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THE ROLE OF INTESTINAL WALL COMPLIANCE IN THE REGULATION OF INTESTINAL BLOOD FLOW

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CHAPTER I

INTRODUCTION

Blood flow through a vascular bed is primarily regulated through changes in the caliber of small vessels by contraction or relaxation of its smooth muscle. However, in an organ which contains much extravascular smooth muscle that exhibits wide variations in both its contractile state and rhythmical activity, the passive changes in blood vessel caliber caused by visceral smooth muscle activity may considerably influence the blood flow. Sidky and Bean (1) state that rhythmic and tonic contractions of intestinal muscle are important determinants of blood flow and blood reservoir capacity of the intestine. Furthermore, they speculate that the rhythmic activity of intestinal muscle serves as an important booster pump in the return of the blood to the heart.

The activity of intestinal smooth muscle can be affected by many humoral agents which also affect vascular smooth muscle. The responses of these two types of muscle to the same agents, however, are often opposite in direction. Many intestinal smooth muscle stimulants, such as bradykinin and acetylcholine, are vasodilators. The total effect of an agent on the intestinal vascular resistance, thus, may result from two

opposing actions. For example, an infusion of 160 μg/min acetylcholine can produce a decrease in intestinal blood flow. But at lower infusion rate (5 μg/min) when the intestinal muscle is apparently not stimulated, an increase in blood flow may be seen (2). Similarly, if the responses of the visceral and vascular smooth muscle are in the same direction, the vascular action of an agent may be over-estimated if its effect on visceral muscle is not considered. Thus, in order to assess the direct vasoactivity of an agent in the intestine, the action of the agent on the intestinal smooth muscle must also be known.

Previous studies have demonstrated local effects of many vasoactive substances on the intestinal vascular bed (3, 4). In addition to the vascular effects, their effects on the intestinal motility were also evaluated. However, the intestinal motility was measured by recording intraluminal pressure, either with an open-tip catheter (3) or a balloon (4). Of the agents tested, only methacholine chloride (3), KCl, acetylcholine and serotonin (4) at higher infusion rates, produced significant changes in intraluminal pressure. The vasodilator effects of these four agents were found to be masked by their stimulating effefts on the intestinal muscle. All other agents that did not cause changes in the intraluminal pressure could have also affected intestinal wall tension. Since the assessment of the intestinal wall tension by recording the intraluminal pressure is probably not sensitive enough to detect small changes in the intestinal wall tension, the vasoactivity of the agents tested in these studies may have been over- or under-estimated.

The reason why a particular vasoactive agent has different effects on different peripheral vascular beds is not well understood. For example, the calcium ion produces constriction in most of the peripheral

vascular beds but produces a vasodilatation in the stomach (5). Epinephrine is a potent vasoconstrictor in the kidney but it produces a vasodilation in the coronary circulation. Possibly, the sensitivity of the vascular smooth muscle may differ in various vascular beds. It is also possible that the activity of the extravascular component may play a more important role in determining vascular resistance in some organs than in others. The intestine, because of its anatomical structure, presents the opportunity for assessment of the role played by the activity of visceral muscle in the regulation of intestinal blood flow.

Intestinal smooth muscle tension is generally studied *in vitro* with isolated muscle strips. However, an occasional attempt has been made to study it *in vivo*. White *et al*. (6) in 1940 devised a method to measure compliance of the colon in men and the method was used in the investigation of neurogenic disturbances of the colon. In their method, water was infused through the anus at a certain rate and intraluminal pressure measured simultaneously. A change in the slope of the pressure-volume curve indicated a change in the colon wall tension. Although the same method was used again in 1949 by Scott and Cantrell (7) to study the nervous control of colon motility in dogs, no further systematic study on intestinal compliance has been attempted. The need for study of intestinal compliance as a means for understanding the function of intestinal smooth muscle was emphasized in a recent symposium on gastrointestinal research (8).

The purpose of the present study was two-fold. First, to enlarge our understanding of the influence of extravascular tension as it affects vascular resistance, and second, to begin a systematic study of intestinal compliance. A method has been devised which allows a

simultaneous measurement of intestinal compliance and motility, and its vascular resistance *in situ*. The method also allows the detection of small changes in intestinal wall tension.

CHAPTER II

METHODS

In anesthetized dogs, the influence of ileal wall compliance and motility on ileal vascular resistance was studied by simultaneously measuring these three parameters during several experimental procedures. The procedures were: (1) alteration of the rate of local blood flow, (2) local infusion of various naturally occuring substances, (3) systemic intravenous infusion of epinephrine, (4) hemorrhage, and (5) bilateral carotid artery occlusion.

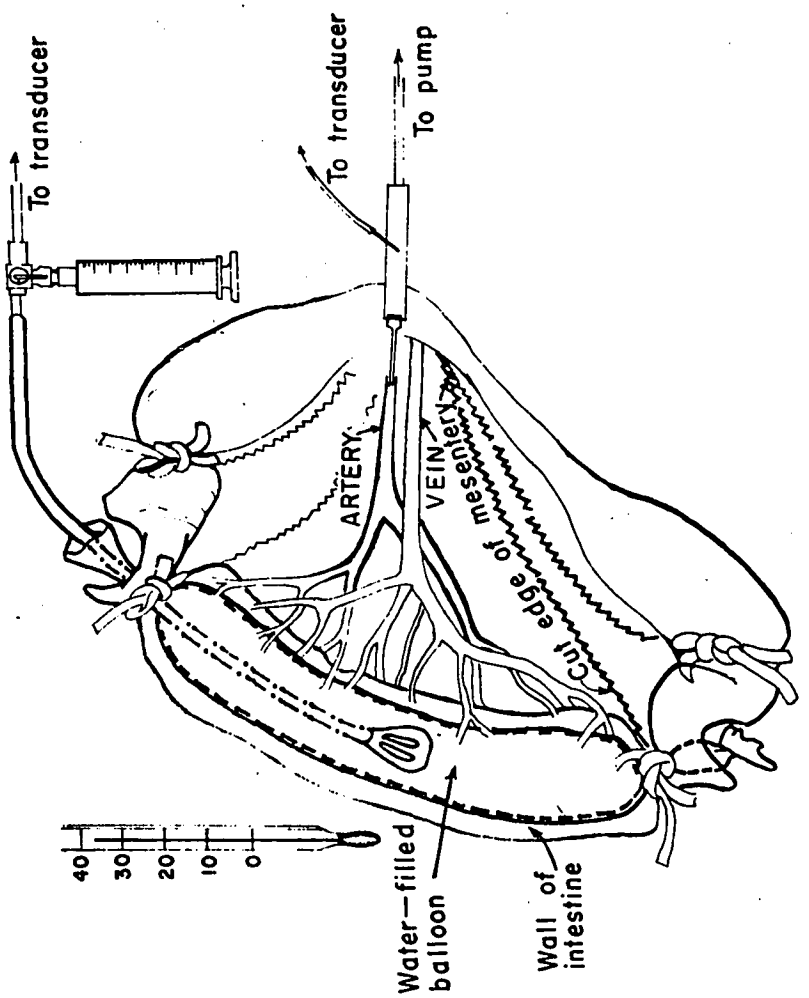
The study was performed on mongrel dogs of both sexes, weighing 12 to 18 Kg. The dogs were anesthetized with pentobarbital sodium (30 mg/kg) and anticoagulated with heparin sodium (6 mg/kg). After a midline incision, a segment of terminal ileum was exteriorized which weighed 20 to 30 gm and was 10 to 15 cm in length. The segments were located about 15 to 30 cm from ileocecal junction. The main artery of the segment was dissected free from the adjacent tissue and care was taken to minimize damage to periarterial nerves. The segment was tied securely at both ends and the mesentery cut to exclude collateral flow. A thin wall rubber balloon (Trojan-Enz^{R}, Youngs Rubber Co., N Y.), which had an unstressed volume greater than 200 ml was connected to a No. 12 Fr. gastric tube and was inserted into the ileal lumen. Each end of the balloon was tied to the end of the segment. The portion of the gastric

tube within the balloon had several holes for infusion and withdrawal of water. In the middle part of the gastric tube, a three-way stopcock was interposed for infusing the water. The other end of the tube was connected to a pressure transducer (Model P23 Gb, Statham Lab. Los Angeles, Calif.). The tube was filled with water and the air was carefully excluded from the balloon. The preparation is schematically shown in Figure 1.

The main artery was cannulated with a right angle cannula made from a 15 gauge needle that was attached to the perfusion tubing. The segment was perfused at constant flow by interposing an extracorporal circuit, which contained a Sigmamotor pump (Model TM 10), between a branch of intestinal artery and the femoral artery. Interposed in the extracorporal polyethylene perfusion tubing were two short segments of latex rubber tubing. The first segment was placed in the Sigmamotor pump and the second one just preceded the right angle cannula and was needled for the measurement of perfusion pressure. The pressure drop through this cannula was 2, 2, 5, 6, and 9 mm Hg for flow rates of 3, 5, 10, 16.5 and 23.5 ml/min respectively. Systemic arterial pressure was measured through a catheter inserted via the femoral artery into the aorta. Perfusion pressure and aortic pressure were measured with a Statham pressure transducer (P23 Gb). The pressures were recorded on a direct writing oscillograph (Model 296, Sanborn Co., Waltham, Mass.). Blood was pumped at a rate which produced a perfusion pressure equal to or 10 - 20 mm Hg below the aortic pressure. Blood flow was maintained constant throughout an experiment except in those experiments designed to study the effects of rate of blood flow.

After all operative procedures were completed, the exteriorized

Figure 1. Schematic drawing of the ileal preparation showing placement of ligatures and rubber balloon, threeway stopcock and gastric tube for the infusion and withdrawal of water and for the recording of ileal luminal pressure. The cannula, connected to the intestinal artery allowed perfusion of the ileal segment with blood from the femoral artery by a pump.



ileum was moistened with warm saline and carefully covered with a sheet of plastic film. A thermometer was fixed against the ileum and a heat lamp was used to maintain the temperature of the segment at 36°-38°C. Ileal compliance was determined by measuring the change in ileal intraluminal pressure that were produced by given changes in intraluminal volumes. An aliquot (5 or 10 ml) of warm water (37°C) was infused through the three-way stopcock into the balloon to increase, stepwise, the balloon volume to 5, 10, 15, 20, 30, and 40 ml. It was found, during the course of this study, that the change in luminal pressure caused by introducing 5 or 15 ml of water was not significantly different from that by introducing 10 or 20 ml of water. The sequence of the measurement of compliance was, therfore, changed to 10, 20, 30 and 40 ml. Intestinal intraluminal pressure and perfusion pressure were allowed to become steady before increasing volume. This procedure was repeated several times (an average of 5), until reporducible values of intraluminal pressure at each balloon volume were achieved. After reproducible results were obtained, it was assumed that the compliance of the ileum had reached a steady state. When the intraluminal pressure showed small regular variations as a result of rhythmic contractions of the ileum, the value of intraluminal pressure was taken at the valley of the wave. If the rhythmic segmental contraction of the ileum produced wide and irregular variations of the luminal pressure, the experiment was terminated and the data were not used.

Effects of Rate of Blood Flow

The effect of blood flow rate on ileal compliance, motility and vascular resistance was studied by lowering or raising the output of perfusion pump to levels which produced a perfusion pressure of about 30 or

200 mm Hg. In 6 animals, the sequence was as follows: (1) Blood flow was adjusted so that perfusion pressure equaled aortic pressure (control flow). (2) Blood flow was then reduced to 3-3.5 ml/min (low flow). (3) Perfusion was stopped (no flow). (4) Perfusion was then started at a rate equal to control, and the compliance was measured while perfusion pressure was rising (reactive dilation). (5) Control flow. (6) Flow was increased to about 30 ml/min (high flow). (7) Control flow. In 4 dogs the sequence was reversed, i.e., control, high flow, control, low flow, no flow, reactive dilation and control. Ileal compliance was measured at each step when perfusion and intraluminal pressure were steady (except during reactive dilation). Each step lasted for several minutes.

Local Infusion of Various Vasoactive Agents

This study consisted of three steps: (1) A control period. (2) Intra-arterial infusion of an isotonic solution of the agent upstream to the perfusion pump. A Harvard infusion/withdrawal pump (Harvard Apparatus Co., Inc. Dover, Mass.) was used for infusion of the agent. (3) A post-infusion control period. Ileal compliance was measured during each step when perfusion pressure was in a steady state. Eleven agents were studied. These were epinephrine (Adrenalin chloride, Parke, Davis & Co., Detroit, Michigan), acetylcholine (Acetylcholine chloride, Merck & Co., Rahway, New Jersey), bradykinin (Sandoz Pharmaceuticals, Hanover, New Jersey), serotonin (5-hydroxytryptamine creatinine sulfate, Sigma Chem. Co., St. Louis, Missouri), adenosine (Nutritional Biochem. Co., Cleveland, Ohio), Adenosine-5'-triphosphate (ATP, Sigma Chem. Co., St. Louis, Missouri), potassium, magnesium and calcium chlorides (Fisher Scientific Co., Fair Lawn, New Jersey), phenoxybenzamine hydrochloride

(Dibenzyline^{R}, Smith Kline & French Labs., Philadelphia, Pennsylvania), and propranolol hydrochloride (Inderal^{R}, Ayerst Lab. Inc., New York). The infusion rates were computed as the salts of agents, and mean blood flow of these agents are listed in Table 1.

In a study of the effects of the adrenergic receptor blocking agents, phenoxybenzamine hydrochloride (Dibenzyline^{R}, Smith Kline & French Labs., Philadelphia) and propranolol hydrochloride (Inderal^{R}, Ayerst Lab. Inc., N. Y.) on the response to epinephrine, the sequence of the experiment was as follows: (1) control, (2) i.a. infusion of epinephrine 0.2 μg/min, (3) control, (4) i.a. infusion of phenoxybenzamine 0.4 mg/min, or propranolol 20 - 40 μg/min for about 10 min. (at this time, the vascular effect of epinephrine or isoproterenol was blocked), (5) i.a. infusion of epinephrine at 0.2 μg/min + phenoxybenzamine or propranolol, (6) post-control. Ileal compliance was determined during the steady state of each period.

Hemorrhage, Bilateral Carotid Artery Occlusion and Intravenous Infusion of Epinephrine

All three procedures were performed in the same dog. The sequence of experiments was: intravenous infusion of epinephrine at 12 μg/min, bilateral carotid artery occlusion and hemorrhage. Hemorrhage was produced by bleeding from the femoral artery 20 - 25 % of calculated blood volume (the total blood volume was assumed to be 70 ml per kilogram body weight). After measurement of ileal compliance, the blood was reinfused via a vein. Hemorrhage lasted for about 10 min. Both common carotid arteries were clamped suddenly below the carotid sinuses with bulldog clamps for about 4 min. and then released. In these three procedures ileal compliance was measured, after perfusion and aortic pres-

TABLE 1

SUMMARY OF AGENTS AND MANEUVERS STUDIED

	No.	Infusion rate	Mean Blood Flow ml/min/gm ileum
Local Effects			
Blood flow rate	10	. .	0 - 1.21
Epinephrine	10	0.2 μg/min	0.55
Acetylcholine	8	4 μg/min	0.60
Bradykinin	10	0.1 μg/min	0.60
Serotonin	10	2 μg/min	0.58
Adenosine	10	10 μg/min	0.65
A T P	10	10 μg/min	0.66
Phenoxybenzamine	10	about 0.3 mg/Kg	0.55
Propranolol	10	about 30 μg/Kg	0.57
$CaCl_2$	10	0.12 mEq/min	0.58
$MgCl_2$	10	0.12 mEq/min	0.60
KCl	10	0.02 mEq/min	0.60
KCl	8	0.07 mEq/min	0.59
KCl	8	0.18 mEq/min	0.60
Systemic Effects			
I.V. Epinephrine	8	12 μg/min	0.45
Hemorrhage	8	20-25 % calculated total blood volume	0.45
Carotid Occlusion	6	. .	0.53

sures were steady, (1) during a pre-control period, (2) during the procedure, and (3) during post-control period. An i.v. infusion of epinephrine at 12 μg/min was found to increase systemic arterial pressure to a level similar to that produced by bilateral carotid artery occlusion.

Presentation, Calculation, and Statistical Analysis of Results

The results are displayed by plotting steady-state mean perfusion pressure and ileal intraluminal pressure, against the corresponding ileal balloon volume. Since the definition of compliance is: Compliance = Δ volume/Δ pressure in ml/mm Hg, the slope of the luminal pressure-volume curve is inversely proportional to compliance. Thus, the less the slope the greater the compliance. Ileal compliance was calculated by dividing the highest volume introduced into the balloon (30 or 40 ml) by the difference between the intraluminal pressure at 0 and 30 or 40 ml balloon volume. Compliance calculated by this way was not significantly different from those calculated with values obtained at 20 or 30 ml balloon volume. An increase in ileal compliance indicates a less rigid ileal wall, and is considered to reflect a decrease in ileal wall tension. The slope of the perfusion pressure-volume curves, is directly proportional to the rise in resistance caused by the increment in ileal balloon volume.

The results were also analyzed qualitatively by comparing the degree of ileal motility during the control period with the motility seen during the experimental procedures. Motility was judged by the rate and amplitude of the fluctuations of intraluminal pressure. The ileal motility was further divided into three categories: (1) spontaneous movements seen at a zero balloon volume, (2) movements appearing during distension of the ileum and (3) movements appearing upon withdrawal of the water in

the balloon.

Ileal vascular resistance (in mm Hg/ml/min) was calculated by dividing perfusion pressure at zero balloon volume by blood flow rate. Since ileal vein pressure was not measured, this pressure was not taken into account in the calculation of vascular resistance. All the data were statistically analyzed by the conventional pair comparison method (9). The compliance and resistance during each experimental procedure was compared with the pre- and post- experimental control values in the same dog. A p value of less than 0.05 was considered to be statistically significant.

