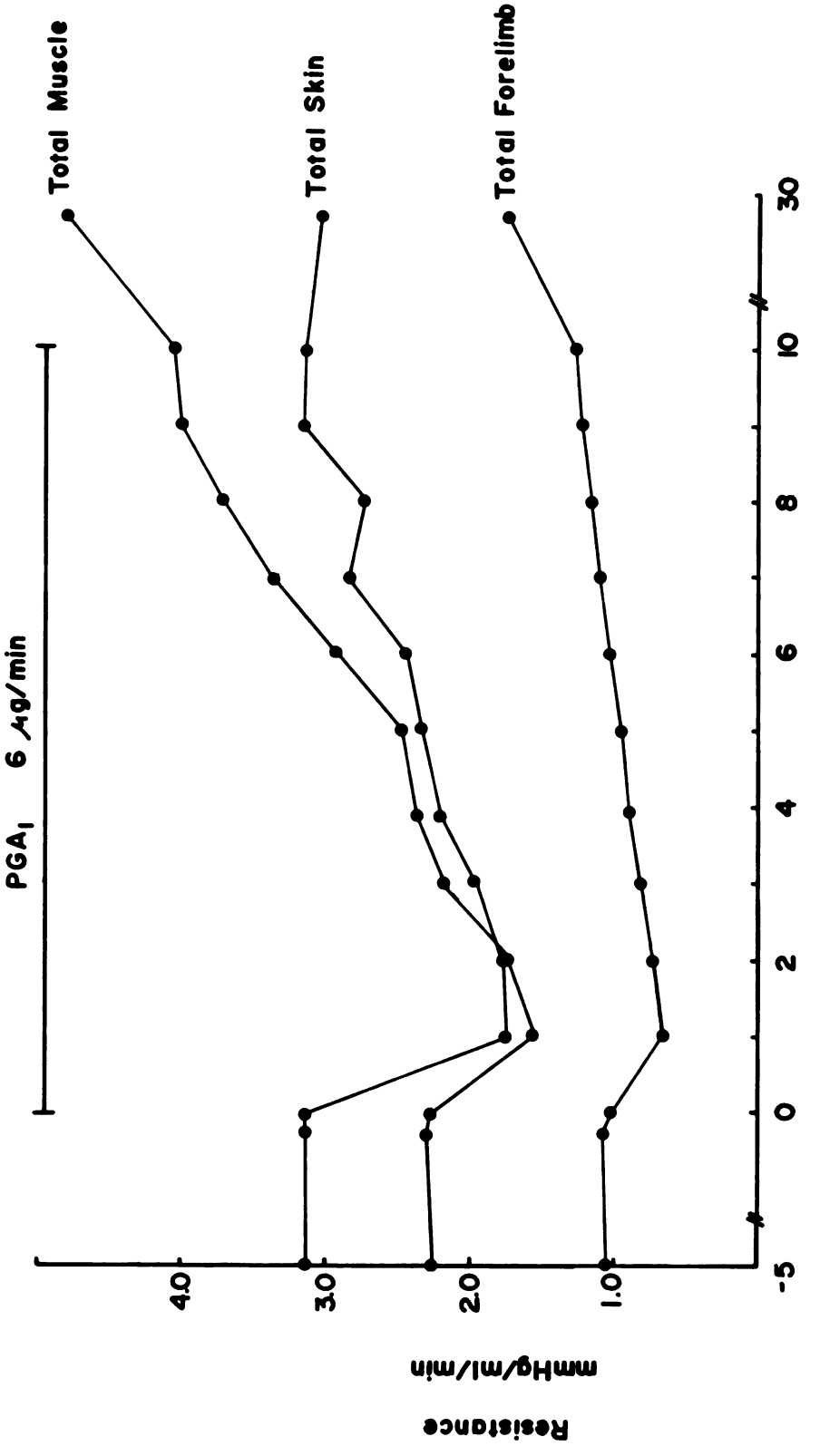

Total Muscle
Total Skin
Total Forelimb
PGA1 6 µg/min
Resistance
mmHg/ml/min
4.0
3.0
2.0
1.0
-5
0
2
4
6
8
10
30
Time (min)

Figure 7

Figure 8. Segmental resistance responses to intravenous infusion (6 μg/min) of prostaglandin A_1. Data from experiments illustrated in Figure 6.

