Interrelation of Ileal Wall Compliance and Vascular Resistance

CHING-CHUNG CHOU, M.D., PH.D.,* and J. M. DABNEY, PH.D.*

STRONG CONTRACTIONS of the intestine decrease the inflow of blood and a lessening of intestinal wall tension augments intestinal blood flow.[1, 2] Since many vasoactive substances also affect intestinal wall tension, their direct vascular effect can be modified by their effects on intestinal wall tension. For example, it appears that the vasodilator effect of acetylcholine,[3, 4] serotonin,[3] or plasma kinins[5] on the intestinal vasculature is attenuated or reversed by a concurrent action of these substances on intestinal smooth muscle.

In these previous studies, intestinal wall tension was inferred from changes in intestinal luminal pressure; but luminal pressure alone is unsatisfactory for the estimation of changes of intestinal wall tension.[6] We reported previously a method for the measurement of intestinal wall compliance with evidence to indicate that compliance is a better index of intestinal wall tension than is luminal pressure.[6] Using this method, an increase in compliance indicates a decrease in wall tension and a decrease in compliance indicates an increase in tension. The method takes into account the geometric factor of tension and can reveal changes in wall tension that are not revealed by any change in luminal pressure. Furthermore, the procedure used for the measurement of compliance allows for a simultaneous determination of intestinal vascular resistance.

Complete deprivation of blood flow to the intestine has been shown to increase intestinal motility with a rise in intestinal lumen pressure.[3, 7] Thus, intestinal wall tension may be affected by its blood flow.

In view of the interrelation of intestinal blood flow and intestinal motility, and since vasoactive agents may affect both of these, we studied in the anesthetized dog: (1) the effect of changes of local blood flow on ileal wall compliance, and (2) the effects of epinephrine, acetylcholine, bradykinin, serotonin, adenosine, and ATP on ileal vascular resistance and ileal wall compliance at dosages which did not cause changes in ileal intraluminal pressure.

METHODS

The technic has been described in detail in a previous communication.[6] The study was performed in 40 mongrel dogs, anesthetized with pentobarbital

From the Department of Physiology, Michigan State University, East Lansing, Mich., and the University of Oklahoma Medical School, Oklahoma City, Okla.

*Present address: Department of Physiology, Michigan State University, East Lansing, Mich.

sodium (30 mg./kg. body weight) and anticoagulated with heparin sodium (6 mg./kg. body weight). A segment of the ileum was perfused at a constant blood flow by interposing a pump between a femoral artery and the artery perfusing the segment. Systemic arterial pressure, perfusion pressure, and ileal intraluminal pressure were recorded with Statham pressure transducers and a direct writing oscillograph. Vascular resistance was calculated by dividing the perfusion pressure at zero balloon volume by the blood flow. Ileal volume was increased in steps from 0 to 40 ml. by infusing water (37° C.) into the balloon inside the ileum, and ileal luminal pressure was measured at each step. Ileal compliance was calculated by dividing the change in luminal volume by the change in luminal pressure ($C = \Delta V/\Delta P$). All experiments were performed after vascular resistance and ileal compliance were in steady states.[6]

The effect of blood flow on ileal compliance and vascular resistance was studied by lowering or raising the output of a perfusion pump. In 6 animals the sequence of flow change was as follows:

1. Blood flow was adjusted so that perfusion pressure equaled aortic pressure (control flow).
2. Blood flow was then reduced to about one-fifth of the control flow (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 slowly rising toward control (reactive dilation).
5. Control flow.
6. Flow was increased to about twice the control (high flow).
7. Control flow.

In 4 dogs the sequence was reversed, i.e., first high flow, followed by low flow. Ileal compliance was measured at each step (except reactive dilation) when perfusion and ileal intraluminal pressure were steady. Each step lasted for 5–7 min.

Ileal compliance was also measured before, during, and after stopping the intra-arterial infusion of each of the following agents dissolved in 0.9% NaCl solution: epinephrine (0.2 μg./min.), acetycholine (4 μg./min.), bradykinin (0.1 μg./min.), serotonin (2 μg./min.), adenosine (10 μg./min.), or adenosine-5-triphosphate (ATP, 10 μg./min.). Each agent was infused upstream to the perfusion pump with an Harvard infusion pump* and was tested in 10 animals.