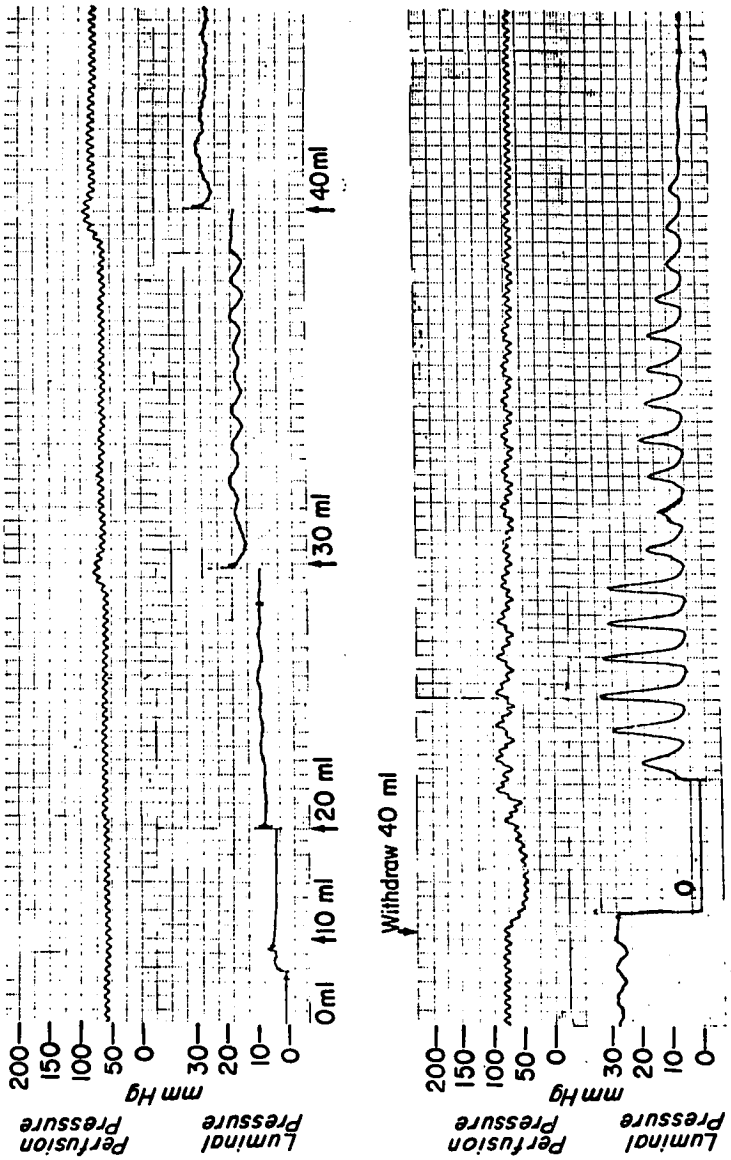
CHAPTER III

RESULTS

The Pattern of Changes in Ileal Motility and Vascular Resistnace during Compliance Measurements

A typical trace of the variables necessary to determine ileal compliance is shown in Figure 2. As the balloon volume was increased stepwise from 0 to 40 ml, a concurrent increase in perfusion and intraluminal pressure was observed. At the moment of infusing water into the balloon (indicating by arrows), perfusion pressure rose transiently and then fell to a steady state. In Figure 2, this is seen clearly at 30 or 40 ml balloon volume. Intraluminal pressure was not recorded during this transient, nor during the withdrawal of water. Perfusion pressure declined sharply upon withdrawal of water from the balloon. The withdrawal caused potent segmental contractions and peristalsis which show on the recording as a spike-like rise and fall in intraluminal pressure. Concurrent with these contractions, fluctuations of perfusion pressure appeared. We have named these ileal movement "after-kicks". The after-kicks were usually not seen during the infusion of agents which increased ileal compliance. Since they were seen even in a completely denervated ileal segment, the after-kicks were probably due to either a local neural reflex and/or inherent properties of visceral smooth muscle.

Figure 2. A typical recording during the measurement of ileal compliance. Arrows indicate infusions or withdrawal of water into or from the balloon. The balloon volume was increased in 10 ml steps to a total of 40 ml and the 40 ml total was withdrawn in one step.



Stretching the ileum by introducing water into the balloon generally produced segmental rhythmic contractions which were reflected on the recording as wavy fluctuations of the intraluminal pressure with concomitant fluctuations of perfusion pressure. In Figure 2, they are most evident at the 30 ml volume. In smaller segments of ileum, the rhythmic contractions usually appeared at 10 or 20 ml volume but disappeared at 30 or 40 ml volume. In larger segments of ileum, the rhythmic contractions appeared at 30 or 40 ml volume. Thus, there seemed to be an optimal level of pressure (about 10 - 20 mm Hg) which elicited the rhythmic contractions.

Occasionally a decrease of perfusion pressure, instead of an increase, was observed when ileal volume was increased. The decrease in perfusion pressure might appear at a 10, 20, or 30 ml volume but very rarely appeared at a 40 ml volume. The intraluminal pressure, however, always increased stepwise as balloon volume was increased.

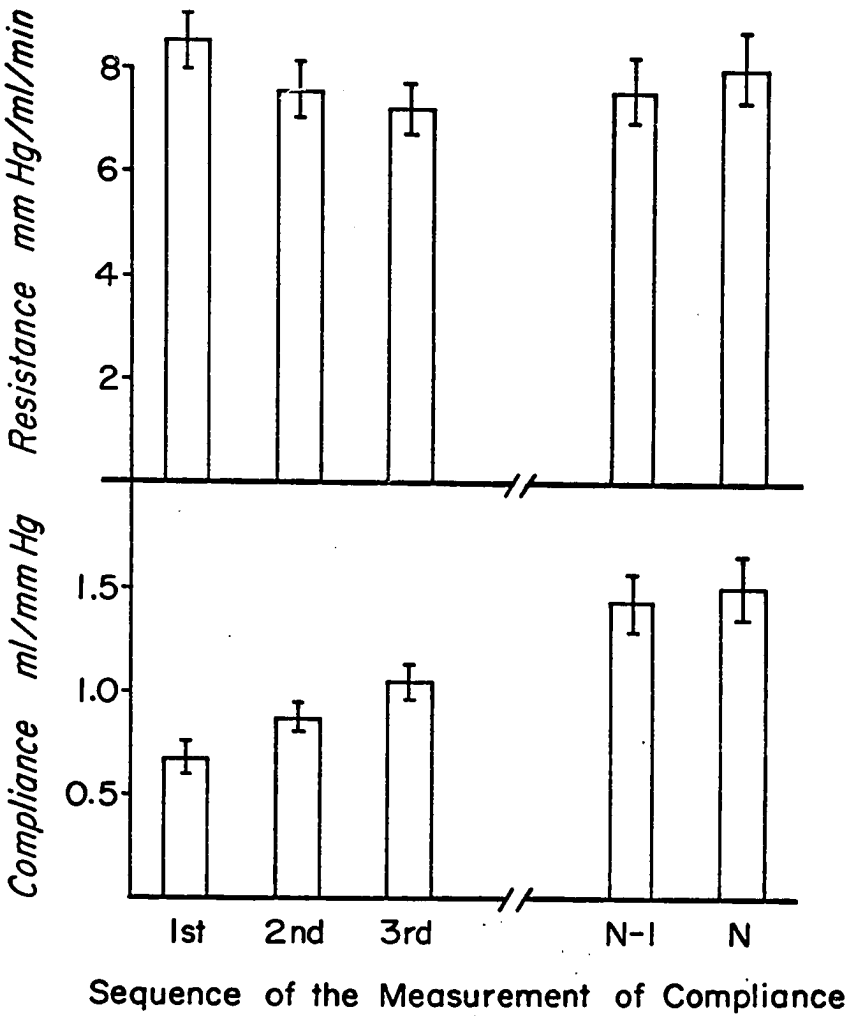
The mean values of the increment in the perfusion pressure and ileal intraluminal pressure produced by introducing 30 ml of water into the ileum were 25.6 $\pm$ 4.2 (Mean $\pm$ S.E.) and 33.2 $\pm$ 3.2 mm Hg in the less compliant ileal segments. In the more compliant segments, they were 9.1 $\pm$ 2.7 and 13.1 $\pm$ 1.0 mm Hg. These values were obtained from 10 animals which had the most compliant ileum and from the other 10 animals which had the least compliant ileum. The mean weights of ileal segments of these two groups were similar. Further, these values were the compliance of the ileum at a steady state, i.e., after the ileum had been distended several times. Although the increment in the absolute value of perfusion pressure was larger in the less compliant ileum, the percentage of the pressure which was transmitted from ileal lumen to the blood vessel

(△ perfusion pr./△ luminal pr. x 100) was little different from the more compliant ileum. In the less compliant ileum, 77% of the luminal pressure was transmitted to the perfusion pressure and in the more compliant ileum 70%.

The effect of stretching the ileum on its compliance and vascular resistance is shown in Figure 3. The ileum became progressively more compliant as the measurements of compliance were repeated but it eventually became constant. As shown in Figure 3, compliance at the last measurement (N) and the one before the last (N - 1) were the same. On the average N equaled 5. As the compliance increased, the vascular resistance decreased and became constant after several stretchings. As with compliance, the resistance at N - 1 and N were the same but the first and the third values were significantly different. The mean compliance and resistance when first measured were 0.68 ± 0.08 ml/mm Hg and 8.50 ± 0.52 mm Hg/ml/min. At the third measurement they were 1.04± 0.09 and 7.20 ± 0.50 respectively.

The compliance measured in this study was that of the entire segment of the ileum including the smooth muscle and elastic tissue. In order to find out what part of the living tissue contributed most to the compliance at the volume used, a piece of ileum of the same size was removed from the animal. When after several hours, it no longer responded to acetylcholine or epinephrine, the same procedure for the measurement of compliance was carried out. The ileum was very rigid in the first measurement due to postmortum changes, but became constant after a few stretchings. The intraluminal pressure stayed at 0 mm Hg until the ileum was distended to 30 or 40 ml, when the pressure rose sharply to 20-30 mm Hg. This study seemed to indicate that the

Figure 3. Ileal compliance and vascular resistance during the first control measurements of compliance. N. indicates the time when the compliance of the ileum became constant. Depending upon the ileum, N varied from 4 to 8. Straight lines perpendicular to the top of bars indicate standard errors. The values are the mean of 15 randomly selected experiments.



compliance measured in vivo is most likely a reflection of the contractile state of the smooth muscle. In the inanimate ileum, no pressure developed until the volume reached 30 or 40 ml. The pressure developed at these volumes is presumed to be from the elastic property of elastic tissue and smooth muscle.

Effect of Rate of Blood Flow

The purpose of this study was twofold. One purpose was to see if altering blood flow through the ileum could alter ileal motility, and the second purpose was to see if changes in intravascular pressure, resulting from changes in blood flow rate, could alter ileal wall compliance. Elucidation of the second question was essential for the interpretation of the effect of various vasoactive agents on ileal compliance. It seemed possible that these agents might alter ileal compliance indirectly by affecting the wall tension of ileal intramural blood vessels.

The results of this study are shown in Figures 4 and 5 and Tables 2 and 3. Ileal compliance was not altered by either a decrease or an increase in flow rate which attend a perfusion pressure ranging from 10 to 200 mm Hg. However, compliance during "no flow" was significantly increased as compared with those during "control 1" and "low flow". This seemed to indicate that "no flow" decreased ileal wall tension. Vascular resistance was not significantly increased by decreasing blood flow from 0.67 ml/min/gm ileum to 0.14 ml/min/gm. However, it was significantly decreased during reactive dilation and during the period of high flow (1.21 ml/min/gm ileum). The ileal motility was usually accentuated (7 out of 10 dogs) during "no flow". The accentuation was usually seen during the measurement of compliance but rarely seen at the zero balloon

Figure 4. Average effects of decreasing blood flow rate on the perfusion pressure and ileal intraluminal pressure at various ileal balloon volumes. Arrows indicate the point where the blood flow is changed. Dotted lines indicate the changes of pressures which occured when the ileal balloon volumes were zero.

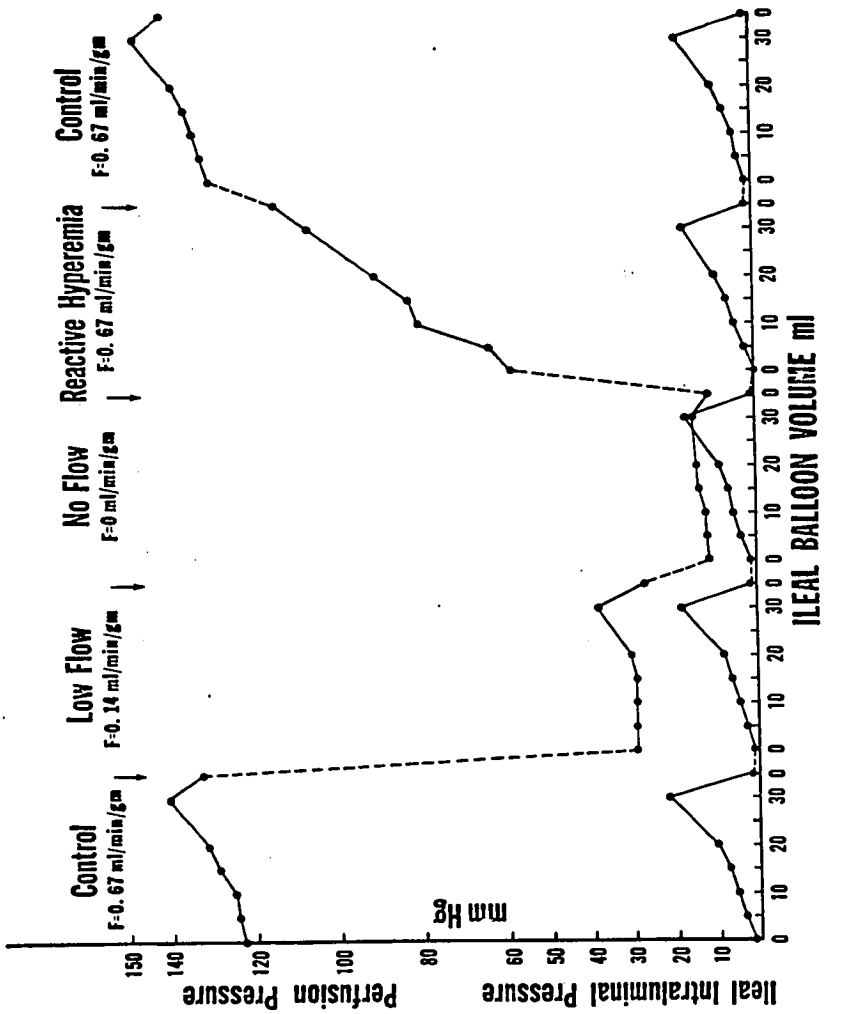


Figure 5. Average effects of increasing blood flow rate on the perfusion pressure and ileal intraluminal pressure at various ileal balloon volumes.

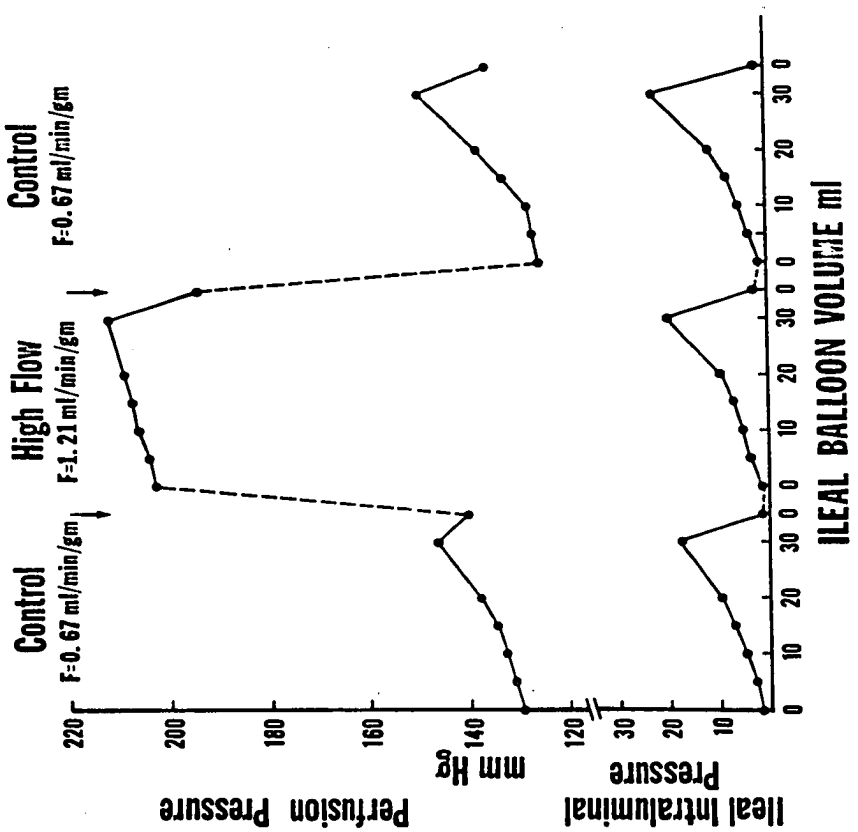


TABLE 2

AVERAGE EFFECTS OF DECREASING BLOOD FLOW ON COMPLIANCE AND RESISTANCE (N = 10)

	Control 1	Low Flow	No Flow (0)	Reactive Hyperemia (R.H.)	Control 2
Blood Flow ml/min/gm	0.67	0.14	0	0.67	0.67
Compliance ml/mm Hg	1.71	1.77	2.24[a]	1.90	1.96
Resistance mm Hg/ml/min	7.41	8.73	. .	3.49	7.63[a]

d ± S.E. (difference between two means ± its standard error)

Compliance:		Resistance:	
Low vs Control 1:	+ 0.06 ± 0.14	Low vs Control 1:	+ 1.32 ± 0.90
0 vs Low:	+ 0.47 ± 0.19[b]	R.H. vs Control 2:	- 4.13 ± 0.10[b]
0 vs Control 1:	+ 0.53 ± 0.14[b]		
0 vs Control 2:	+ 0.28 ± 0.19		
0 vs R.H.:	+ 0.34 ± 0.17		

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

[b] Denotes that the difference between two values compared is statistically significant at p value less than 0.05.