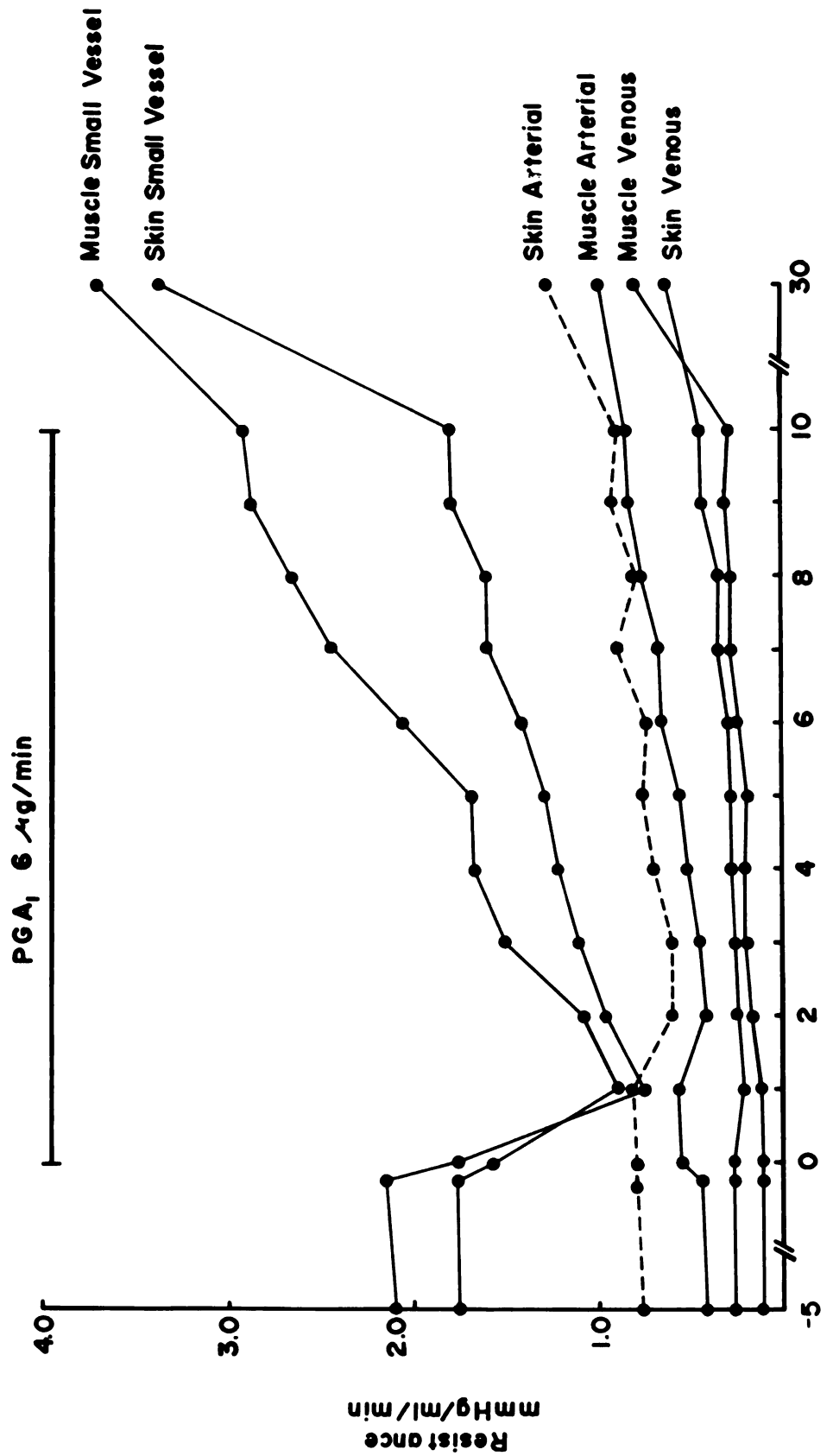

Muscle Small Vessel
Skin Small Vessel
Skin Arterial
Muscle Arterial
Muscle Venous
Skin Venous
PGA1 6 µg/min
Resistance
mmHg/ml/min
4.0
3.0
2.0
1.0
-5
0
2
4
6
8
10
30
Time (min)

Figure 8

On the average, skin arterial resistance was decreased by minute 2 ($P < 0.05$) and then gradually increased to levels above control. Muscle arterial resistance gradually rose and at minute 10 was significantly above control levels ($P < 0.05$). Both skin ($P > 0.05$) and muscle ($P < 0.05$) venous resistances demonstrated a gradual, steady rise during PGA_1 infusion. Both arterial and venous resistances rose following infusion.