RESULTS

Effects of Changing Local Blood Flow

The effects of altering ileal blood flow for periods of 5–7 min. are shown in Fig. 1 and 2. Lowering the flow from a control value of 0.67 to 0.14 ml./min./gm., stopping flow, or raising it to 1.21 ml./min./gm. produced no sig-

*Harvard Apparatus Co., Dover, Mass.

nificant change from control values in luminal pressure at any luminal volume. Thus, compliance was not significantly altered by these maneuvers. Perfusion pressure fell or rose as the blood flow was decreased or increased. Vascular resistance was decreased during reactive dilation and during high flow. Calculated values for compliance and vascular resistance are shown in Table 1.

Effects of the Local Infusion of Vasoactive Agents

The effects of intra-arterial infusion of epinephrine, acetylcholine, bradykinin, serotonin, adenosine, and ATP are shown in Tables 2 and 3. Epinephrine (0.2 μg./min.) increased ileal compliance but did not significantly alter vascular resistance. Acetylcholine (4 μg./min.), bradykinin (0.1 μg./min.), ATP (10 μg./min.), and adenosine (10 μg./min.) decreased compliance and vascular resistance. Serotonin (2 μg./min.) decreased compliance but did not significantly alter vascular resistance. An increase in compliance by epinephrine or a decrease in compliance by bradykinin and serotonin are shown in Fig. 3–5 as a decrease or increase in the slope of luminal pressure-volume

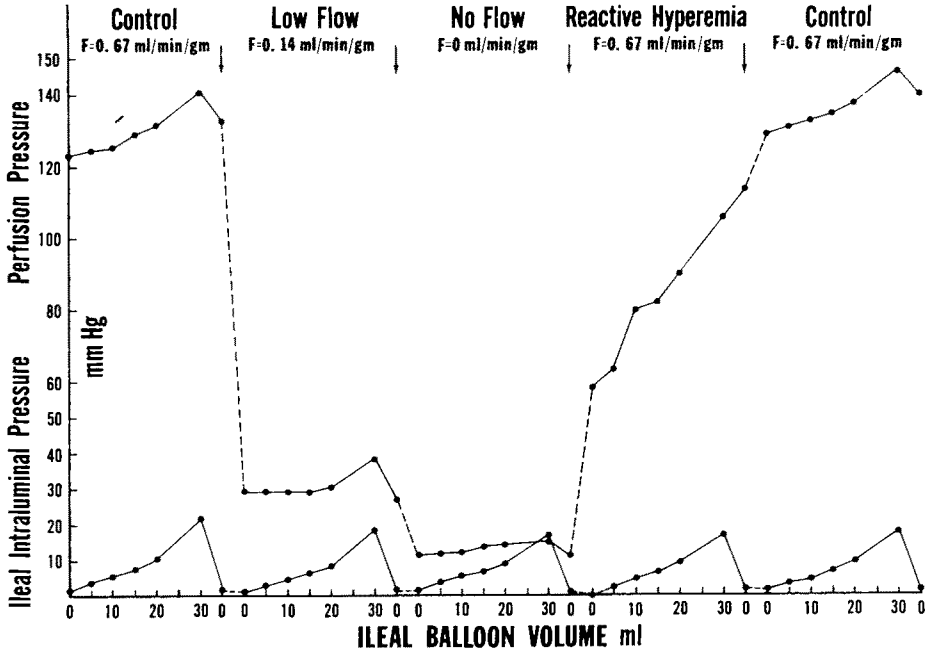

Fig. 1. Average effects of decreasing local blood flow (*F*) on ileal perfusion pressure and intraluminal pressure at various ileal balloon volumes. Arrows indicate point where blood flow is changed; dotted lines, changes of pressures which occurred when ileal volumes were zero. ($N = 10$)

curves. At the same ileal volume, the luminal pressures during the infusion of epinephrine were lower, and pressures during bradykinin or serotonin were higher than during the control periods. However, the ileal intraluminal pressure at zero balloon volume (dotted lines) was not significantly altered by these agents even though significant changes in ileal wall compliance were observed. The effects of acetylcholine, ATP, or adenosine on perfusion and ileal intraluminal pressures at different balloon volumes were similar to those of bradykinin.