TABLE 3

AVERAGE EFFECTS OF INCREASING BLOOD FLOW ON COMPLIANCE AND RESISTANCE (N = 10)

	Control 1	High Flow	Control 2
Blood Flow ml/min/gm	0.67	1.21	0.67
Compliance ml/mm Hg	1.99	1.84	1.70
Resistance mm Hg/ml/min	7.79	6.81[a]	7.52[a]

d ± S.E.	Compliance:	Resistance:
High vs Control 1:	- 0.14 ± 0.12	- 0.98 ± 0.27[b]
High vs Control 2:	+ 0.14 ± 0.13	- 0.71 ± 0.23[b]

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

[b] Denotes that the difference between two values compared is statistically significant at p value less than 0.05.

volume (only 2 out of 10). Occasionally, the ileal movement was diminished during the "high flow" (3 out of 10), but, in general, the findings during high flow were inconsistent.

Effects of Local Infusion of Various Vasoactive Substances

Eleven agents were studied. These were epinephrine, acetylcholine, bradykinin, serotonin, adenosine, ATP, potassium, magnesium and calcium chlorides, phenoxybenzamine, and propranolol. The blocking actions of phenoxybenzamine and propranolol on epinephrine-induced changes were also studied. The infusion rate of each agent was chosen according to its effects on the ileal motility. When using agents which inhibit ileal motility, such as epinephrine, the infusion rates chosen produced a minimal vascular effect. With agents which stimulate ileal motility, infusion rates were selected which had minimal to moderate effects on the ileal motility, so that the ileal movement would not become so active as to cause wide and irregular variations of ileal intraluminal pressure. In all experiments, the systemic pressure was not altered significantly by local infusion of these agents. The infusion rates of agents used, number of dogs tested and the mean blood flow are shown in Table 1 (Chapter II, page 12).

The effects of epinephrine on ileal compliance and vascular resistance are shown in Figure 6, and Tables 4 and 5. In Figure 6, and in all subsequent Figures, the arrows indicate starting and stopping the infusion of the agents. The dotted lines indicate pressure changes at zero balloon volume unless indicated otherwise. An infusion of 0.2 μg/min of epinephrine significantly increased compliance but did not alter ileal vascular resistance at zero balloon volume. However, the

Figure 6. Average effects of epinephrine (0.2 μg/min, i.a.) on perfusion pressure and intraluminal pressure at various ileal balloon volumes. Arrows indicate starting and stopping epinephrine infusion. Dotted lines indicate pressure changes at zero balloon volume. N is numbers of dogs tested, and F means blood flow.

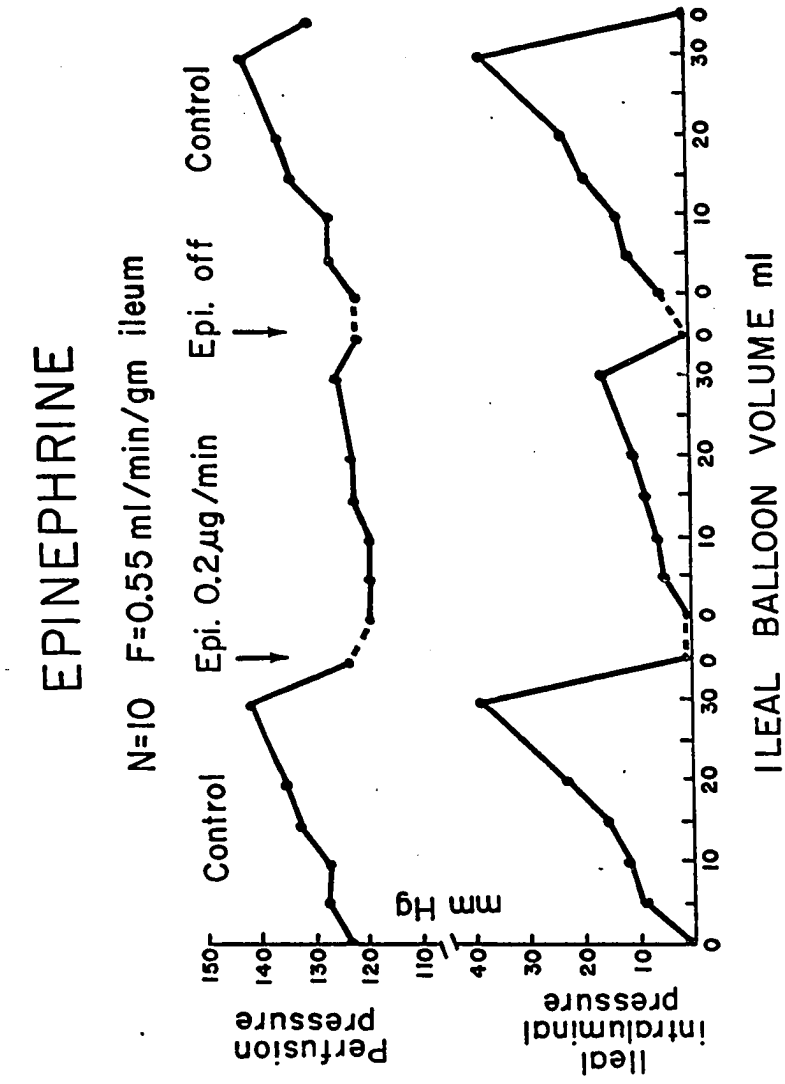


TABLE 4

LOCAL EFFECTS OF VARIOUS AGENTS ON MEAN ILEAL COMPLIANCE

Agents	Control 1	During Infusion (E)	Control 2	d_1 : E - Control 1 Mean ± S. E.	d_2 : E -Control 2 Mean ± S.E.
Epinephrine	0.88	2.15[a]	1.24[a]	+ 1.27 ± 0.28	+ 0.91 ± 0.22
Acetylcholine	1.13	0.93[a]	1.01	- 0.20 ± 0.05	- 0.08 ± 0.03 (0.1 > p > 0.05)
Bradykinin	1.42	1.05[a]	1.41[a]	- 0.37 ± 0.13	- 0.36 ± 0.14
Serotonin	1.48	0.99[a]	1.31[a]	- 0.49 ± 0.15	- 0.33 ± 0.15
Adenosine	1.41	1.28[a]	1.43[a]	- 0.13 ± 0.04	- 0.15 ± 0.04
ATP	1.45	1.21	1.39	- 0.24 ± 0.11	- 0.17 ± 0.09
$CaCl_2$	1.12	2.10[a]	0.97[a]	+ 0.97 ± 0.23	+ 1.13 ± 0.26
$MgCl_2$	1.07	1.65[a]	1.12[a]	+ 0.58 ± 0.13	+ 0.53 ± 0.15
KCl (0.02 mEq)	1.00	1.06	. .	+ 0.06 ± 0.06	. .
KCl (0.07 mEq)	1.34	1.65[a]	1.12[a]	+ 0.31 ± 0.07	+ 0.53 ± 0.09
KCl (0.18 mEq)	1.27	1.10[a]	1.11	- 0.17 ± 0.05	- 0.01 ± 0.04

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

TABLE 5

LOCAL EFFECTS OF VARIOUS AGENTS ON MEAN ILEAL VASCULAR RESISTANCE

	Control 1	During Infusion	Control 2	d_1 : E -Control 1	d_2 : E-Control 2
Epinephrine	7.81	7.47	7.74	- 0.35 ± 0.23	- 0.27 ± 0.21
Acetylcholine	9.42	8.42[a]	8.92[a]	- 1.00 ± 0.20	- 0.50 ± 0.21
Bradykinin	8.10	6.44[a]	8.15[a]	- 1.66 ± 0.49	- 1.71 ± 0.47
Serotonin	6.99	6.63	6.67	- 0.36 ± 0.29	- 0.04 ± 0.29
Adenosine	7.28	4.79[a]	7.21[a]	- 2.49 ± 0.46	- 2.42 ± 0.51
ATP	7.12	4.73[a]	7.08[a]	- 2.40 ± 0.51	- 2.35 ± 0.59
$CaCl_2$	8.45	7.80	8.27	- 0.66 ± 0.33	- 0.47 ± 0.30
MgCl	8.37	6.25[a]	8.49[a]	- 2.12 ± 0.51	- 2.24 ± 0.41
KCl (0.02 mEq)	7.96	7.62[a]	. .	- 0.31 ± 0.13	. .
KCl (0.07 mEq)	8.97	6.29[a]	9.09[a]	- 2.68 ± 0.69	- 2.80 ± 0.57
KCl (0.18 mEq)	8.98	12.88[a]	9.54[a]	+ 3.90 ± 0.61	+ 3.34 ± 0.47

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

degree of increment in perfusion pressure during the measurement of compliance was lowered, i.e., the slope of the curve of perfusion pressure vs ileal balloon volume during epinephrine was less than that during the controls (Figure 6). The rhythmic activity and the after-kicks were diminished or abolished by the infusion of epinephrine.

The interrelationship between the vascular effect and the visceral effect of epinephrine on vascular resistance is well demonstrated in the lower panel of Figure 7. The experiment was done at zero ileal volume. As can be seen in this figure, when the ileal movement was active and the intraluminal pressure was high, a single injection of 0.5 μg epinephrine decreased intraluminal pressure and eliminated fluctuations of lumen pressure concurrent with a decrease in perfusion pressure. One minute later, when intraluminal pressure was still low, injection of the same dose of epinephrine produced an increase in perfusion pressure. Thus, during the first injection, the vasoconstrictive action of epinephrine was presumably masked by its inhibitory action on the ileal muscle.

Acetylcholine, bradykinin, and serotonin are known to contract isolated ileal smooth muscle. In order to avoid wide and irregular fluctuations in the ileal luminal pressure, the infusion rates of these agents during the study of compliance were chosen to produce minimal to moderate effects on ileal motility. The effects of these agents on the compliance and vascular resistance are shown in Figrues 8, 9, 10, and Tables 4 and 5. All three agents decreased compliance. While acetylcholine and bradykinin significantly lowered the vascular resistance, serotonin did not significantly alter it.

At zero balloon volume the responses of the ileum to these three agents were different. Bradykinin and serotonin produced an initial fall

Figure 7. Effects of injection of epinephrine or acetylcholine on perfusion pressure (P_p) and ileal luminal pressure (P_L) at zero balloon volume in two dogs. Upper panel shows the effect of acetylcholine at 1 μg and 10 μg, and lower panel the effect of epinephrine at 0.5 μg. In the upper left chart, x1 and x5 indicate the attenuation of pressure recording. After the injection of 10 μg acetylcholine, the luminal pressure rose above 40 mm Hg such that the attentuation had to be increased to x5.

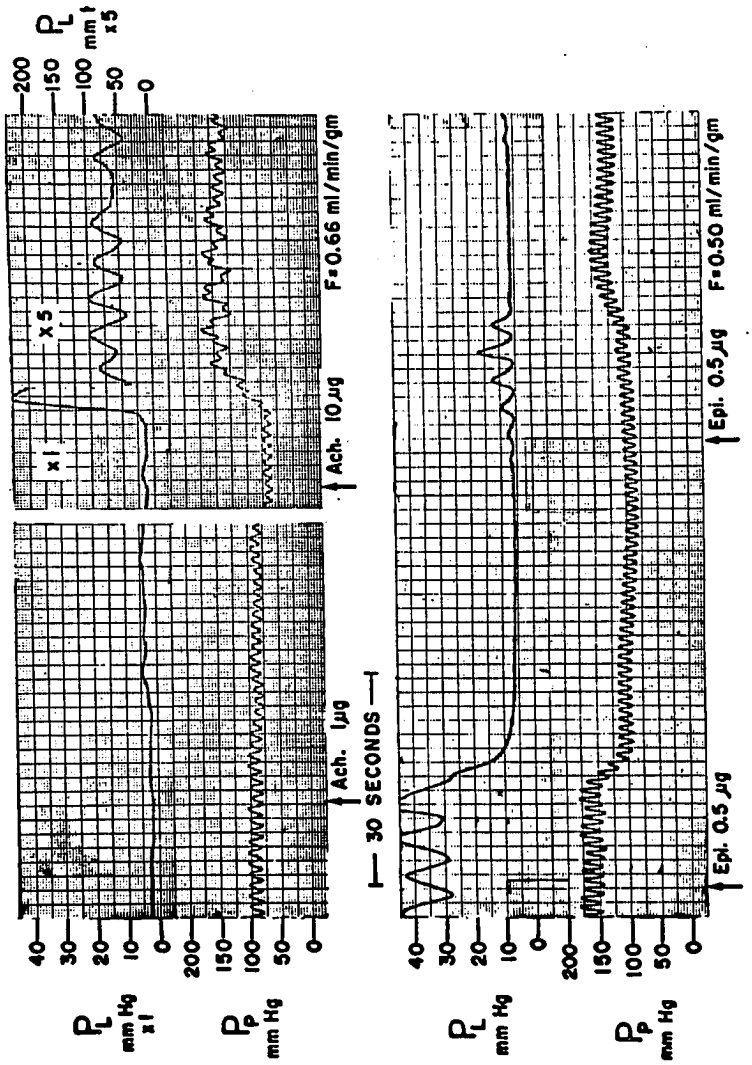


Figure 8. Average effects of acetylcholine (4 μg/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

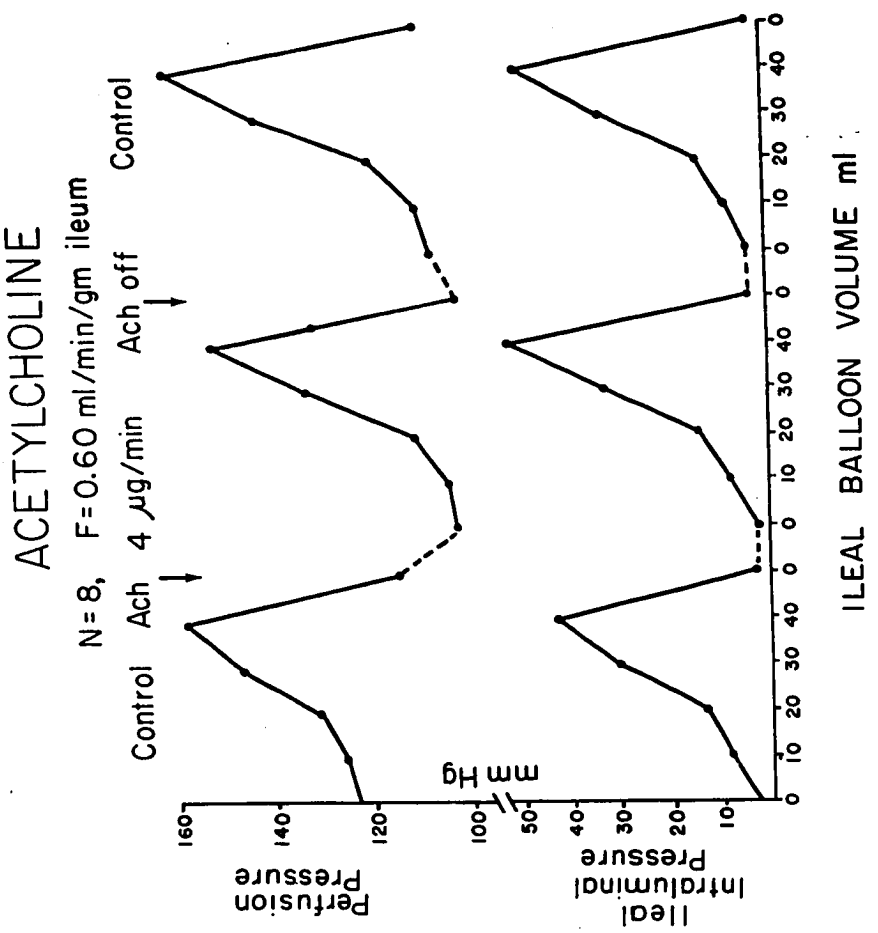


Figure 9. Average effects of bradykinin (0.1 μg/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