CHAPTER V

DISCUSSION

Flow Effects

Locally increasing plasma PGA_1 concentration increases flow in muscle and skin vascular beds of the dog forelimb. In the natural flow preparations, PGA_1 caused an initial increase in blood flow in both skin and muscle, which began to wane concommitantly with the decrease in aortic pressure. This suggests that the local effect of PGA_1 is to dilate the two vascular beds and thereby increase blood flow, and the following decrease in blood flow is most likely due to the decreased systemic pressure initiating the baroreceptor reflex and increasing peripheral resistance. Part of the decrease in flow is also due to the decreased pressure gradient across the limb caused by the decreased aortic pressure. In this regard, when PGA_1 infusion was discontinued, aortic pressure rose, but limb outflow continued to fall, indicating that some degree of the dilatory action of PGA_1 had been occurring at the higher dose levels, compromising the reflex vasoconstriction.

The large increases in the brachial and cephalic vein outflows suggest similar effects on resistance in the

parallel coupled skin and muscle vascular beds. This is supported by observations at constant flow where disproportionate changes in skin and muscle resistances would have been reflected by opposite changes in cephalic and brachial venous outflows. Both doses at constant arterial inflow (0.2-10.0 µg/min and 0.02-0.20 µg/min) reduced brachial artery pressure but did not change flow in the two veins. This vasodilator action of PGA_1 is similar to that previously reported of PGE_1 (Daugherty, 1971) and acetylcholine and bradykinin (Daugherty et al., 1968) which have been shown to produce proportionate decreases in skin and muscle resistances. In addition, Daugherty (1971) reports that when infused intravenously (1-20 µg/min) in the same preparation, PGE_1 increases both skin and muscle blood flow. In the present study, intravenous PGA_1 infusions (6 µg/min) increased both skin and muscle blood flows very transiently, and then flows began to decrease to values well below control. The difference between these two observations may result from the dose level administered, or the time period, or the relative potence of the two prostaglandins. The systemic pressure decreased further and more quickly during the PGA_1 infusion, thereby inhibiting any longer lasting increase in flow such as that seen with PGE_1. It appears that the primary mechanism causing the decrease in flows was the decreased driving pressure gradient, as the flows began to decrease while the vascular resistances were still below control.

Resistance

In the naturally perfused limbs, local infusion of low doses of PGA_1 increased blood flows concommitantly with decreasing arterial pressure, suggesting an active increase in vessel calibre and decrease in resistance. These findings were confirmed in the constant flow preparations, where, in the absence of flow shifts, passive changes in vessel calibre do not mask active changes. In these limbs, low dose PGA_1 infusions (0.02-0.20 µg/min) proportionately decreased the arterial pressures (perfusion and small artery) of the limb without altering any of the other parameters. This represents an active decrease in total forelimb resistance due to proportionate decreases in skin and muscle small vessel resistances. Thus the major site of the dilatory action of PGA_1 is at the small vessel level in both of the parallel and series coupled vascular beds of the forelimb. As the arterioles are the major site of the resistance in the small vessel segment, the probable site of activity is at the arteriolar level. In addition, these studies indicate some degree of activity of PGA_1 upon the arterial segment. This was shown most clearly in the constant flow low dose series (Figure 5) in which the mean transmural pressure (distending pressure) across the arterial segment decreased continually during the infusion period. This would tend to passively increase resistance in this segment, when in fact, no significant arterial resistance change was observed.

Thus, a dilatory action of PGA_1 upon the arteries prevented the expected passive decrease in vessel calibre.

At the higher dose rates (1.0-10.0 μg/min) in both constant and natural flow, arterial resistances began to rise again, concommitantly with the significant decrease in arterial pressure. During natural inflow, this response coincides with the decreases in flows seen during the same time period, and is apparently the combined result of a barostatic reflex and a passive vasoconstriction due to the decreasing transmural pressure.