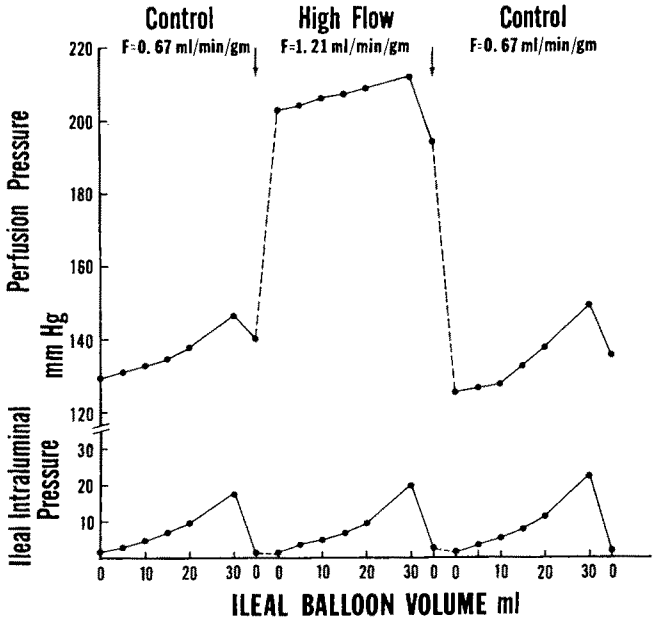

Fig. 2. Average effects of increasing local blood flow (F) on ileal perfusion pressure and intraluminal pressure at various ileal balloon volumes. ($N = 10$)

TABLE 1. AVERAGE EFFECTS OF CHANGING BLOOD FLOW ON COMPLIANCE AND RESISTANCE ($n = 10$)

	Sequence of blood flow							
Variable	*Control*	*Low*	*No*	*Reactive dilation*	*Control*	*Control*	*High*	*Control*
Blood flow (ml./min./gm.)	0.67	0.14	0	0.67	0.67	0.67	1.21	0.67
Compliance (ml./mm. Hg)	2.06	2.14	2.38	2.16	2.26	2.33	2.10	1.96
Resistance (mm. Hg/ml./min.)	7.41	8.73	—	3.49*	7.63*	7.79	6.81*	7.52*

*Statistically significant at $p < 0.05$ as compared with preceding value.

TABLE 2. LOCAL EFFECTS OF VARIOUS AGENTS ON MEAN ILEAL COMPLIANCE

	Ileal compliance				
Agent	*Control 1*	*During infusion (E)*	*Control 2*	d_1* *(Mean ± S.E.)*	d_2† *(Mean ± S.E.)*
Epinephrine	0.88	2.15	1.24	+ 1.27 ± 0.28	+ 0.91 ± 0.22
Acetylcholine	1.13	0.93	1.01	− 0.20 ± 0.05	− 0.08 ± 0.03
Bradykinin	1.42	1.05	1.41	− 0.37 ± 0.13	− 0.36 ± 0.14
Serotonin	1.48	0.99	1.32	− 0.49 ± 0.15	− 0.33 ± 0.15
Adenosine	1.41	1.28	1.43	− 0.13 ± 0.04	− 0.15 ± 0.04
ATP	1.45	1.21	1.39	− 0.24 ± 0.11	− 0.18 ± 0.09

Values for E and Control 2 are statistically significant at $p < 0.05$ as compared with preceding value.

*E − Control 1.

†E − Control 2.

TABLE 3. LOCAL EFFECTS OF VARIOUS AGENTS ON MEAN ILEAL VASCULAR RESISTANCE

	Ileal-vascular resistance				
Agent	*Control 1*	*During infusion (E)*	*Control 2*	d_1*	d_2†
Epinephrine	7.81	7.47	7.74	− 0.35 ± 0.23	− 0.27 ± 0.21
Acetylcholine	9.42	8.42‡	8.92‡	− 1.00 ± 0.20	− 0.50 ± 0.21
Bradykinin	8.10	6.44‡	8.15‡	− 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‡	7.21‡	− 2.49 ± 0.46	− 2.42 ± 0.51
ATP	7.12	4.73‡	7.08‡	− 2.40 ± 0.51	− 2.35 ± 0.59

*E − Control 1.

†E − Control 2.