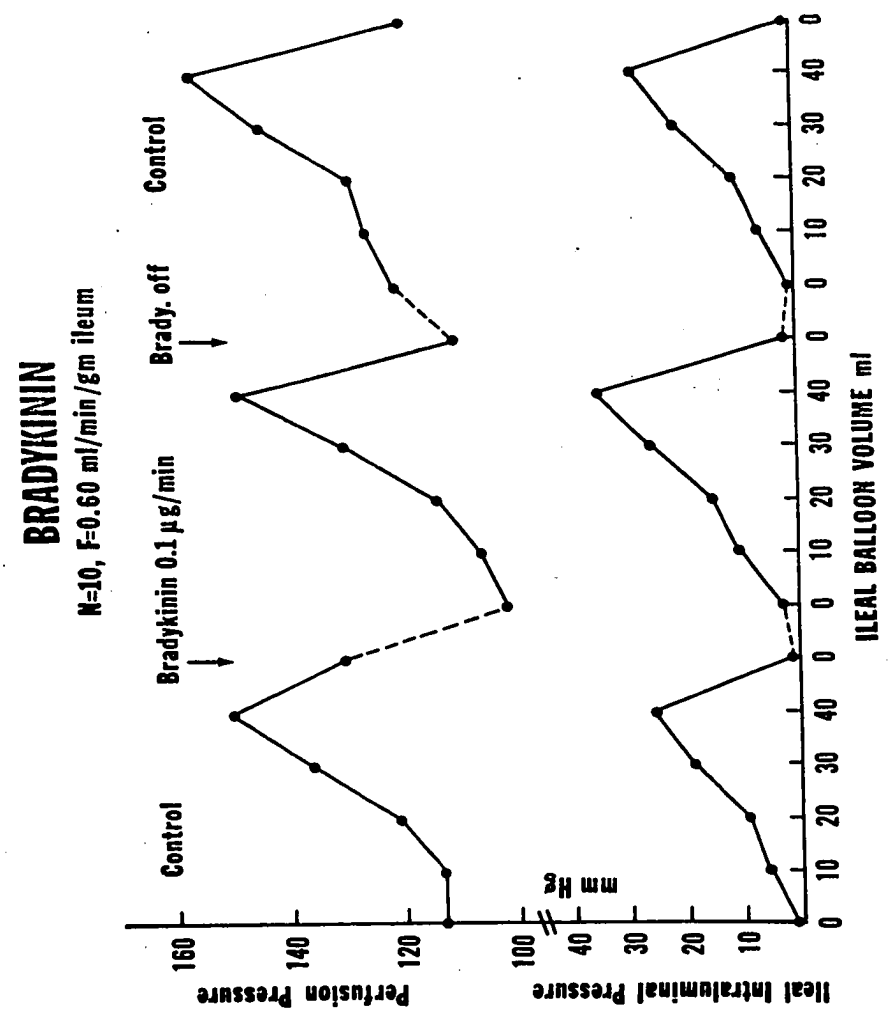


Figure 10. Average effects of serotonin (2 μg/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

in perfusion pressure followed by a rise. The rise in perfusion pressure occured concurrently with a rise in ileal luminal pressure. This appears to indicate that the rise in perfusion pressure is due to the stimulatory effect of either agent on the ileal muscle. In the steady state, the perfusion pressure seen during infusion of bradykinin was lower than before infusion. On the other hand, the response to serotonin was quite variable. In half of the experiments, the perfusion pressure in the steady state was higher during the infusion of serotonin than before infusion, although the perfusion pressure was transiently lowered by serotonin. In the other half, the perfusion pressure was lowered or unchanged by serotonin. Thus, the mean perfusion pressure in 10 experiments was not significantly altered by serotonin. However, if the infusion rate was increased, either agent regularly produced a marked rise in ileal luminal pressure and perfusion pressure and an increase in ileal movement. The time of onset of the response by the ileal muscle was different between these two agents. Bradykinin took 1 to 2 minutes to initiate a rise in ileal luminal pressure, whereas, serotonin took about 30 seconds.

Acetylcholine at the infusion rate used to study compliance (4 μg/min) did not increase the luminal pressure at zero balloon volume. However, if the infusion rate was increased to 10 μg/min, acetylcholine raised luminal pressure sharply and produced wide fluctuations in luminal pressure. Figure 7 shows the effect of a single injection of 1 and 10 μg acetylcholine on the perfusion and ileal luminal pressures at zero balloon volume. At 1 μg, it produced a slight increase in luminal pressure. At 10 μg, it increased luminal pressure with a concurrent increase in perfusion pressure. The results obtained with these three agents

infused at higher rates clearly show that when the ileum is active, the vascular resistance can rise even in the presence of a vasodilator at the concentration which will produce a fall in vascular resistance in other vascular beds.

Adenosine and ATP at an infusion rate of 10 μg/min markedly decreased vascular resistance but did not greatly alter compliance. Their effects are shown in Figures 11, and 12, and Tables 4 and 5. The decrease in compliance, though small, was consistent with adenosine (10 out of 10 experiments). On the average, ATP decreased compliance more than did adenosine but the results varied greatly in different experiments. The statistical analysis revealed a significant change with a p value of less than 0.01 for adenosine. On the other hand, the response to ATP was so variable that no significant change was obtained. While ileal motility was not affected by adenosine and ATP infused at 10 μg/min, a single injection of 100 μg adenosine or ATP raised ileal luminal pressure with an increase in the amplitude of the rhythmic contractions. The increase in ileal activity, however, did not cause a rise in perfusion pressure, instead, it fell markedly. With adenosine and ATP, the vasodilator action appears to be far more potent than the action on the ileal muscle.

The effects of magnesium chloride and calcium chloride are shown in Figures 13, and 14, and Tables 4 and 5. Both ions increased compliance. While the magnesium ion significantly lowered the vascular resistance, the calcium ion did not alter it significantly. Ileal movements were diminished or abolished by both ions.

The effects of potassium chloride were complicated, and the responses varied with the infusion rate. Three infusion rates, low

Figure 11. Average effects of adenosine (10 μg/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

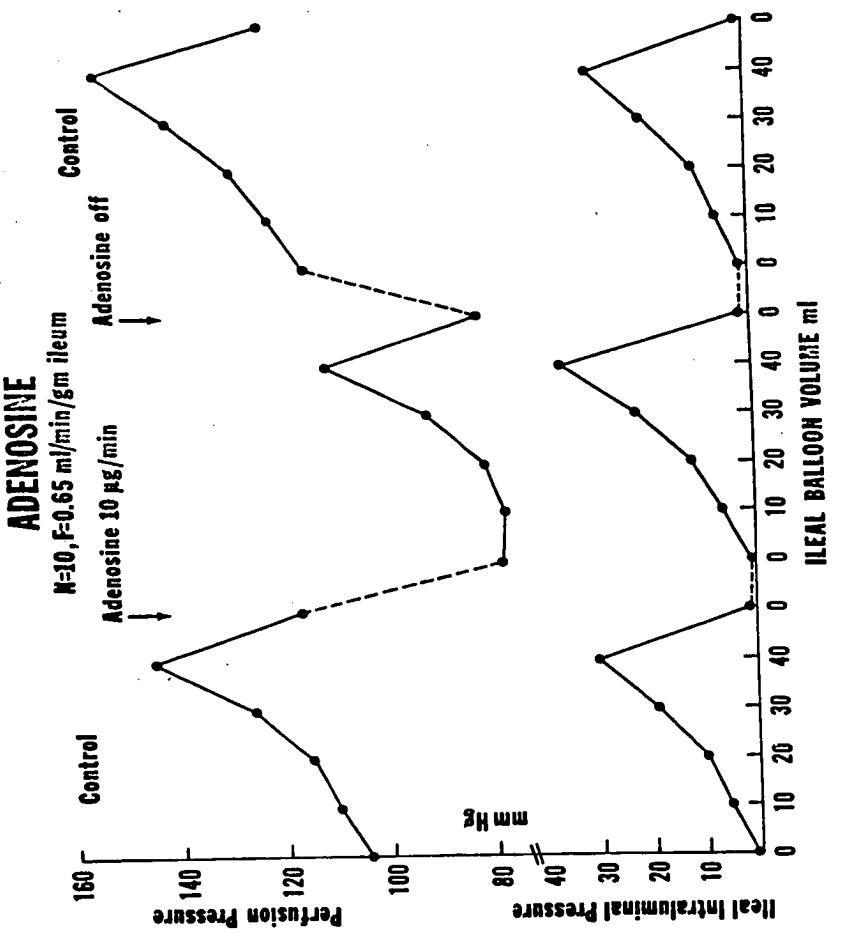


Figure 12. Average effects of ATP (10 μg/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

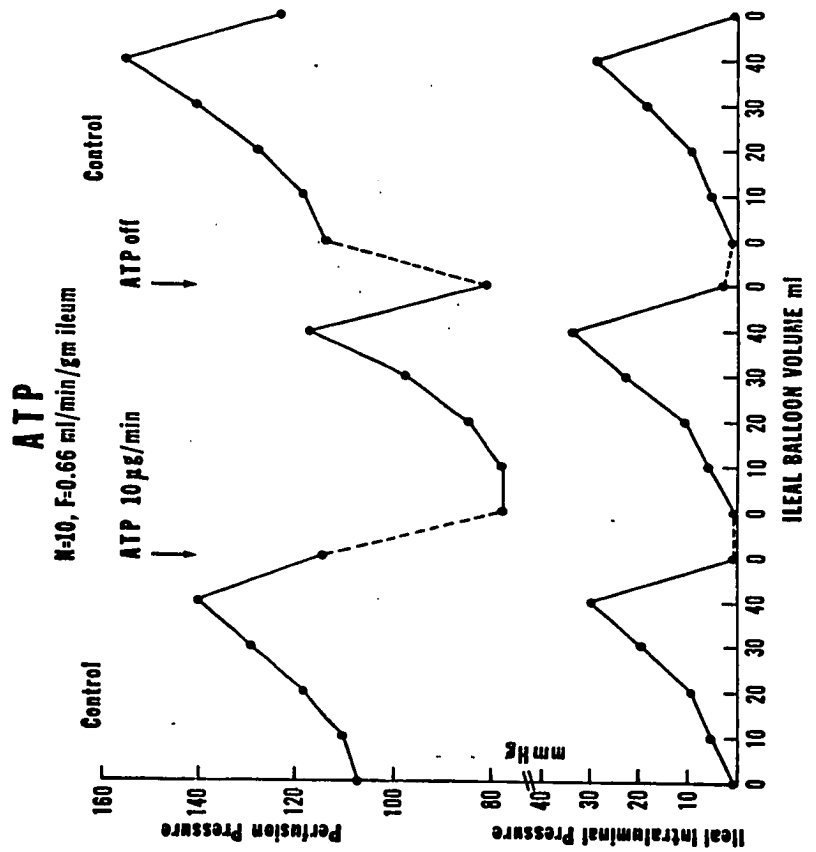


Figure 13. Average effects of magnesium chloride (0.12 mEq/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

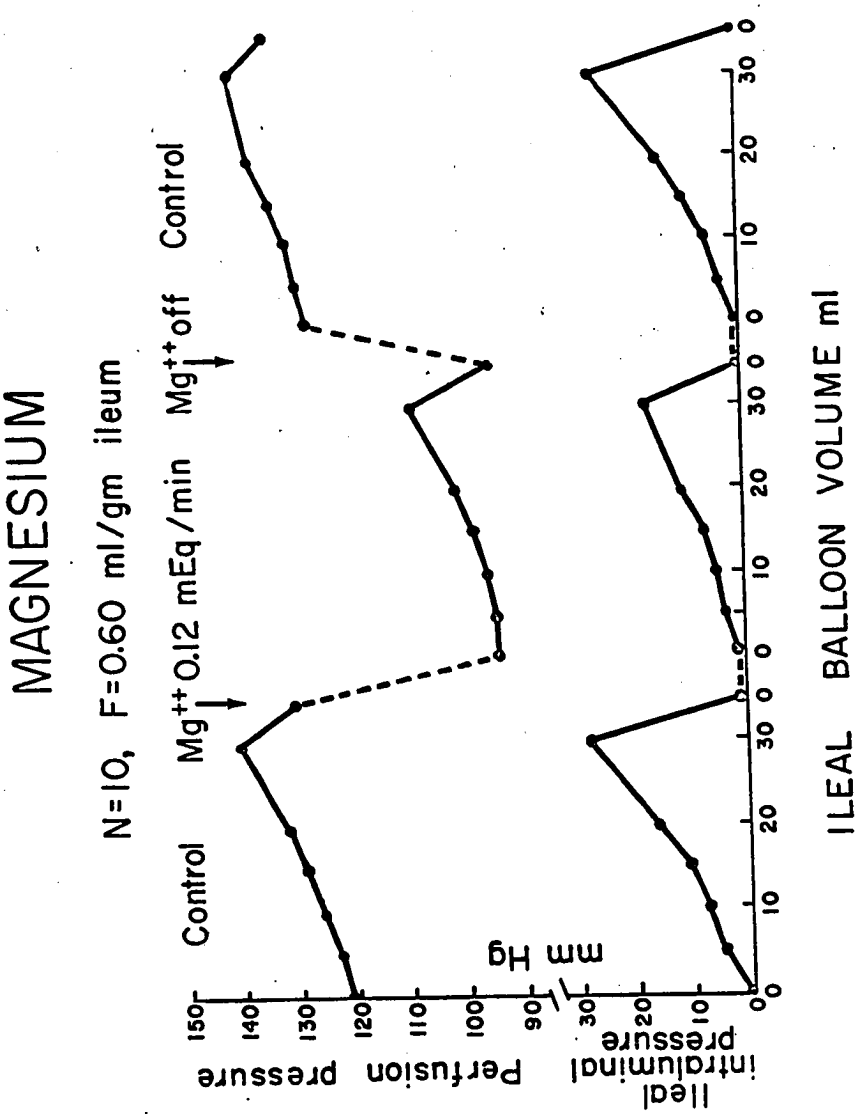
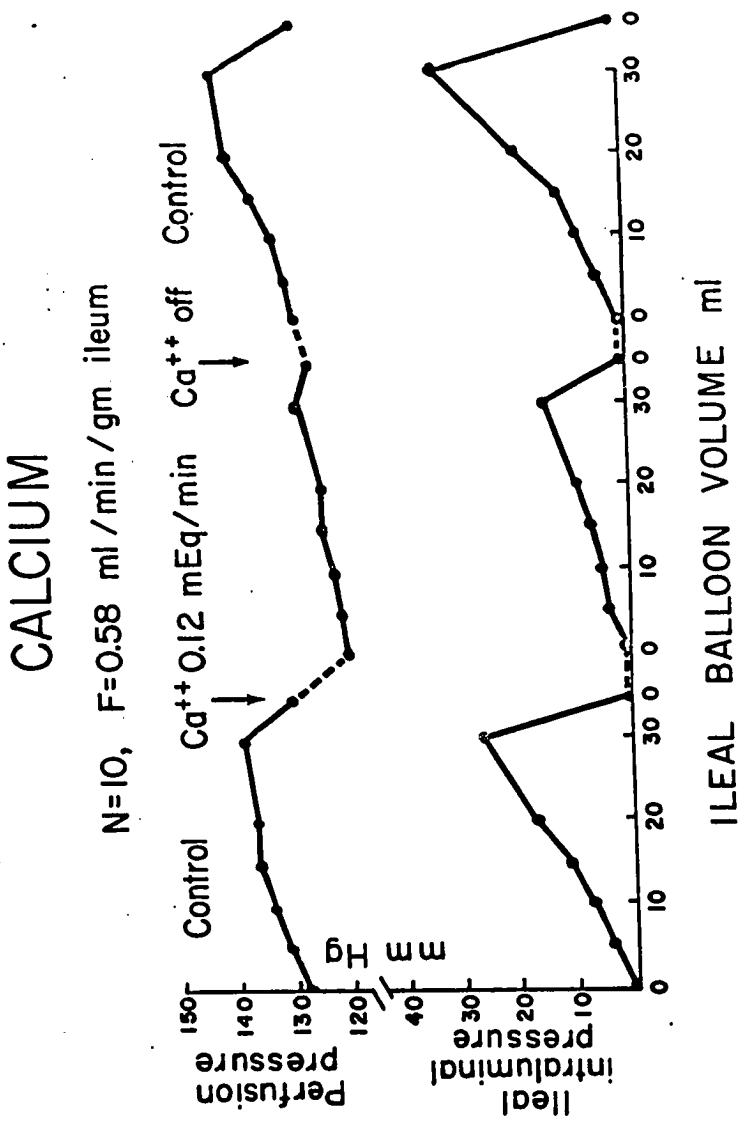


Figure 14. Average effects of calcium chloride (0.12 mEq/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.



(0.02 mEq/min), intermediate (0.07 mEq/min) and high (0.18 mEq/min), were used. These results are shown in Figures 15, 16, and 17, and Tables 4 and 5. At low infusion rate, KCl decreased resistance but did not alter compliance. At the intermediate infusion rate, it increased compliance and decreased resistance. At a high infusion rate, it decreased compliance and increased resistance. Thus, the ileum was made more compliant by the intermediate infusion rate of KCl but became more rigid with the higher infusion rate. Figure 17 further shows a biphasic response of perfusion and ileal luminal pressure to the higher infusion rate of KCl. At zero balloon volume, it produced a fall in perfusion and ileal luminal pressure followed by a rise in both pressures. An infusion of 0.18 mEq/min KCl seemed to cause a prolonged change in ileal tension since the post-infusion compliance never came back to the preinfusion control value. In some instances, the experiment had to be terminated, because of wide fluctuations of ileal luminal pressure after the infusion of 0.18 mEq/min KCl. Nevertheless, acetylcholine (4 μg/min) could further decrease ileal compliance after the infusion of 0.18 mEq/min KCl. This demonstrates that the ileal smooth muscle was not rendered unresponsive by the infusion of KCl at 0.18 mEq/min.