Several authors have reported an effect of the prostaglandins upon the venous segment of the forelimb or hindlimb. Daugherty (1971) reports that at constant arterial inflow, PGE_1 produced a tendency for a decrease in muscle small vein pressures, indicating a possible active relaxation, but having no effect upon the skin small vein pressures. The decrease, however, was small in muscle, occurring in seven out of ten experiments, and in six out of eleven in skin. Greenburg and Sparks (1969) report that in addition to their action upon resistance vessels, both PGE_1 and PGA_1 cause active relaxation of venous smooth muscle, in both isolated muscle venous strips and in the isolated perfused hindlimb. Although data was shown for PGE_1, none was illustrated for the effect of PGA_1 upon the venous segment of the hindlimb. In their study, both PGE_1 and PGA_1 at natural arterial inflow increased the vascular capacity of the

perfused hindlimb, but this may have been due to the passive distension of the venous segment by the increased flow, rather than by actual relaxation of the smooth muscle of the capacitance vessels. In contrast to the above, none of the present experiments performed at either dose of PGA_1 during constant flow perfusion demonstrated any effect upon the venous segment of the vasculature. All the small and large vein pressures remained constant during the entire period of infusion. The failure to observe this venous effect may theoretically be due to 1) subthreshold doses or 2) maximally dilated veins prior to drug administration. However, initial venous resistances in this study were comparable to or greater than those reported in the study by Daugherty (1971) in which he reported an active decrease in venous resistance. In addition, the dose level administered was slightly greater. Thus, it appears that the veins show little responsiveness to infusions of PGA_1, at least at these dose levels.

Strong and Bohr (1967) found a biphasic response of skeletal muscle artery strips to prostaglandins, relaxing upon exposure to low concentrations, and contracting in response to high concentrations. PGA_1 was the most potent in producing both relaxation and contraction. The current study did not demonstrate this response, perhaps because of the differences in the dose levels administered, or differences in experimental procedure, that is, in vitro versus in vivo preparations.

Thus, a pronounced dilatory effect upon the resistance vessels was observed, although the data fail to provide evidence for an effect of PGA_1 upon the smooth muscle of capacitance vessels.

Weight and Transcapillary Fluid Fluxes

Weight increases seen in the lower rates of infusion at natural flow may theoretically be due to increased vascular volume, interstitial fluid volume, intracellular fluid volume or some combination of the three. In this study, the initial weight gain was associated with increased flows, increased venous pressures, and decreased segmental resistances. The decreased resistances suggest that much, if not all of the weight gain may be attributed to increased vessel calibre and hence increased vascular volume. However, it is possible that a small increase in interstitial fluid volume occurred, due to filtration caused by an increase in the transmural hydrostatic pressure gradient in the capillaries. Indeed, the small vein pressures, which represents a minimum for capillary pressure, are increased during this period. A rise in the capillary pressure would occur if the decreased arterial pressure and trend toward a decrease in venous (post-capillary) resistances were overcome by the decrease in precapillary resistance. Thus, although it is clear that the increased vascular volume could have contributed the majority of the weight gain during the period when the flows were increased,

it is possible that some degree of pressure dependent filtration may have occurred. Indeed, at natural inflow, upon cessation of infusion, vascular resistances in the forelimb were either at or above control levels (Figures 2 and 3), although the limb weight was significantly above control levels. The constant or increased vascular resistances suggest that the mean vessel calibres were either constant or decreased, and thus that an increased intravascular volume could not have accounted for the maintenance of the increased weight following infusion.

These data provide no direct evidence that prostaglandin A_1 infusions change the microvascular permeability to protein. Other vasodilators such as acetylcholine and histamine have been shown to cause edema and increase lymph protein concentrations when administered locally (Haddy et al., 1972; Grega et al., 1972), via microvascular pressure dependent mechanisms. These workers showed that, in addition, histamine apparently increases protein permeability by a pressure independent mechanism. In the current study, the natural flow data show a possible slight pressure dependent increase in filtration, although effects upon permeability cannot be directly concluded from this. At constant inflow, unlike histamine, low dose PGA_1 infusions did not change limb weight at all, indicating no probable pressure independent effect of PGA_1 upon net fluid filtration. It is theoretically possible that the lymph vessels may have carried off some or all

of any fluid filtered, although this seems unlikely considering the complete lack of weight gain in the low dose infusions. The picture is complicated somewhat by the 5.4 gram weight increase in the high dose infusions. However, as seen in Figure 4, these limbs were not completely isogravimetric during the control period. Perhaps this explains the weight gain and the disparity between the two groups. Thus, although this experiment provides no evidence for an effect of PGA_1 upon permeability to protein, if an increase did occur, it was not apparently sufficient to cause an increase in interstitial volume during constant arterial inflow at the lower local dose.