‡Statistically significant at $p < 0.05$ as compared with preceding value.

In Fig. 6 is shown the effect of acetylcholine (1 or 10 μg.) or epinephrine (0.5 μg.), injected intra-arterially as a single bolus, on ileal intraluminal (P_L) and perfusion (P_P) pressures. In these experiments the balloon volume was kept constant at about 3 ml. One microgram of acetylcholine slightly increased luminal pressure and decreased perfusion pressure indicating a slight increase in ileal wall tension and decrease in vascular resistance. However, 10 μg. acetylcholine markedly raised ileal luminal pressure from about 2 mm. Hg to 50–100 mm. Hg. Concomitantly, perfusion pressure rose and fluctuated in rhythm with the fluctuation of ileal luminal pressure. Thus, at low dosage, the effect of acetylcholine was to dilate the vasculature directly with minimal effects on ileal wall tension. But at high dosage acetylcholine raised ileal wall tension such that not only was its dilator action masked, but local vessels were actually compressed and vascular resistance was markedly increased.

The vascular effect of epinephrine can also be reversed by its effect on ileal motility and tension. When the ileal wall tension and motility were pronounced, as shown in Fig. 6 by the high and fluctuating luminal pressure, a single injection of 0.5 μg. epinephrine produced a sharp decrease in intra-

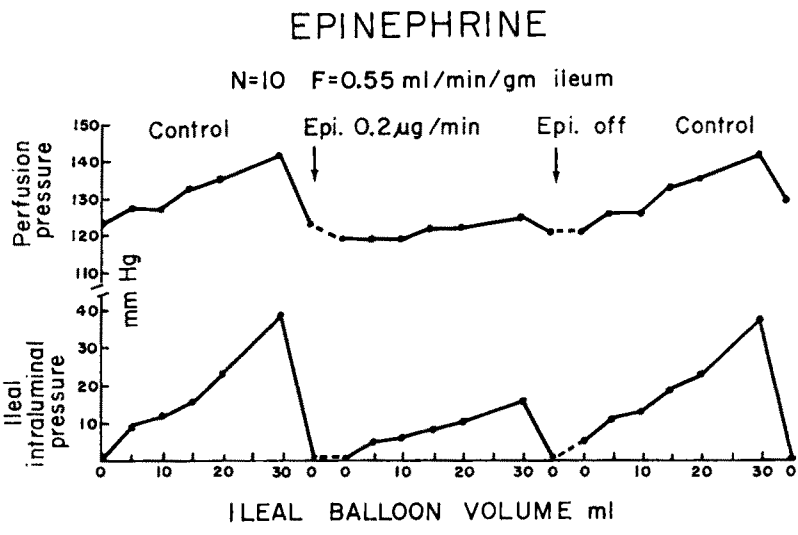

Fig. 3. Average effects of epinephrine (0.2 μg./min., intra-arterially on ileal perfusion pressure and intraluminal pressure at various ileal balloon volumes. Arrows indicate starting and stopping infusion; dotted lines, pressure changes at zero balloon volume; *N*, number of dogs tested; *F*, average blood flow.

luminal pressure and also eliminated the fluctuations. Concurrent with these changes in ileal wall activity was a decrease in vascular perfusion pressure. One minute later, when the intraluminal pressure was low and steady, the injection of the same dose of epinephrine produced an increase in perfusion pressure without significant change in ileal luminal pressure. Thus, depending on the state of intestinal motor activity, the same dose of epinephrine can increase or decrease intestinal vascular resistance.

DISCUSSION

These studies show that a complete deprivation of local blood flow for 5–7 min. does not alter ileal wall compliance, but it is possible that a change in compliance might occur with a longer period of complete ischemia. Zfass *et al.*[7] found that prolonged occlusion of the superior mesenteric artery or vein generally increases the amplitude of small intestinal intraluminal pressure waves with or without changes in base-line pressure. The time interval in their study between arterial occlusion and pressure changes was found to vary from 5 to 40 min. with an average of 17 min. But even prolonged ischemia may not