The rhythmic activity and after-kicks were generally diminished or abolished by the intermediate or high infusion rate of KCl and was occasionally diminished by the low infusion rate. The effects of the infusion of KCl at various infusion rates on ileal motility and perfusion pressure at zero balloon volume are shown in Figure 18. An infusion of KCl at 0.4 ml/min (0.07 mEq/min) abolished rhythmic contractions and decreased intraluminal pressure. When 2.0 ml/min (0.36 mEq/min) KCl was infused, the ileal luminal pressure rose sharply as soon as the agent

Figure 15. Average effects of potassium chloride (0.02 mEq/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

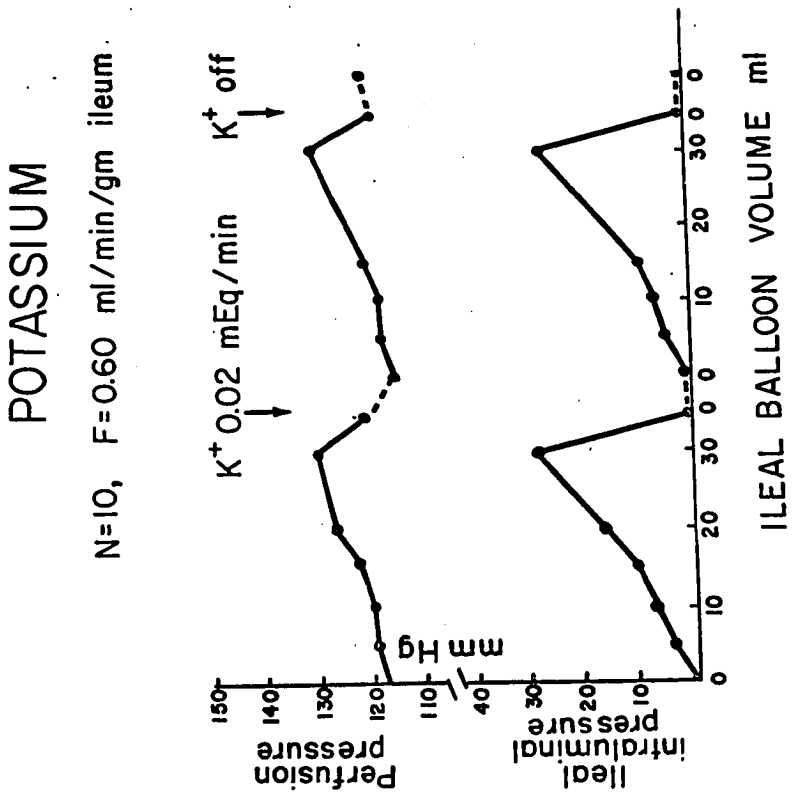


Figure 16. Average effects of potassium chloride (0.07 mEq/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

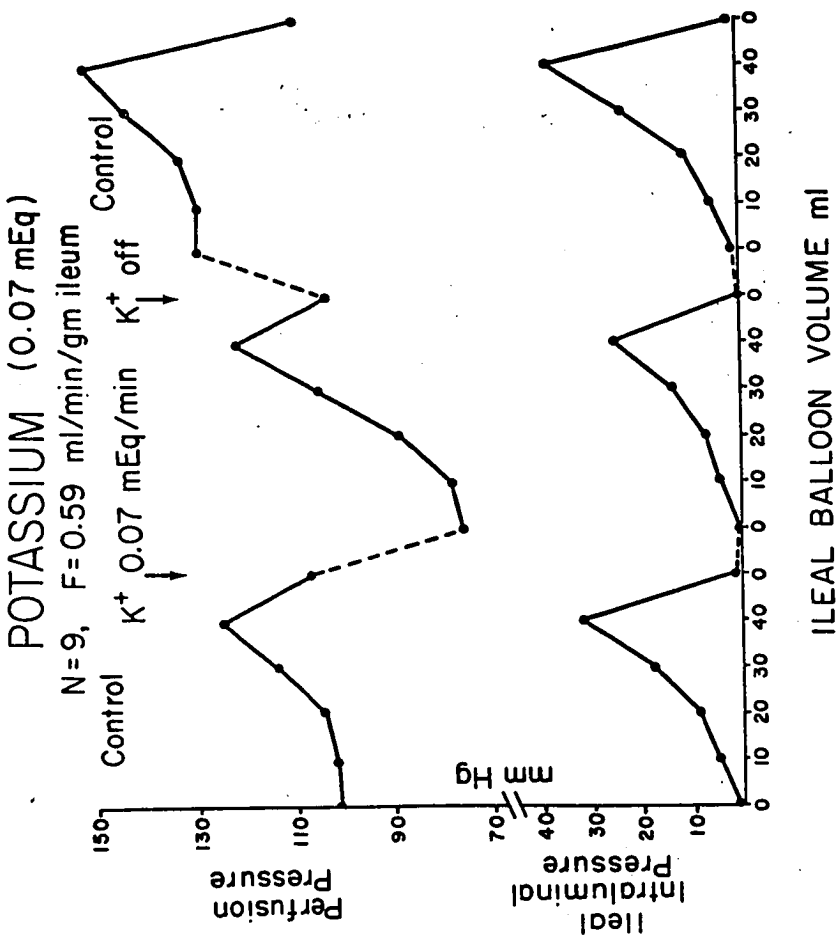


Figure 17. Average effects of potassium chloride (0.18 mEq/min) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

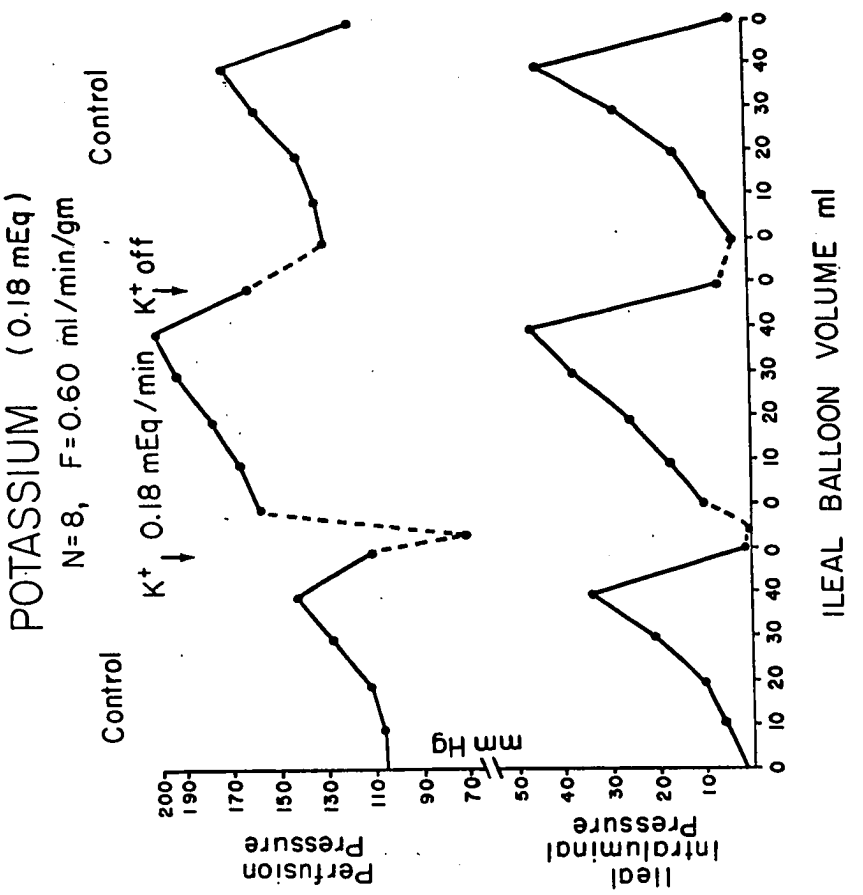
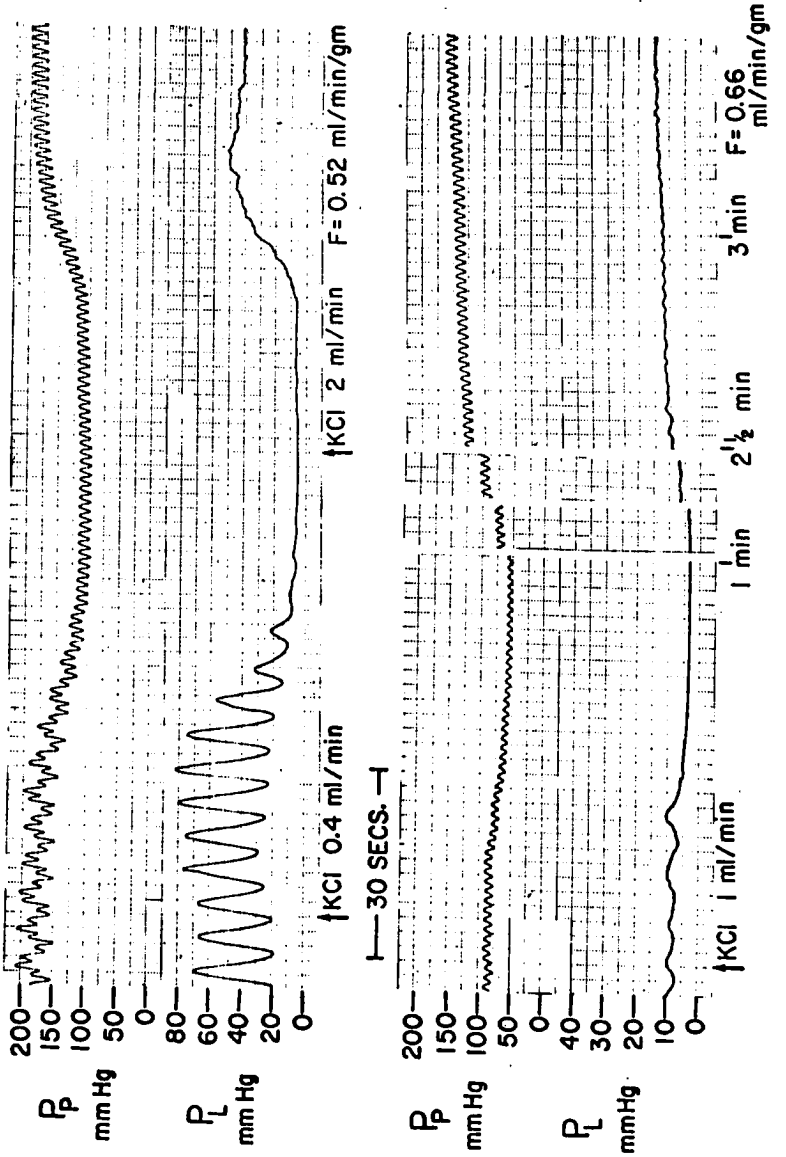


Figure 18. Effects of an infusion of an isotonic solution of potassium chloride in two experiments at 0.4 ml/min (0.07 mEq/min), 2 ml/min (0.36 mEq/min) or 1 ml/min (0.18 mEq/min) on perfusion pressure (Pp) and ileal luminal pressure (P_L) at zero balloon volume.



reached the intestine. A biphasic response, i.e., an initial fall followed by a gradual rise in intraluminal pressure, was observed when 1 ml/min (0.18 mEq/min) of KCl was infused. With all three infusion rates, KCl produced a concurrent change in perfusion pressure and in the same direction as ileal luminal pressures.

The effects of phenoxybenzamine on epinephrine-induced compliance and resistance changes are shown in Figure 19, and Table 6. Epinephrine at 0.2 μg/min alone produced an increase in compliance but no change in vascular resistance. Phenoxybenzamine, itself, caused a fall in resistance and a rise in compliance. After pretreatment with phenoxybenzamine, epinephrine did not alter compliance but decreased vascular resistance. Thus, phenoxybenzamine altered both intestinal and vascular responses to epinephrine. Phenoxybenzamine, like epinephrine, also abolished or diminished the rhythmic activity and after-kicks in most experiments (8 out of 10). In the other experiments, in which phenoxybenzamine did not alter ileal motility, the infusion of epinephrine abolished ileal motility.

The effects of propranolol are shown in Figure 20, and Table 7. Propranolol, itself, produced an increase in compliance and resistance. After pretreatment with propranolol, epinephrine further increased compliance and resistance. Thus, propranolol altered the vascular response of the ileum to epinephrine but not its effect on compliance. Ileal movements were not altered by propranolol. Following the administration of propranolol, epinephrine did not inhibit the rhythmic activity and after-kicks. It seemed, therefore, that although propranolol blocked the inhibitory effect of epinephrine on the ileal movement, it did not block the effect of epinephrine on compliance.

Figure 19. Effects of phenoxybenzamine (Dibenzyline^{R}) on the epinephrine-induced changes in perfusion pressure and ileal intraluminal pressure at various balloon volumes.

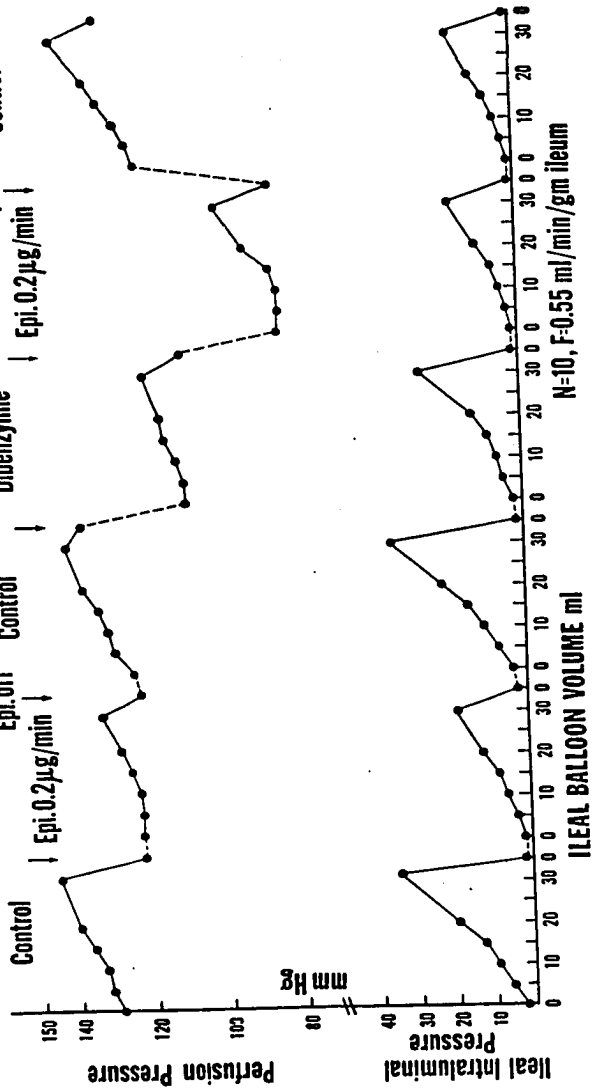


TABLE 6

AVERAGE EFFECTS OF PHENOXYBENZAMINE (P) ON CHANGES IN COMPLIANCE AND RESISTANCE INDUCED BY EPINEPHRINE (E)

	Control 1	E	Control 2	P_1	(P + E)	P_2
Compliance	0.92	1.78[a]	0.95	1.99[a]	1.89	1.99
Resistance	8.22	8.39	8.62	7.15[a]	5.43[a]	7.82[a]

d ± S.E.

Compliance:		Resistance:	
E - Control 1:	+ 0.86 ± 0.20[b]	E - Control 1:	+ 0.17 ± 0.58
P_1 - Control 2:	+ 1.04 ± 0.25[b]	P_1 - Control 2:	- 1.47 ± 0.53[b]
(P + E) - P_1:	- 0.10 ± 0.14	(P + E) - P_1:	- 1.72 ± 0.33[b]
		(P + E) - P_2:	- 2.39 ± 0.54[b]

[a] Denotes that the value is statistically significant at a P value less than 0.05 as compared with the preceding value.

[b] Denotes that the difference between two values compared is statistically significant at p value less than 0.05.

Figure 20. Effects of propranolol (Inderal^{R}) on the epinephrine-induced changes in perfusion pressure and ileal intraluminal pressure at various balloon volumes.

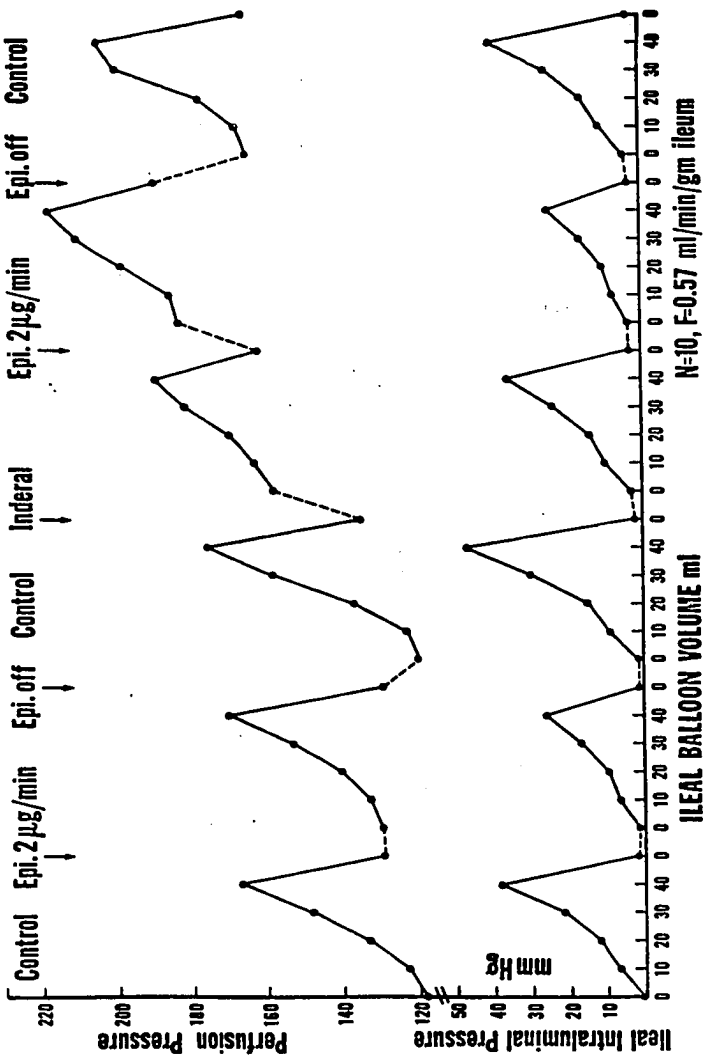


TABLE 7

AVERAGE EFFECTS OF PROPRANOLOL (I) ON CHANGES IN COMPLIANCE AND RESISTANCE INDUCED BY EPINEPHRINE (E)

	Control 1	E_1	Control 2	I_1	(I + E)	I_2
Compliance	1.18	1.72[a]	1.00	1.28[a]	1.95[a]	1.22[a]
Resistance	8.68	8.74	9.09	10.64[a]	12.52[a]	11.07[a]

d ± S. E.