When PGA_1 was infused intravenously, the limb weight increased during the first minute and then gradually fell to below control values. The initial weight gain occurred simultaneously with the increased flows and large vein pressures, indicating that the primary cause of the weight gain is increased intravascular volume. From minutes 2-20, total forelimb resistances and resistances in the capicitance vessels was increasing. These responses suggest that forelimb mean vessel calibre and consequently, intravascular blood volume was decreasing and could explain the loss of weight which occurred during this period.

Other investigators have reported that prostaglandins have no effect upon fluid filtration. Daugherty (1971) reported no evidence for alterations in transcapillary fluid

fluxes with PGE_1 in a similar preparation. He reported a possible proportional dilation of both arteries and veins, resulting in no significant change in precapillary and postcapillary resistance ratios. Thus it is possible that the capillary hydrostatic pressure would not increase with PGE_1. However, PGA_1 may be unlike PGE_1 as no evidence was demonstrated for dilation of the postcapillary vessels. Greenburg and Sparks (1969) reported a large increase in vascular capacity but no net filtration associated with close arterial infusions of either PGE_1 or PGA_1 in the isolated hindlimb.

In summary, locally increasing plasma PGA_1 concentrations causes active vasodilation in skin and skeletal muscle beds of the dog forelimb. The vasodilation is dose related over the range 0.02 µg/min-2.0 µg/min, and appears to affect both vascular beds about equally. The primary site of action is apparently at the small vessel (arteriolar) segment, with an additional affect upon the large arteries. Intravenous infusions caused a very small transientory increase in blood flow followed by a gradual decrease in levels well below control concommitant with the decrease in systemic blood pressure. The data provide no evidence for a significant pressure-independent effect of prostaglandin A_1 upon transcapillary fluid fluxes or permeability. This assumption necessitates further experiments such as analysis of lymph protein concentrations during PGA_1 infusion to fully clarify an effect upon protein permeability.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Locally increasing plasma PGA_1 concentrations in the naturally perfused dog forelimb initially increased total limb blood flow 25% due to increases in both skin and muscle blood flows. When the PGA_1 concentrations reached levels sufficient to cause a decrease in systemic blood pressure, the blood flows in both beds began to fall. The decrease in blood flows is apparently due to the combined effects of the decreased driving pressure gradient and the barostatic reflex although, at least initially, the decrease is due to the decreased pressure gradient across the limb. Intravenous infusions of PGA_1 caused a slight transient rise in flow followed by prominent decreases in both skin and muscle. Thus, PGA_1 infusions increased flows at lower doses (local effect) and decreased both flows concommitantly with the decreasing systemic pressure.

PGA_1 infusions actively decreased resistance in the parallel coupled skin and skeletal muscle vascular beds of the forelimb. The primary site of activity is at the small vessel (arteriolar) level, although the large arteries are also apparently affected to a lesser degree. The vasodilation

is dose related and affects both beds about equally. Thus the local effects of PGA_1 infusion are to decrease resistance and increase blood flows in skin and skeletal muscle, whereas the remote effects tend to decrease systemic blood pressure and thereby decrease flows and increase resistances in the forelimb. No evidence was seen for responsiveness of the venous segment to PGA_1 infusions at the doses administered in this preparation.

PGA_1 may cause a pressure dependent filtration during natural flow, at periods of increased flows. During constant flow it appears that no changes in filtration or permeability to proteins occurred at the dose levels administered. PGA_1 is thus unlike other drugs which have been shown to have an effect upon capillary permeability, such as histamine, and have had dramatic effects upon filtration in this preparation at constant flow. To be certain, more work such as lymph protein analysis needs to be carried out during PGA_1 infusions.

REFERENCES CITED

Abboud, F. M. Vascular responses to norepinephrine, angiotensin, vasopressin and serotonin. Federation Proc., 27:1391, 1968.