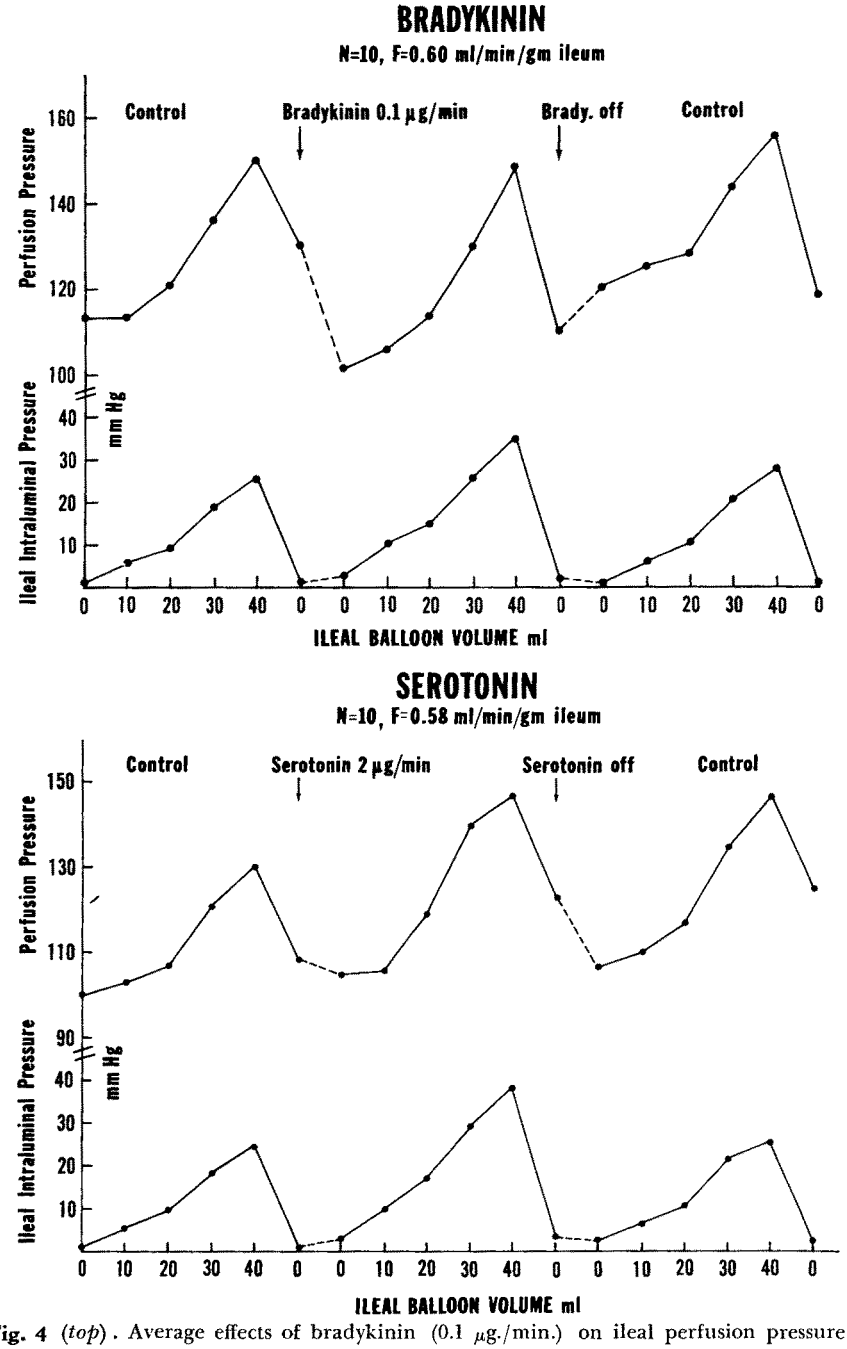

Fig. 4 (*top*). Average effects of bradykinin (0.1 µg./min.) on ileal perfusion pressure and intraluminal pressure. **Fig. 5** (*bottom*). Average effects of serotonin (2 µg./min.) on ileal perfusion pressure and intraluminal pressure. In **Fig. 4** and **5**: arrows indicate starting and stopping infusion; dotted lines, pressure changes at zero balloon volume; *N*, number of dogs tested; *F*, average blood flow.

affect ileal wall tension since in the study by Zfass *et al.*[7] the base-line luminal pressure (generally considered as an indicator of "tonus"[8]) was increased in only 3 of 7 animals with prolonged ischemia. Furthermore, since intestinal wall tension T, is a function of luminal pressure p, and radius r $(T = p \times r)$,