Compaliance:		Resistance:	
E - Control 1:	+ 0.54 ± 0.10[b]	E. - Control 1:	+ 0.06 ± 0.36
I_1 - Control 2:	+ 0.28 ± 0.10[b]	I_1 - Control 2:	+ 1.55 ± 0.28[b]
(I + E) - I_1:	+ 0.67 ± 0.13[b]	(I + E) - I_1:	+ 1.88 ± 0.41[b]
(I + E) - Control 2:	+ 0.95 ± 0.18[b]	(I + E) - I_2:	+ 1.45 ± 0.49[b]
(I + E) - I_2:	+ 0.73 ± 0.14[b]		

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

[b] Denotes that the difference between two values compared is statistically different at p value less than 0.05.

Effects of I.V. Infusion of Epinephrine, Hemorrhage, and Bilateral Carotid Artery Occlusion

The effects of intravenous infusion of epinephrine (12 μg/min), hemorrhage and bilateral corotid artery occlusion are shown in Figures 21, 22, and 23, and Table 8. All three procedures increased ileal compliance, although the increased compliance by carotid occlusion was not statistically significant when it was compared against the first control. Vascular resistance was increased by hemorrhage and carotid artery occlusion but was not changed by i.v. infusion of epinephrine. The systemic arterial pressure was significantly increased by i.v. infusion of epinephrine and carotid artery occlusion but was decreased by hemorrhage. The rhythmic activity and after-kicks were generally diminished or abolished by i.v. infusion of epinephrine and hemorrhage but were not altered by carotid occlusion. Occasionally, spontaneous ileal motility appeared during the course of hemorrhage suggesting that some factors which stimulate the ileal motility were being activated.

Summary of Results

The direction of response of ileal motility, ileal wall tension and ileal vascular resistance which occured in all experiments is shown in Table 9. The direction of change in ileal wall tension was infered from a change in compliance. An increase in compliance was considered as indication of a decrease in ileal wall tension and a decrease in compliance, an increase in ileal wall tension. Epinephrine, $CaCl_2$, $MgCl_2$, phenoxybenzamine, propranolol, and hemorrhage inhibited ileal motility and decreased ileal wall tension. Acetylcholine, bradykinin, serotonin stimulated ileal motility and increased ileal wall tension. Potassium chloride at 0.07 mEq/min inhibited ileal motility and decreased ileal

Figure 21. Average effects of intravenous infusion of epinephrine (12 μg/min) on perfusion and ileal intraluminal pressures at various balloon volumes. SP is the mean systemic arterial pressure.

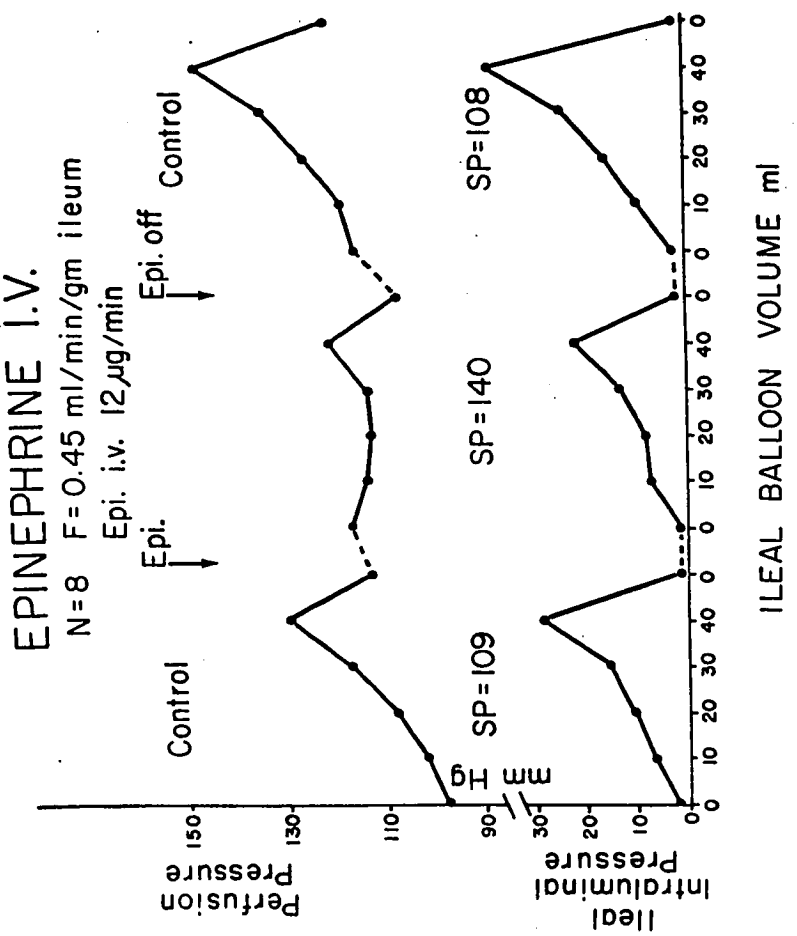


Figure 22. Average effects of hemorrhage (20-25 % of the calculated blood volume) on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

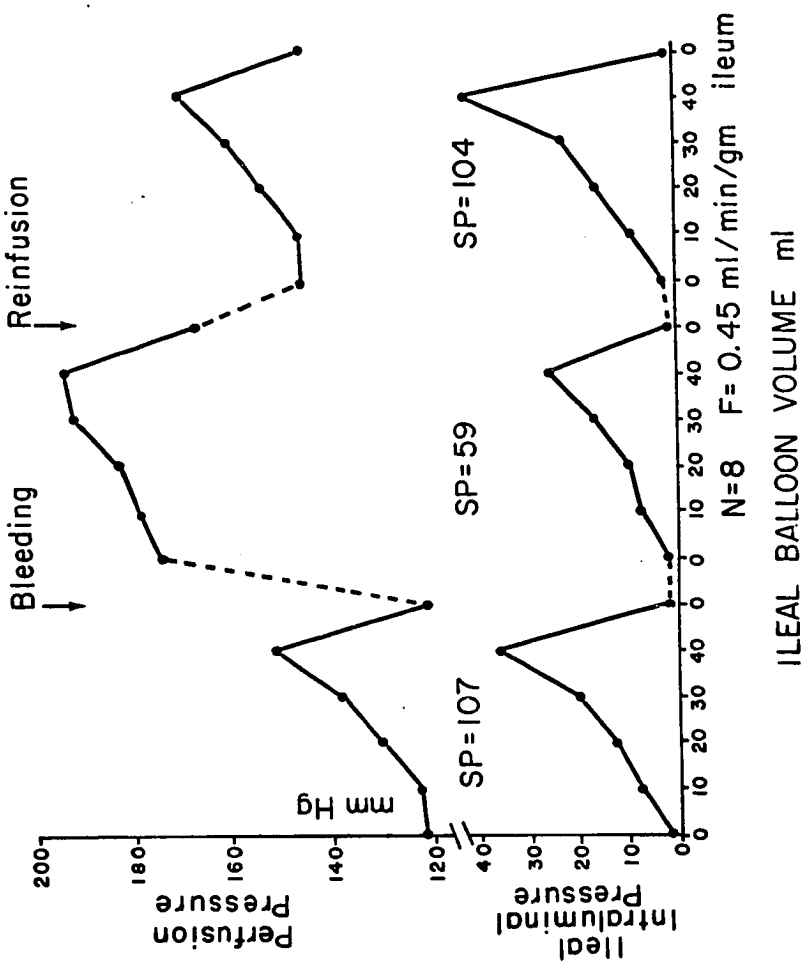


Figure 23. Average effects of bilateral carotid artery occlusion on perfusion pressure and ileal intraluminal pressure at various balloon volumes.

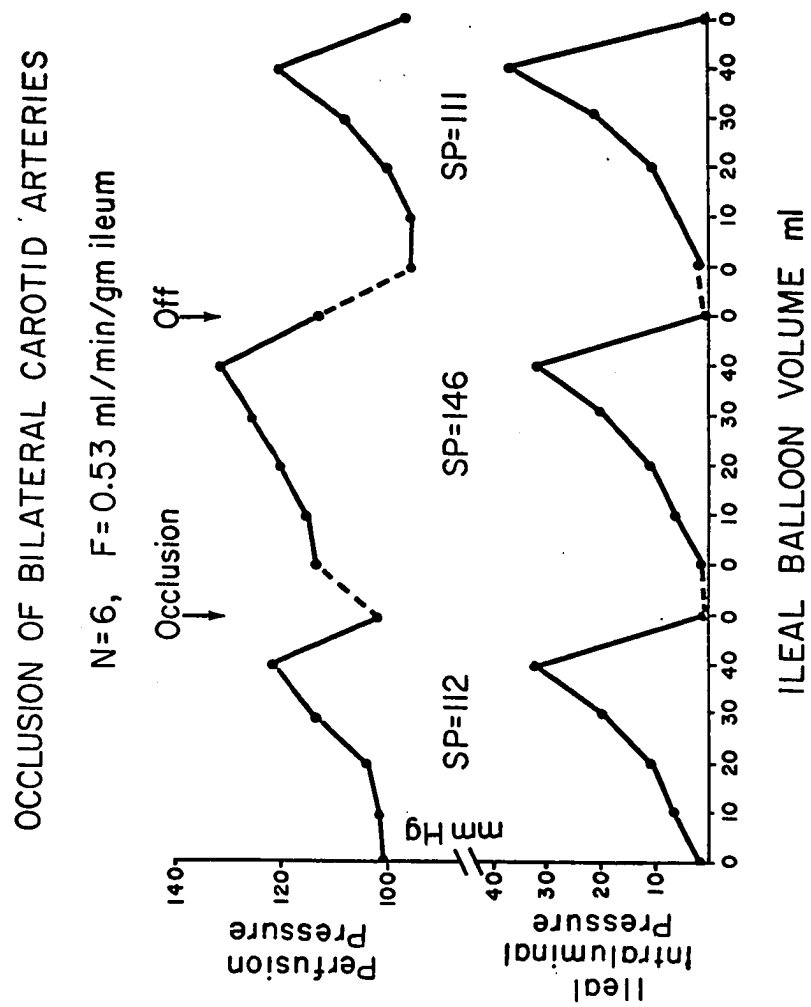


TABLE 8

AVERAGE EFEECTS OF I.V. INFUSION OF EPINEPHRINE, HEMORRHAGE AND BILATERAL COROTID ARTERY OCCLUSION ON ILEAL COMPLIANCE AND VASCULAR RESISTANCE

		Control 1	Exp.[b] (E)	Control 2	d = E - Control 1 d ± S.E.	d = E - Control 2 d ± S.E.
I.V. Epinephrine (12 μg/min)	Syst. Press.	109.0	140.4[a]	107.8[a]	+ 31.4 ± 5.9	+ 32.6 ± 6.1
	Compliance	1.54	1.99[a]	1.24[a]	+ 0.45 ± 0.11	+ 0.75 ± 0.20
	Resistance	8.77	8.95	8.84	+ 0.18 ± 1.24	+ 0.11 ± 0.50
Hemorrhage	Syst. Press.	106.8	59.0[a]	104.4[a]	- 47.8 ± 4.1	- 45.4 ± 4.1
	Compliance	1.30	1.81[a]	1.15[a]	+ 0.51 ± 0.15	+ 0.66 ± 0.18
	Resistance	9.11	13.03[a]	10.95[a]	+ 3.92 ± 0.85	+ 2.08 ± 0.87
Occlusion of Carotid Arteries	Syst. Press.	111.8	146.3[a]	111.3[a]	+ 34.5 ± 6.8	+ 35.0 ± 8.0
	Compliance	1.33	1.38	1.24[a]	+ 0.05 ± 0.10	+ 0.14 ± 0.05
	Resistance	7.94	8.86[a]	7.91[a]	+ 0.92 ± 0.25	+ 0.95 ± 0.33

[a] Denotes that the value is statistically significant at a p value less than 0.05 as compared with the preceding value.

Exp.[b] During the experimental procedure.

TABLE 9

SUMMARY OF THE STUDY

	Ileal Motility[a]	Ileal Wall Tension	Vascular Resistance
Local Effect			
Epinephrine	↓	↓	→
Acetylcholine	↑	↑	↓
Bradykinin	↑	↑	↓
Serotonin	↑	↑	→
Adenosine	↑	↑	↓
ATP	↑	→	↓
$CaCl_2$	↓	↓	→
$MgCl_2$	↓	↓	↓
KCl (0.02 mEq.)	→	→	↓
KCl (0.07 mEq.)	↓	↓	↓
KCl (0.18 mEq.)	↓	↑	↑
Phenoxybenzamine	↓	↓	↓
Propranolol	→	↓	↑
Systemic Effect			
I. V. Epinephrine	↓	↓	→
Hemorrhage	↓	↓	↑
Carotid Occlusion	→	↓or →	↑

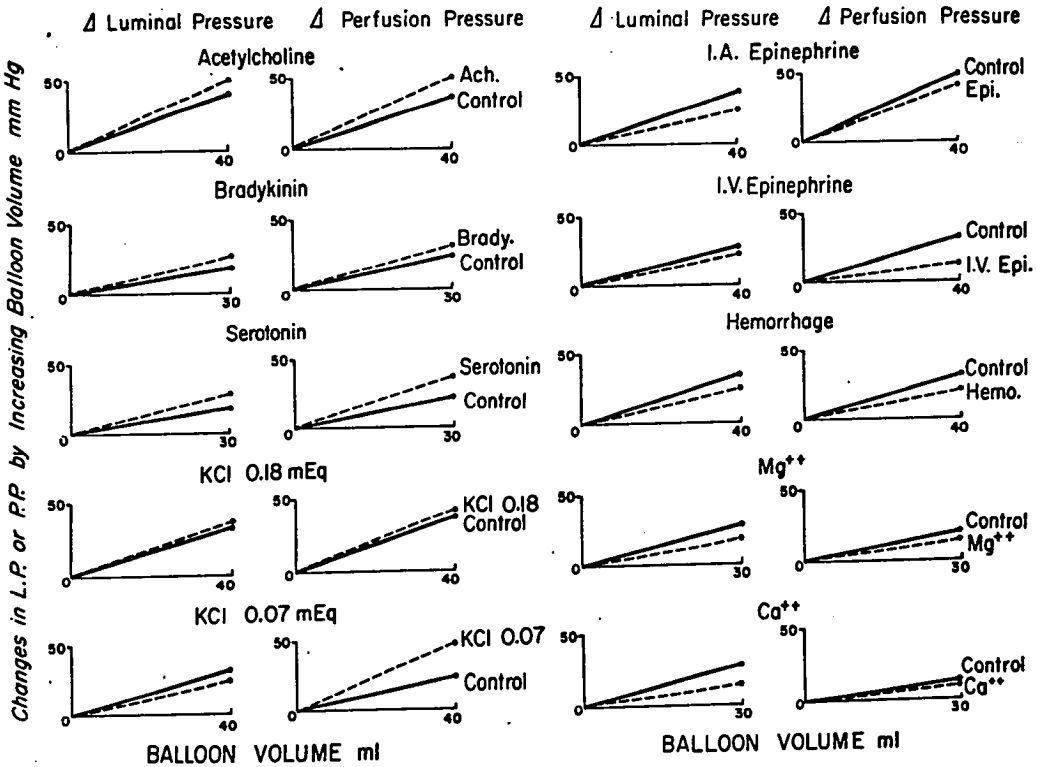
[a] The responses included spontaneous movements at zero balloon volume, rhythmic activity during the distension of balloon, and after-kicks. These changes occured during the infusion of all agents at the infusion rates shown in Table I, except ATP and adenosine. With these two agents, the change could be detected only by a single injection of 100 µg of either agent.

wall tension; at 0.18 mEq/min it inhibited ileal motility but increased ileal wall tension. Adenosine increased ileal wall tension but did not alter ileal motility unless it was infused at a very high concentration. ATP did not significantly alter ileal wall tension.

The responses of ileal smooth muscle and vascular smooth muscle to acetylcholine, bradykinin, adenosine, propranolol and hemorrhage were in opposite directions. The responses to KCl (0.07 mEq/min), $MgCl_2$, and phenoxybenzamine were in the same direction. Epinephrine, serotonin, and $CaCl_2$ at the infusion rates used had no effect on the vascular resistance.

Stretching the ileum increases the extravascular pressure on the intramural vessels and decreases vascular transmural pressure, an effect which tends to passively compress the vessels and increase vascular resistance. The effects of various procedures on this stretch-induced increment of vascular resistance are shown in Figure 24. When the ileum became less compliant, as a result of infusion of acetylcholine, bradykinin, serotonin or KCl (0.18 mEq/min), stretching the ileum produced a higher ileal luminal pressure and a higher perfusion pressure. On the other hand, when the ileum became more compliant as a result of infusion of epinephrine, $MgCl_2$, or $CaCl_2$ or during hemorrhage, stretching the ileum produced a lesser increment in ileal luminal and perfusion pressures.