Alpert, J. S. and R. B. Hickler. Cardiovascular and renal effects of renomedullary prostaglandins. Kidney Hormones, 525 (Ed. J. W. Fisher, 1971).

Barnes, H. B., G. C. Kaiser and J. B. Lee. Effect of prostaglandin A_1 on several vascular beds in man. Clin. Res., 19:110, 1971.

Beal, P. F., J. C. Babcock and F. H. Lincoln. In Nobel Symposium 2, Prostaglandins, 219 (Almquist and Wiksell, Stockholm, 1967).

Bergstrom, S., L. Krabisch and J. Sjovall. Smooth muscle stimulating factors in ram semen. Acta. Chem. Scand. 14:1706, 1960.

Bergstrom, S., F. Dressler, R. Ryhage, B. Samuelsson and J. Sjovall. The isolation of two further prostaglandins from sheep prostate glands. Arkiv. Kemi., 19:560, 1962.

Bergstrom, S., F. Dressler, L. Krabisch, R. Ryhage and J. Sjovall. The isolation and structure of a smooth muscle stimulating factor in normal sheep and pig lungs. Arkiv. Kemi., 20:63, 1962.

Bergstrom, S., L. A. Carlson and L. G. Ekelund. Cardiovascular and metabolic response to infusion of prostaglandin E_1 and to simultaneous infusions of noradrenaline and prostaglandin E_1 in man. Acta. Physiol. Scand., 64:332, 1965.

Bergstrom, S., L. A. Carlson and J. R. Weeks. The prostaglandins: A family of biologically active lipids. Pharmac. Reviews, 20:1, 1968.

Bloor, C. M. and B. E. Sobel. Enhanced coronary blood flow following prostaglandin infusion in the conscious dog. Circulation, Supplement III, 41 and 42, III-123, 1970.

Carlson, L. and L. Oro. Effect of prostaglandin E_1 on blood pressure and heart rate in the dog. Acta Physiol. Scand., 67:89, 1966.

Carlson, L. A., L. Ekelund and L. Oro. Clinical, metabolic and cardiovascular effects of different prostaglandins in man. Acta. Physiol. Scand., 188:553, 1970.

Carr, A. A. Hemodynamic and renal effects of a prostaglandin, PGA_1, in subjects with essential hypertension. Am. Journ. Med. Sci., 259:21, 1970.

Christlieb, A. B., S. Dobrzinsky, C. J. Joyons and B. B. Hickler. Short term PGA_1 infusions in patients with essential hypertension. Clin. Res. 17:234, 1969.

Coceani, F. and L. S. Wolfe. Prostaglandins in brain and the release of prostaglandin-like compounds from the cat cerebellar cortex. Can. J. Physiol. Pharmac., 43:445, 1965.

Coceani, F., C. Pace-Asciak, F. Volta and L. S. Wolfe. Effect of nerve stimulation on prostaglandin formation and release from the rat stomach. Am. J. Physiol., 213: 1056, 1967.

Daniels, E. G., J. W. Hinman, B. A. Johnson, F. P. Kupiecki, J. W. Nelson and J. E. Pike. The isolation of an additional prostaglandin derivative from the enzyme cyclization of homo-y-liolenic acid. Biochemical and Biophysical Research Communications, 21:413, 1965.

Daniels, E. G., J. W. Hinman, B. E. Leach and E. E. Muirhead. Identification of prostaglandin E_2 as the principal vasodepressor lipid of rabbit renal medulla. Nature (London), 215:1298, 1967.

Daugherty, R. M., J. B. Scott and F. J. Haddy. Effects of generalized hypoxemia and hypercapnia on forelimb vascular resistance. Am. J. Physiol., 213:1111, 1967.

Daugherty, R. M., J. B. Scott, T. E. Emerson and F. J. Haddy. Comparison of i.a. and i.v. infusion of vasoactive agents on dog forelimb blood flow. Am. J. Physiol. 214:611, 1968.

Daugherty, R. M. Effects of i.v. and i.a. prostaglandin E_1 on dog forelimb skin and muscle blood flow. Am. J. Physiol., 220:392, 1971.