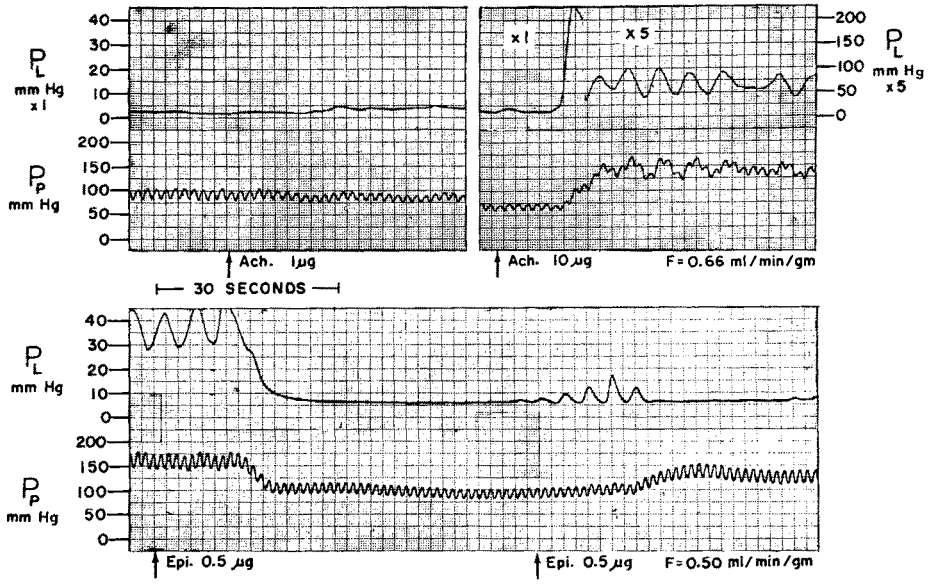

Fig. 6. Effects of acetylcholine (*Ach*) or epinephrine (*Epi*) injection on ileal perfusion pressure (P_P) and luminal pressure (P_L) at constant balloon volume in 2 dogs. Drugs were given as single bolus injection at dosages indicated. Injection of 10 μg. acetylcholine raised luminal pressure above 40 mm. Hg; attenuation had to be increased to × 5. *F*, average blood flow.

a rise in luminal pressure may not indicate a rise in tension if the radius decreases in proportion to the rise in pressure.

The effects of increased or decreased local blood flow on intestinal luminal pressure or tension have not been studied previously. Our study shows that neither doubling flow or reducing flow to one-fifth of control flow altered ileal wall compliance, nor did these maneuvers consistently affect the amplitude or frequency of luminal pressure waves. Ileal vascular resistance was decreased by increasing flow. The fall in resistance most likely resulted from a rise in perfusion pressure which distended vessel caliber. In this study reactive dilation was not accompanied by changes in ileal compliance, suggesting that the mechanisms involved do not affect ileal wall tension.

Local blood flow, on the other hand, can be affected by intestinal motility. We have previously shown that ileal vascular resistance is related to ileal wall tension. As ileal compliance increases (i.e., as ileal wall tension decreases) ileal vascular resistance decreases.[1, 6] Many vasoactive substances that affect vascular

muscle also affect intestinal smooth muscle and these responses are often opposite in direction. One purpose of the present study was to assess the interplay of these responses on intestinal vascular resistance. Figure 6 shows that the vascular effect of acetylcholine can be reversed by its visceral action and the same dose (0.5 μg.) of epinephrine can be either constrictor or dilator, depending on the state of ileal motility. It also shows that ileal vascular resistance can fluctuate concurrently with the fluctuation of the ileal luminal pressure.

Epinephrine administered at 0.2 μg./min. had, on the average, no effect on vascular resistance, whereas it significantly increased ileal compliance. Local infusion of epinephrine has been shown to constrict the vasculature supplied by the superior mesenteric artery.[9] The lack of a change in total vascular resistance by epinephrine in this present study may have resulted from the interplay of vascular and visceral responses to epinephrine. Decreased ileal wall tension decompresses intramural vessels, increases vessel caliber, and lowers vascular resistance. At an infusion rate of 0.2 μg./min. the vasoconstrictor effect of epinephrine appears to be completely offset by its relaxing effect on the intestinal wall so that vessel caliber was not significantly altered by epinephrine.