Figure 24. Effects of various procedures on the stretch-induced increments in ileal luminal and perfusion pressures. The ordinates are the increments in luminal or perfusion pressures resulting from increases in balloon volume from 0 to 30 or 40 ml, i.e., the luminal or perfusion pressure at 30 or 40 ml balloon volume minus those pressures at 0 volume. In the left two columns are the agents which decrease compliance (excepting KCl 0.07 mEq.) and in the right two columns are the procedures or agents which increase compliance. Solid lines indicate preinfusion control values and dotted lines during the infusion of agents or during the procedure. The values are the mean of experiments.



CHAPTER IV

DISCUSSION

This study was designed to investigate the influence of ileal motility and compliance on ileal vascular resistance during various stimuli. The parameters used to calculate compliance and vascular resistnace were measured simultaneously. Thus, the discussion will include the effects of stimuli on ileal motility and compliance, the effects of stimuli on ileal vascular resistance and finally how ileal motility and compliance can influence vascular resistance.

The Pattern of Changes in Ileal Motility and Vascular Resistance during Compliance Measurements

This study shows that intestinal vascular resistance is markedly affected by intestinal motility and wall tension. The influence of the intestinal motility on ileal vascular resistance is well demonstrated during the period of "after-kicks" (Figure 2). Perfusion pressure followed rhythmic changes in the ileal luminal pressure from moment to moment. Since the blood flow was kept constant, changes in perfusion pressure represent changes in vascular resistance. The parallel changes in perfusion and luminal pressure suggest that the changes in resistance are secondary to ileal motility. Indeed, in the natural flow preparations, Sidky and Bean (1) have found fluctuations of blood flow, and thus vascular resistance, from one moment to another in accordance with

the variations in intraluminal pressure.

The influence of the contractile state of the intestinal smooth muscle on the vascular resistance is well demonstrated in Figure 3. Here, as the ileal compliance increased, i.e., as the ileum became less rigid, the vascular resistance decreased until, usually at the third stretching, the increment in compliance was not followed by a further decrease in vascular resistance.

From these data, it does not appear possible to quantitate exactly the influence of luminal pressure and compliance on the vascular resistance. Such a quantitation would be possible if extravascular and intravascular pressures could be determined simultaneously. An increase in visceral muscle tension can increase extravascular pressure. The measurement of compliance was done with the belief that compliance is a direct reflection of visceral muscle tension although it is not a direct measurement of that tension.

Occasionally a decrease in perfusion pressure during the measurement of compliance was observed. This finding is probably due to a rearrangement of the intramural vessels. The rearrangement may produce a decrease in gnarliness of intramural vessels, i.e., a decrease in the degree of contortion (11). A similar finding has been observed during the inflation of the rabbit lung (10, 11). Pulmonary vascular resistance falls as the lung is inflated to a volume of 125 ml. It then rises upon further inflation.

Intestinal movements induced by the filling of the lumen are of two types (12); a continuous rhythmic activity which remains localized, and an intermittent peristaltic contraction which travels along the intestine in an aboral direction. Trendelenburg (13) termed the latter the

"peristaltic reflex" and Bayliss and Starling (14) termed it the "peristaltic contraction". These rhythmic contractions and peristaltic reflex can be induced by increasing the luminal pressure by 1 to 2 cm H_2O. In the present study, ileal movements seen during the distension of the lumen were mostly that of rhythmic contractions and the contractions were seen mostly when the luminal pressure was about 10 to 20 mm Hg. Thus, there appears to be an optimum pressure for the induction of rhythmic contractions. While in this study the pressure was about 10 - 20 mm Hg, Gruber and DeNote (15) reported the optimum pressure to be 15 to 30 cm H_2O. They also showed that at luminal pressures below 5 or above 30 cm H_2O, rhythmic contractions decrease or disappear. The optimum pressure found by them is much lower than that found in this study. Their method, however, is quite different from that of the present study. They used a balloon 38 mm long and 20 mm in diameter to study the activity of a Thiry-Vella fistula in un-anesthetized dogs. The fistula was 20 to 30 cm long and both ends were open to the air. The present study used a balloon of 150 mm long and 30 mm in diameter to study the activity of a pump-perfused ileal segment in deeply anesthetized dogs. The segment was 10 to 15 cm long and both ends were tied. The observation made during the course of the present study indicates that the deepness of anesthesia (pentobarbital sodium) influences considerably ileal motility, the deeper the anesthesia, the quieter the ileal activity. Indeed, the animals were so deeply anesthetized that no spontaneous motility occured at zero balloon volume, even though luminal pressure ranged from 1 to 3 mm Hg during this period. Thus, the deepness and employment of anesthesia might account for the difference in the optimum pressure. Stretching of the ileal segment also, in some degree, inhibits its motility

and increases its compliance. Thus, by repeating the measurement of compliance, the present study might indeed increase the threshold to cause rhythmic contractions. Other factors, such as size of balloon and ileal segment and ileal preparations (15, 16) may also account for the difference.

The after-kicks which are induced by the withdrawal of water from the balloon appears to be a part of the peristaltic reflex. A similar spike-like fluctuation of the luminal pressure occurs during the emptying phase of the peristaltic reflex (16). Withdrawal of water from the balloon is mechanically equivalent to the process of emptying intestinal contents. Furthermore, epinephrine and other inhibitors of ileal motility abolished stretch-induced rhythmic contractions and also abolished after-kicks. Thus, the after-kicks seem to be a part of peristaltic reflex and to be triggered by the same mechanism which induces rhythmic contractions. The spike-like fluctuation of luminal pressure did not occur during the measurement of compliance, because the water in the balloon could not be expelled, i.e., no emptying phase of peristaltic reflex could occur.

Effect of Rate of Blood Flow

This study shows that acute and large changes in blood flow, to the ileum do not alter ileal compliance significantly. Rhythmic contractions and after-kicks, however, appear to be influenced by the supply of blood to the ileum, since during "no flow" they were increased and upon restarting perfusion they were diminished. Scott and Dabney (17) have reported that spontaneous ileal movement is usually increased during ischemia. Their intraluminal pressure was in the range of 10 to 20 mm Hg

which is the optimum pressure for the induction of rhythmic contractions. Similarly, in this present study, a potentiation of ileal movements occured during the measurement of compliance when the ileal luminal pressure was raised, but rarely occured at a zero balloon volume when the luminal pressure was below 5 mm Hg. This seems to indicate that rhythmic contractions depend not only on the chemical environment of the ileal smooth muscle, which is altered by ischemia, but also on the intraluminal pressure. Sensory receptors for the distension of the intestine and thus to the intraluminal pressure have been postulated and their nerve structure studied (18). These receptors seem to be located in the mucous membrane.

Since the ileal compliance during "no flow" was significantly greater than that during either "control 1" or "low flow", complete ischemia may cause a decrease in ileal wall tension at the same time that it causes an increase in the stretch-induced ileal motility. The findings are in accord with that found by Job et al. (19) who reported that anoxia increases the peristaltic reflex followed by a complete paralysis of the intestine. The mechanisms which are involved in the initiation of intestinal motility and which regulate the contractile state of intestinal muscle are different. The dissociation of the responses of ileal motility and compliance found during ischemia was also observed in other experiments. An infusion of 0.18 mEq/min KCl caused a decrease in compliance with an inhibition of ileal motility. Acetylcholine, occasionally, increased ileal motility at the same time it increased ileal compliance. Phenoxybenzamine blocked the epinephrine-induced compliance change but did not block epinephrine-induced inhibition of the motility. On the other hand, propranolol blocked the inhibitory effect of

epinephrine on motility but did not block the change in compliance produced by epinephrine.

The mechanism by which ischemia causes a change in intestinal tension and motility is not clear. Very few studies have been attempted to clarify the mechanism. Baez et al. (20) showed a substance in the portal vein blood of dogs after 4 hours ligation of the superior mesenteric artery, which inhibits the vascular response to epinephrine but contracts isolated rat gastric muscle. However, the mechanism appears to be more complicated and seems to involve the interaction of nervous, chemical and physical factors. The accumulation of endogenous metabolites, a decrease in pO_2, an increase in pCO_2 and possibly release of some unknown agents during ischemia may all be involved in this phenomenum. It is known that stimulation of the mesenteric afferent nerves produces a reflex intestinal vasoconstriction and reflex inhibition of intestinal motility with a decrease in intestinal luminal pressure (21). A very small amount of ATP decreases the tension of isolated taenia coli (22), but at a very high concentration, ATP and adenosine increase ileal motility, as shown in this present study. The effects of acetylcholine on the vascular and visceral smooth muscles are augmented by increasing local blood pCO_2 (2).

Although the mechanism involved in the responses of intestine to ischemia is not clear, the direction of responses appears to be a compensatory process. A decrease in intestinal wall tension tends to decrease its vascular resistance and an increase in rhythmic contractions tends to facilitate inflow and outflow of the blood through this organ. Both responses act in a direction which tends to improve the blood supply to this organ during ischemia.

As shown in Table 2 and 3, vascular resistance was increased by decreasing blood flow and decreased by increasing flow. These responses reflect the passive changes in the caliber of vessels resulting from a decrease or an increase in the intravascular pressure. The autoregulatory response in this vascular bed is operable over the pressure range 50 to 200 mm Hg (4). The mean perfusion pressure at "low flow" or "high flow" was 29 and 203 mm Hg respectively, which is beyond the range of autoregulation. When the interrupted blood supply is re-established, the initial vascular resistance is usually lowered than pre-occlusion resistance. This response is called reactive dilation (or reactive hyperemia). Scott and Dabney (17) could not regularly obtain this response because of an increment in ileal motility. In this present study, the response was seen in all experiments, perhaps because ileum was relatively quiet such that the vascular resistance was not affected by ileal motility.

Effects of Local Infusion of Various Vasoactive Substances

The ileum consists of three layers of smooth muscles and five nerve plexuses. The observed local effects of agents in this study are the sum of their effects on the muscle and nerve plexuses and it is impossible to differentiate their actions on the muscle and the nerve plexuses. Several studies have been done to elucidate the action of these agents on the longitudinal and circular muscle or on the nerve plexuses. The response of the longitudinal and circular muscles appear to be different (23). For example, bradykinin stimulates the longitudinal but not the circular muscle (23). Further, the response of the muscle and nerve plexuses are, in some cases, opposite in direction, e.g.,

serotonin stimulates the muscle but inhibits the nervous plexuses after a transient stimulation (18).

The changes in ileal compliance caused by vasoactive agents theoritically may be due, secondarily, to their effects on vascular smooth muscle, since ileal wall tension may be influenced by the wall tension of intramural vessels. This possibility is ruled out by the fact that a change in perfusion pressure from 10 to 200 mm Hg by changing blood flow rate does not alter ileal compliance (Figures 4 and 5). This degree of changes in perfusion pressure should have altered vascular wall tension significantly. Thus, the changes in ileal compliance seem to be due to their direct action on the ileal smooth muscle.

The effects of epinephrine on vascular and visceral smooth muscle are opposite in direction. Epinephrine at the infusion rate 0.2 μg/min increased compliance but did not alter vascular resistance. By calculation, using the formula: Δ blood concentration = infusion rate/blood flow rate, this infusion rate would increase local blood concentration of epinephrine by 0.013 μg/ml. The mean blood flow rate of the present study was 15.7 ml/min. This infusion rate is equivalent to 1.3 μg/min intra-arterial infusion of epinephrine to a constantly-perfused dog hindlimb where the mean blood flow is about 100 ml/min. From this writer's experience, an infusion of 1 μg/min epinephrine to dog hindlimb regularly produces an increase in local vascular resistance. The failure of epinephrine to produce a resistance increase in this study may be due to, a) a higher threshold or lower sensitivity of ileal vascular smooth muscle to epinephrine, or b) a lessening of the compressive effect of visceral smooth muscle on the intramural vessels. The first possibility is not likely. Injection of 0.5 μg epinephrine, as shown in Figure

7, clearly shows that the vascular response to epinephrine can be influenced by ileal movements and wall tension. Epinephrine causes a relaxation of the visceral smooth muscle and thus increases vascular transmural pressure which results in a passive decrease in vascular resistance.

In their classic papers, Dale (24), Rapport, Green and Page (25), and Rocha e Silva, Beraldo and Rosenfeld (26), show that acetylcholine, serotonin and bradykinin stimulate visceral smooth muscle and cause hypotension. All three agents markedly dilate small vessels of mesenteric vascular bed (3). This present study demonstrates that acetylcholine and bradykinin at the infusion rate used, decrease ileal compliance and vascular resistance. In the steady state, the vascular effect of serotonin at the infusion rate used appears to be masked by its stimulatory effect on the visceral muscle. At a high infusion rate, all three agents produced an increase in vascular resistance as a result of potent activation of the intestinal movements. Figure 7 clearly shows this effect. Thus, the intestinal vascular resistance can be raised during activation of intestinal motility even in the presence of potent vasodilators. Others have also reported this finding (2, 27, 28).

It is possible that the increases in vascular resistance produced by these three agents are due to local or systemic release of epinephrine and norepinephrine. However, the alpha adrenergic blocking agent, phenoxybenzamine which blocks the constrictor effect of the catecholamines, does not block a bradykinin-induced rise in intestinal vascular resistance (27). In reserpine-treated animals, a high concentration of acetylcholine still causes an increase in intestinal vascular resistance (28). It is also possible that at higher concentrations these three agents may actually produce a vasoconstriction in the intestine.

This possibility is not likely. These three agents, at higher infusion rates, usually produce an initial fall followed by a rise in perfusion pressure. Further, the subsequent rise in perfusion pressure always occurs after or concurrently with a rise in ileal luminal pressure and an increase in ileal motility. It seems, therefore, that the increased intestinal vascular resistance caused by these three agents results indirectly through their effect on visceral smooth muscle.

ATP is a vasodilator in the dog forelimb, kidney and ileum, and adenosine is a dilator in the forelimb and ileum and a constrictor in the kidney (4, 29). Their effects on intestinal smooth muscle have not been reported. This study shows that ATP and adenosine are vasodilators in the ileal vascular bed. Both agents appeared to increase ileal muscle tension and ileal motility at very high infusion rates. However, the changes produced at 10 μg/min were very small. At this infusion rate, ATP did not alter either motility or compliance, whereas, adenosine decreased compliance without altering motility. Bueding and Bülbring (22) find an inhibitory effect of ATP on the isolated taenia coli when a very small amount of ATP is added to the bath. The difference may be explained in four ways: a) a difference in technique, i.e., in vivo vs in vitro, b) a difference in concentration, c) a difference in tissue studied, i.e., a segment of dog ileum vs guinea pig taenia coli, and d) a difference in innervation, i.e., an absence of nerve tissue in the taenia coli preparation.

Calcium, magnesium or potassium ions at 0.07 mEq/min increase compliance, whereas K^+ at a higher infusion rate (0.18 mEq/min) decreases compliance. These findings are in accord with that found by Ambache (30). In the isolated mammalian ileum, calcium, magnesium and

low concentration of KCl inhibit whereas KCl at high concentration stimulates ileal motility (30).

The local vascular effects of these ions are known in various regional vascular beds. Magnesium ion and potassium ions in low concentration generally dilate the vessels of the forelimb (31), kidney (32), heart (33), ileum (4) small intestine and stomach (5) in dogs. The calcium ion raises the vascular resistance in all of these organs except the stomach. In this organ, the vascular resistance declines proportionally as the dosage is increased over the range from 0.1 to 1.1 mEq/min. The action of K^+ has been found to depend upon the concentration (32,33). A dilatation occurs when the plasma concentration of K^+ is raised over the range 4 - 9 mEq/ml, and a constriction occurs when the plasma concentration is further increased. The vascular effect of K^+ and Mg^{++} observed in the present study is in accord with that found in other vascular beds.

In this present study, Ca^{++} did not alter vascular resistance. It is possible that (a) Ca^{++}, at the infusion rate used, has no effect on the ileal vascular smooth muscle, or (b) that the vascular effect was masked by its relaxing effect on the ileal wall. The effect of Ca^{++} mimics that of epinephrine. A decrease in vascular resistance during relaxing effect on the gastric smooth muscle. Similarly, the reason Mg^{++} is relatively more potent vasodilator in the mesenteric vascular bed than in other vascular beds (5) may be also due to its relaxing effect on the intestinal smooth muscle.

Parallel changes in perfusion pressure and intraluminal pressure at various dosages of K^+ (Figure 18) indicate that the vascular and vis-

ceral actions of K^+ are qualitatively the same, i.e., potassium ion has a biphasic action on both types of muscle. Furthermore, these actions are always in the same direction and therefore always additive. From the present study alone, it is not clear whether the biphasic (initial fall in resistance followed by a rise in resistance) effect of infusion of 1 ml/min KCl is due to active dilation and subsequent constriction of the vasculature or to relaxation and subsequent contraction of intestinal wall. Atropine sulfate simultaneously blocks the potassium-induced vasoconstriction and increase in ileal motility (4). However, in the kidney which contains no extra-vascular muscle, K^+ also has a biphasic effect (32). Further, in an isolated segment of artery, a high concentration of K^+ produces constriction (34). It seems, therefore, that the vascular effects of K^+ found in this study are not entirely secondary to actions on the visceral muscle. A rise in intraluminal pressure without fluctuation during infusion of 1 or 2 ml/min KCl indicates that under this circumstance the ileal muscle is in sustained contraction. Vogt (35) also found in the isolated intestine, that larger concentration of KCl produce a powerful contraction without accompanying rhythmic movements.