Emerson, T. E., Jr., G. E. Jelks and R. M. Daugherty, Jr. Effects of prostaglandin E_1 and $F_{2\alpha}$ on venous return and other parameters in the dog. Am. J. Physiol. 220: 243, 1971.

Goldblatt, M. W. A depressor substance in seminal fluid. J. Soc. Chem. Ind. (London), 52:1056, 1933.

Greenburg, R. A. and H. V. Sparks. Prostaglandins and consecutive vascular segments of the canine hindlimb. Am. J. Physiol., 216(3):567, 1969.

Grega, G. J., R. L. Kine, D. E. Dobbins and F. J. Haddy. Mechanisms of edema formation by histamine administered locally into canine forelimb. Am. J. Physiol. (submitted for publication, 1972).

Haddy, F. J., J. I. Molnar and R. W. Campbell. Effects of denervation and vasoactive agents on vascular pressures and weight of dog forelimb. Am. J. Physiol., 201:631, 1961.

Haddy, F. J., J. B. Scott and G. J. Grega. Effects of histamine upon lymph protein concentration and flow in the dog forelimb. Am. J. Physiol. (submitted for publication, 1972).

Herzog, J., H. Johnston and D. Lauler. Effects of prostaglandins E_1, E_2 and A_1 on renal hemodynamics, sodium and water excretion in the dog. Clin. Res., 16:386, 1968.

Higgins, C., S. Vatner, D. Franklin, and E. Braunwald. Augmentation of coronary blood flow and cardiac output in conscious dogs by intravenous prostaglandin A_1. Circulation, Supplement III, 41 and 42: III-123, 1970.

Higgins, C. B., S. F. Vatner, D. Franklin, T. Patrick and E. Braunwald. Effects of prostaglandin A_1 on the systemic and coronary circulations in the conscious dog. Circulation Res., 28:638, 1971.

Higgins, C. B., S. F. Vatner, D. Franklin and E. Braunwald. Effects of prostaglandin A_1(PGA_1) on left ventricular dynamics in conscious dogs. Clin. Res., 19:350, 1971.

Hinman, J. W. Prostaglandins: A report on early clinical studies. Postgraduate Medical Journal, 46:562, 1970.

Horton, E. W. and J. H. M. Main. Central nervous actions of the prostaglandins and their identification in the brain and spinal cord. In Prostaglandins, Proc. 2nd Nobel Symp. (Almquist and Wiksell, Stockholm, 1967).

Horton, E. W. and R. L. Jones. Prostaglandin A_1, A_2, and 19-hydroxy A_1; their actions on smooth muscle and their inactivation on passage through the pulmonary and hepatic portal vascular beds. Br. J. Pharmac., 37: 705, 1969.

Kadowita, P. J., C. S. Sweet and M. J. Brody. Blockade of adrenergic vasoconstrictor responses in the dog by prostaglandins E_1 and A_1. J. Pharm. Exptl. Ther., 179:563, 1971.

Kurzrok, R. and C. C. Lieb. Proc. Soc. Exptl. Biol., 28: 268, 1930.

Lee, J. B. Cardiovascular implications of the renal prostaglandins. In Prostaglandin Symposium Worcester Foundation for Experimental Biology, 131 (Interscience, New York, 1961).

Lee, J. B., G. B. Covino, F. L. Takman and E. R. Smith. Renomedullary vasodepressor substance:Medullin. Circulation Res., 17:57, 1965.

Lee, J. B., J. Z. Gougoutas, B. H. Takman, E. G. Daniels, M. F. Grostic, J. E. Pike, J. W. Hinman and E. E. Muirhead. Vasodepressor and antihypertensive prostaglandins of PGE type with emphasis on the identification of medullin as PGE_2-217. J. Clin. Invest., 45:1036, 1966.

Lee, James B. Prostaglandins. Physiologist, 13:379, 1970.

Lee, J. B., J. C. McGiff, K. Hartmut, Y. Aykent, G. Mudd and T. Fraeley. Prostaglandin A_1: Antihypertensive and renal effects. Annals Int. Med., 74:703, 1971.

McGiff, J. C., N. A. Terragno, J. C. Strand. Selective passage of prostaglandins across the lung. Nature (London), 223:742, 1969.

Murphy, G. P., V. E. Hesse, J. L. Evers, G. Hobika, J. W. Mostert, A. Szolnoky, R. Schoones, J. Abramczyk and J. T. Grace. The renal and cardiodynamic effects of prostaglandins (PGE_1, PGA_1) in renal ischemia. J. Surg. Research, 10:533, 1970.

Nakano, J. Effect of prostaglandins E_1, A_1 and $F_{2\alpha}$ on cardiovascular dynamics in dogs. Prostaglandin Symposium of the Worcester Foundation for Experimental Biology, 201 (Intersceince, New York, 1961).

Nakano, J. and J. R. McCurdy. Effects of prostaglandins E_1 (PGE_1) and A_1 (PGA_1) on the systemic venous return and pulmonary circulation. Clin. Res., 15:409, 1967.

Nakano, J. Effects of prostaglandins E_1, A_1, and $F_{2\alpha}$ on the coronary and peripheral circulations. Proc. Soc. Exptl. Biol. Med., 127:1160, 1968.

Nakano, Kiro and J. R. McCurdy. Hemodynamic effects of prostaglandins E_1, A_1, and $F_{2\alpha}$ in dogs. Proc. Soc. Exptl. Biol. Med., 128:39, 1968.

Nakano, J., M. Perry and D. Denton. Effect of prostaglandins E_1 (PGE_1), A_1 (PGA_1), and $F_{2\alpha}$ ($PGF_{2\alpha}$) on the peripheral circulation. Clin. Res., 14:110, 1968.

Nakano, J., A. V. Prancan, and J. M. Kessinger. Effect of prostaglandins E_1 and A_1 on the gastric circulation in dogs. Clin. Res., 19:399, 1971.

Nutter, D. O. and H. Crumley. Coronary myocardial responses to prostaglandins E_1 and A_1. Circulation Supplement III, vols. 41 and 42:III-124, 1970.

Page, Irvine H. Prostaglandins. Modern Medicine., March 28, 1966, 627.

Ramwell, P. W., J. E. Shaw and J. Kucharski. Prostaglandin release from the rat phrenic nerve-diaphragm preparation. Science (New York), 149:1390, 1965.

Ramwell, P. W., J. E. Shaw, W. W. Douglas and A. M. Poisner. Efflux of prostaglandin from adrenal glands stimulated with acetylcholine. Nature (London), 210:273, 1966.

Samuelsson, B. The identification of prostaglandin $F_{2\alpha}$ in bovine lung. Biochim. Biophs. Acta., 34:707, 1964.

Schoones, R., V. E. Hesse, J. Mostert, G. H. Hobika, J. Abramczyk, A. Szolnoky, G. M. Kenney and G. P. Murphy. Renal and cardiodynamic effects of prostaglandins in normal and hypertensive dogs. Surg. Forum, 21:536, 1970.

Strong, C. G. and D. F. Bohr. Effects of prostaglandins E_1, E_2, A_1 and $F_{1\alpha}$ on isolated vascular smooth muscle. Amer. J. Physiol., 213:725, 1967.

Viguera, M. G. and F. A. Sunahara. Microcirculatory effects of prostaglandins. Can. Journ. Physiol. Pharmac., 47:627, 1969.

von Euler, U. S. Zur Kenntris der pharmakologischen Wirkugen von Nativseketren und Extrakten mannlicher accessorischer Geschlectsdrusen. Arch. Exptl. Pathol. Pharmakol., 175:78, 1934.

von Euler, U. S. On the specific vasodilating and plane muscle stimulating substances from accessory glands in man and certain animals (prostaglandin and fesiglandin). J. Physiol., 88:213, 1936.

Weeks, James R. The prostaglandins: Biologically active lipids with implications in circulatory physiology. Circulation Res., Supplement 1, 24 and 25:I-123, 1969.

Weeks, J. R., N. Chandra Sikhar and D. W. DuCharme. Relative activity of prostaglandins E_1, A_1, E_2 and A_2 on lipolysis, platelet aggregation, smooth muscle and the cardiovascular system. J. Pharm. Pharmac., 21:103, 1969.

Westura, E. E., H. Kannegiesser, J. P. O'Toole, and J. B. Lee. Antihypertensive effects of prostaglandin A_1 in essential hypertension. Circulation Res. Supplement III, 41 and 42:III-123, 1970.

MICHIGAN STATE UNIVERSITY LIBRARIES
3 1293 03142 7564