The mechanisms by which epinephrine acts on the vascular and intestinal muscle and by which phenoxybenzamine or propranolol blocks the effects of epinephrine are not well understood. Epinephrine produces many effects in the body, e.g., a vascular constriction in the kidneys, a vasodilation in the heart, a cardiac muscle stimulation, an intestinal muscle inhibition, glycogenolysis and free fatty acid mobilization, etc. These actions have been classified into two groups according to the relative potency ratio of catecholamines (36). Another classification is

based on the response in the presence of blocking agents (55). Ahlquist (36) is the first to use the terms "alpha" and "beta" receptors to distinguish these two types of responses. His classification is based on the relative potency ratio of catecholamines. Alpha receptor mediates the responses for which the relative potencies of the three most used catecholamines are: epinephrine > norepinephrine > isoproterenol. Beta receptor mediates responses for which the relative potencies are: isoproterenol > epinephrine > norepinephrine (55). It should be made clear here that the term "receptor" does not denote anatomical structure. It denotes the reaction, similar to that occurs in enzyme-substrate complex, which involves or initiates the actions of catecholamines. There are also two groups of adrenergic receptor blocking agents. One of them blocks only the alpha receptor and the other blocks only the beta receptor. The alpha blocking agents are phenoxybenzamine, phentolamine and dihydroergotamine. The beta blocking agents are dihydrochloroisoproterenol, propranolol, and pronethalol (55).

In a classic paper, Ahlquist (36) classified the inhibitory response of the intestine to catecholamines as the alpha type. Recently Ahlquist and Levy (37) and Furchgott (38) showed that both alpha and beta adrenergic receptors are present in the small intestine. Rossum (39), however, has reported that the intestinal effect of the sympathomimetic drugs concerns only on the alpha receptor, although both receptors may be present in the intestine. The present study indicates that the mechanism in ileal muscle associated with changes in compliance is of the alpha type while ileal movements resulting from stretching are related to beta mechanism. This is suggested because the inhibitory

effect of epinephrine on ileal compliance was blocked by phenoxybenzamine but not by propranolol and also because the effect of epinephrine on ileal movements was blocked by propranolol but not by phenoxybenzamine. The dissociation of the effects of epinephrine on stretch-induced ileal movements from its effect on compliance may be explained by the possibility that reflex ileal movements involve not only ileal smooth muscle but also intrinsic neural plexuses.

The effect of phenoxybenzamine on ileal compliance and motility was found to mimic that of epinephrine. It inhibited ileal motility and increased compliance. It is, therefore, possible that the ileal smooth muscle is relaxed to a maximum state by phenoxybenzamine such that no further relaxation can be achieved with epinephrine. However, in some experiments in which ileal motility was not inhibited by phenoxybenzamine, epinephrine, in the presence of phenoxybenzamine, did inhibit ileal motility but did not increase compliance. The vascular effect of epinephrine was significantly altered by phenoxybenzamine. Although propranolol increased ileal compliance, it did not alter motility nor block the effect of epinephrine on the ileal compliance. It is possible that the dosage of propranolol used was not enough to block the effect of epinephrine on ileal compliance, even though it was sufficient to influence its effect on the vascular smooth muscle and on the reflex arc which initiates ileal motility upon stretching the ileum.

Several papers in the literature purport to delineate the site of aplha and beta receptors in the small intestine. Kosterlitz and Watt (40) suggested that in longitudinal muscle of the ileum, alpha receptors are situated in the neurones innervating the longitudinal muscle and beta receptors in the muscle itself. Wilson (41) also reported that

beta receptors are present in the longitudinal smooth muscle. In the circular muscle, the inhibitory action of epinephrine seems to be of the alpha type and the receptor is said to be located at the post-ganglionic neuro-effector junctions (42). It is also postulated that no beta receptor is present in the circular muscle since the inhibitory action of epinephrine is not blocked by dichloroisoproterenol (42). McDougal and West (43) reported that the inhibitory effect of epinephrine on the peristaltic reflex of longitudinal muscle in guinea pig ileum is of the alpha type and the receptor may be located in the parasympathetic ganglia.

Visual inspection of the change in shape and size of the ileum during the measurement of compliance indicates that both circular and longitudinal muscles are stretched. However, if the alpha receptor is present in only the circular muscle and the beta receptor in only the longitudinal muscle, as suggested by others (40, 41, 42), and if the effect of epinephrine on ileal compliance is blocked by the alpha adrenergic blocking agent but not by the beta blocking agent, as shown by this present study, then the ileal compliance of this study seems to reflect mostly the contractile state of circular muscle.

Some other investigators, disregarding the presence of alpha and beta receptor, suggest that the inhibitory effect of epinephrine is mediated by the effect of epinephrine on the metabolic rate. This hypothesis (44) implies that every observed response of smooth muscle to epinephrine has to be regarded as the result of two opposing actions: the direct action on the membrane permeability and the metabolic effect which leads to a stabilization of the membrane potnetial. The intestinal smooth muscle membrane is very unstable. Procedures which increase metabolic rate, such as epinephrine or a rise of temperature, stabilize the mem-

brane potential at a high resting value. Agents which inhibit metabolic rate such as dinitrophenol and iodoacetate reverse or abolish the inhibitory action of epinephrine. If this theory is true, the blocking effect of phenoxybenzamine and propranolol may be also via metabolic pathways.

Effects of I.V. Infusion of Epinephrine, Hemorrhage, and Bilateral Carotid Artery Occlusion

Carotid sinus and aortic reflexes play an important role in the homeostatic regulation of arterial blood pressure by influencing the activities of the autonomic nervous system and adrenal glands. The present study demonstrates that the same mechanism is also involved in the regulation of intestinal motility and intestinal wall tension. Hemorrhage, intravenous infusion of epinephrine, and in lesser degree, bilateral carotid artery occlusion all increase ileal compliance and inhibit spontaneous ileal movements and the peristaltic reflex. The relatively small increase in ileal compliance and vascular resistance produced by carotid occlusion may be due to an effective collateral blood supply (mainly via vertebral arteries) to the carotid sinuses that is usually present in dogs. Others have reported that a fall of pressure in the carotid sinus produces a mesenteric vasoconstriction, gastric atonia, and decrease in intestinal movement (45).

Reports concerning the effect of hemorrhage on small intestinal motility are contradictory. Necheles *et al*. (46) stated that while ileal motility is not altered by hemorrhage, gastric and upper small intestinal motility decrease and the colon motility increases. Other investigators found a decrease in small intestinal (47) and duodenal (48) motility when 20 - 30 % of the blood volume is removed. At a systemic blood pressure of approximately 40 mm Hg, the motility is completely abolished

and upon reinfusion of the lost blood volume, the motility returns to the control (47, 48). On the other hand, Van Liere et al. (49) reported that hemorrhage (3 % of body weight) produces an increase in propulsive force of the small intestine. Thus, hemorrhage seems predominantly to stimulate parasympathetic system of the intestine, although in lesser degree the sympathetic system may be also affected. This possibility was further studied later by the same group of investigators by pretreating dogs with cocaine, an epinephrine-potentiating agent, before hemorrhage (50). In dogs so treated, hemorrhage causes a decrease in propulsive force of the small intestine.

The sympathico-adrenal system is activated during the hemorrhage. Epinephrine and norepinephrine can produce an intestinal vasoconstriction and an inhibition of intestinal wall tension and motility. In adrenalectomized dogs, hemorrhage produces no, or minimal reduction in duodenal tension or peristalsis (48). It is not clear to what degree the parasympathetic nervous system is involved in the responses of the small intestine to hemorrhage (49). In addition to the autonomic nervous system and adrenal glands, other endogenous agents, such as angiotensin, vasopressin, tissue hormones and metabolites may be released locally or into the general circulation and may affect intestinal motility and vascular resistance during hemorrhage. Both angiotensin and vasopressin are potent vasoconstrictors in the small intestine (3). Angiotensin contracts isolated intestinal segment in vitro, but this effect is not easy to detect in vivo (51). Intravenous injection of vasopressin abolishes small intestinal movement in dogs (52). In man, vasopressin causes an inhibition of the small intestine but a stimulation of colon movement (53), a finding which is very similar to that

found during hemorrhage in dogs (46). Thus, it is possible that there are factors, in addition to the autonomic nervous system and circulating catecholamines, which participate in the intestinal and vascular responses to hemorrhage.

A few preliminary experiments were done during the course of this present study to test for the presence of agents other than catecholamines. In these experiments, hemorrhage was produced after pretreatment with phenoxybenzamine. The effect of hemorrhage was studied on either an innervated or completely denervated ileal preparation. While vascular and ileal responses to locally infused epinephrine or norepinephrine were blocked by phenoxybenzamine, hemorrhage induced increases in compliance and resistance that were not blocked by either phenoxybenzamine or complete denervation of the segment. These preliminary studies suggest that circulating substances other than catecholamines may indeed be involved in the responses of intestinal and vascular smooth muscles to hemorrhage.

One of the homeostatic responses to hemorrhage is mobilization of blood volume from the splanchnic vascular bed into the systemic circulation. During hemorrhage, the vascular resistance in this vascular bed is markedly raised and the splanchnic organs are underperfused. A decrease in intestinal wall tension, as shown in this study would passively increase vessel caliber and thus improve the perfusion of intestine. How effective this compensation operates during hemorrhage is not clear.

The observation of Selkurt *et al.* (54) seems to indicate that pooling of blood in the mesenteric vascular bed can occur during a prolonged hemorrhagic hypotension in dogs. This pooling of blood would decrease the systemic venous return, thus, further aggravate hypotension.

An increase in intestinal wall compliance during hemorrhage, as shown in this present study might augment this pooling by increasing the caliber of small veins. Since portal vein pressure is elevated during a prolonged hemorrhagic hypotension, capillary hydrostatic pressure would also rise. An increase in compliance can cause a decrease in tissue pressure. Thus, effective capillary filtration would increase, contributing further to a loss of circulating blood volume. To some degree, this pooling may be attenuated by an increased intestinal motility that often results during underperfusion of the intestine. Obviously, the compensatory responses to hypotension are complicated and in the intestine the extravascular determinant of transmural pressure and fluid exchange may be critically involved.

General Discussion

This study demonstrates that intestinal wall compliance and motility can affect vascular resistance of the intestine in the following manner. Perfusion pressure and thus vascular resistance fluctuates concurrently with ileal rhythmic contraction and peristalsis (Figures 2, 7, and 18). When the intestine contracts the vascular resistance rises; when the intestine relaxes the resistance falls. The vascular resistance is also influenced by intestinal compliance. As the intestine becomes more compliant, the vascular resistance falls (Figure 3). Stretching the intestinal wall by increasing the volume of the segment increases local vascular resistance. The degree of increment in resistance is related to the wall tension then existing in the segment. When the intestine becomes more compliant, as the result of infusing epinephrine etc., the stretch-induced incrment in vascular

resistance is less than the increment during the control stretching (Figure 24). In contrast, the increment in vascular resistance is greater than the control during the infusion of agents which decrease compliance.

Concurrent measurements of intestinal vascular resistance and intestinal wall compliance shows the qualitative and simultaneous effects of various stimuli on both the vascular and visceral smooth muscle. A contraction of the visceral muscle produces an increase in intestinal wall tension which in turn decreases vascular transmural pressure and, therefore, passively decreases the caliber of intramural vessels. If the agent being tested has opposite effects on visceral and vascular smooth muscle, its vasoactive potency may be underestimated because the vascular effect is masked or attenuated by its visceral effect. All agents tested except phenoxybenzamine, KCl and $MgCl_2$, have opposite effects on visceral and vascular muscle. Direct vascular effects of epinephrine, $CaCl_2$ and serotonin are masked by their effects on the visceral muscle to such a degree that these three agents do not alter significantly the intestinal vascular resistance. Phenoxybenzamine, KCl, and $MgCl_2$, affect visceral and vascular muscle in the same direction, their vascular effects may be potentiated and vasoactive potency over-estimated.

The measurement of compliance is a more sensitive indicator of the intestinal wall tension than is the estimation of wall tension from absolute intraluminal pressure. This is shown by the fact that even though the luminal pressure at zero balloon volume was not altered during most experimental procedures the compliance usually was changed significantly. For example, an infusion of $CaCl_2$ did not lower luminal pressure

at zero balloon volume but significantly increased compliance (Figure 14). Qualitatively, the results of this study are in accord with those of others who use different techniques to measure intestinal tension and motility. This confirms the validity of the method used in this study. The method further provides a way to study the effects of various stimuli on spontaneous as well as reflex-induced intestinal movements. Some investigators regard either intestinal wall tension or motility as a reliable indicator of intestinal smooth muscle action. For example, from an increase in intestinal motility, it is infered that wall tension is also increased. Indeed, in this present study, when wall tension and motility were affected by an experimental procedure, they usually responded in the same direction. (Table 9). However, some experiments in this present study show that these two parameters do not follow each other. The dissociation of the responses of these two parameters have been observed during the infusion of 0.18 mEq/min KCl, during ischemia, and occasionally during the infusion of 10 μg/min acetylcholine. The blocking actions of phenoxybenzamine and propranolol on the inhibitory effects of epinephrine on these two parameters were not effective on both parameters but only on one of them.

Thus, from the above, it can be seen that the design of this study has distinct advantages over previous attempts to investigate the property of visceral and vascular smooth muscle in the intestine. These advantages are: (1) it is an <u>in vivo</u> approach, (2) a simultaneous measurement of intestinal wall tension, intestinal motility, and vascular resistance can be made, and (3) compliance is much more sensitive measure of the level of intestinal wall tension than is intraluminal pressure.

CHAPTER V

SUMMARY AND CONCLUSIONS

Blood flow through an organ is regulated by active and passive changes in vascular caliber when the systemic arterial pressure and viscosity are constant. While active changes in vessel caliber have been widely studied, the passive changes have not been thoroughly investigated. Since the blood vessels of the intestinal wall are encased by visceral smooth muscle that can impart both a continuous and a rhythmic compression, passive changes in vascular caliber may be functionally important in the regulation of blood flow through this organ.

This study was designed to elucidate the relationship of ileal wall tension and ileal motility in the regulation of ileal vascular caliber hence resistance. Ileal compliance and motility were measured to clarify the response of ileal smooth muscle to various stimuli. Perfusion pressure at constant blood flow allowed the calculation of total vascular resistance. The experiments included alteration of local blood flow rate, local and systemic infusion of vasoactive agents, hemorrhage, and bilateral carotid artery occlusion.

Ileal compliance and vascular resistance were measured simultaneously in a pump perfused, in situ ileal segment of dogs before, during and after various experimental procedures. Compliance was calculated by dividing the changes in the ileal luminal volume by changes in the

ileal luminal pressure. The aortic and perfusion pressures were constantly recorded.

An acute change in blood flow over the range 0.14 to 1.21 ml/min/gm ileum did not alter compliance. Complete ischemia appeared to increase ileal compliance and motility. While vascular resistance was not altered by decreasing blood flow, it was decreased by increasing flow to 1.21 ml/min/gm ileum. A reactive dilation after a period of no flow was also observed.

Ileal compliance was increased by local infusion of epinephrine (0.2 μg/min), $CaCl_2$ (0.12 mEq/min), $MgCl_2$ (0.12 mEq/min), KCl (0.07 mEq/min), phenoxybenzamine (0.3 mg/Kg in 10 min) and propranolol (30 μg/Kg in 10 min) (these dosages were sufficient to block the vascular effect of epinephrine and isoproterenol). Ileal compliance was also increased during intravenous infusion of epinephrine (12 μg/min), hemorrhage (20-25 % of calculated total blood volume), and bilateral carotid artery occlusion. It was decreased by the local infusion of acetylcholine (4 μg/min), bradykinin (0.1 μg/min), serotonin (2 μg/min), adenosine (10 μg/min), and KCl (0.18 mEq/min). It was not altered during the local infusion of ATP (10 μg/min) and KCl (0.02 mEq/min).

Ileal vascular resistance was increased during local infusion of KCl (0.18 mEq/min) or propranolol (30 μg/Kg in 10 min) and during hemorrhage or carotid artery occlusion, but decreased during local infusion of acetylcholine (4 μg/min), bradykinin (0.1 μg/min), adenosine (10 μg/min), ATP (10 μg/min), $MgCl_2$ (0.12 mEq/min), phenoxybenzamine (0.3 mg/Kg in 10 min) and KCl (0.02 and 0.07 mEq/min). It was not altered during i.a. (0.2 μg/min) or i.v. (12 μg/min) infusion of epineprhine, i.a. infusion of serotonin (2 μg/min) or i.a. infusion of

$CaCl_2$ (0.12 mEq/min). The lack of vascular effects of these three agents appeared to be due to their effects on visceral muscle. Depending on the ileal motility, a single injection of 0.5 μg epinephrine caused either an increase or a decrease in vascular resistance.

These findings indicate that:

1) Intestinal vascular resistance and thus the blood flow through this organ can be altered by passive changes in vessel caliber subsequent to changes in intestinal wall tension and motility. An increase in the intestinal wall tension or motility passively decreases vessel caliber. A decrease in the intestinal wall tension or motility increases vessel caliber.

2) Since the visceral smooth muscle is sensitive to various chemical and nervous stimuli, as is the vascular smooth muscle, and since the responses of these two types of muscle may be either in the same or in the opposite direction to the same stimulus, the total effect of a given stimulus on vascular resistance may be augmented or attenuated by the response of the visceral smooth muscle.

3) Phenoxybenzamine, an alpha adrenergic blocking agent, blocks the effect of epinephrine on compliance but does not block its inhibitory effect on motility. Propranolol, a beta adrenergic blocking agent, blocks the inhibitory effect of epinephrine on motility but does not block its effect on compliance.

4) Intestinal compliance appears to be a more sensitive indicator of intestinal wall tension than is luminal pressure. While an agent which increases intestinal wall tension generally increases motility, wall tension and motility do not always change in the same

direction.

5) Intestinal wall tension and motility may functionally participate in the regulation of the blood flow through intestine during either physiological or pathological conditions, such as during hemorrhage.

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