Serotonin, on the average, did not significantly alter the vascular resistance but significantly decreased ileal compliance. An increase in ileal wall tension produced by serotonin may completely mask its vasodilator effect. Indeed, in 5 animals whose vascular resistance was raised by serotonin administration, their ileal compliance was decreased more than 0.6 ml./mm. Hg, whereas, in the other 5 animals whose vascular resistance was decreased, the ileal compliance fell not more than 0.3 ml./mm. Hg. Thus, the wall tension of the former group was raised sufficiently to reverse the vasodilator effect of serotonin; but wall tension in the latter group was not raised enough to mask its vasodilator effect. Scott and Dabney[3] found that serotonin (1–20 μg./min.) markedly increased luminal pressure but did not alter blood flow of an ileal segment. They suggested that the vasodilator effect of serotonin may be masked by its effect on the ileal motility. Our study further shows that even in the absence of increased luminal pressure, the vasodilator effect of serotonin can be masked if ileal wall tension is increased. Texter *et al.*[9] found that in the absence of changes in luminal pressure, serotonin (8.7 μg./min.) effects a decrease in small-vessel vascular resistance of the superior mesenteric vascular bed. Since serotonin was administered into the superior mesenteric artery when the mean blood flow was 188 ml./min., the local serotonin concentration in the study of Texter *et al.*[9] was much lower than the concentration used in the present work. Their dosage might not have been high enough to increase gut wall tension to a degree sufficient to offset the vasodilator effect.

Acetylcholine at 4 μg./min. and bradykinin at 0.1 μg./min. decreased both ileal compliance and vascular resistance (Tables 2 and 3). Since ileal wall

tension is increased by both of these substances, their vasodilator effect must be attenuated by their effect on intestinal muscle. Figure 6 shows that the net vascular effect of 1 μg. of acetylcholine is dilation. At a higher dosage (10 μg.) it is a constrictor as a result of marked rise in ileal wall tension. Other studies[4, 5] also indicated that the vasoconstrictor effect of acetylcholine or bradykinin on the intestinal vasculature results from their effect on the intestinal muscle and not from their direct action on the vessels or from the liberation of catecholamines.

Adenosine and ATP markedly decreased ileal vascular resistance and slightly increased ileal wall tension. ATP also dilates the dog forelimb and kidney vessels. Adenosine dilates the forelimb and constricts the kidney vasculature.[10] The effect of adenosine compounds on intestinal motility has not been previously studied in vivo. Our study shows that a dosage of 10 μg. adenosine or ATP per minute decreases ileal compliance. In contrast to our finding, Bueding and Bülbring[11] found that in an in-vitro preparation 10^{-6} M of ATP reduces, and adenosine has no effect on, the tension of teniae coli of guinea pigs. This difference in results may be due to technic and preparation since the dosage appears to be virtually the same. Based on infusion rate and blood flow rate, the local blood concentration of ATP or adenosine when infused at 10 μg./min. ranged from 0.8×10^{-6} to 1.6×10^{-6} M. ATP or adenosine was given at a higher dose (100 μg. in a single injection) on several occasions in our study. In the presence of phasic luminal pressure waves neither ATP nor adenosine affects the pressure. On one occasion, when luminal pressure was low and phasic pressure waves were absent, 100 μg. ATP produced rhythmic phasic pressure waves with a rise in base-line pressure. Thus, our findings show that if ATP has any effect on the intestinal motility it is a sitmulator.

SUMMARY AND CONCLUSIONS

1. The effects of changing local blood flow and local infusion of epinephrine, acetylcholine, bradykinin, serotonin, ATP, or adenosine on ileal wall compliance and vascular resistance were studied in the constantly pump-perfused in-situ dog ileal segment. Simultaneous measurement of ileal wall compliance and vascular resistance allows for the assessment of the interrelation between ileal wall tension and ileal blood flow.

2. Complete ischemia, doubling blood flow, or reducing flow to one-fifth of control flow for several minutes did not alter ileal wall compliance. Vascular resistance was decreased by doubling blood flow.

3. Epinephrine (0.2 μg./min.) increased compliance but did not alter vascular resistance. Acetylcholine (4 μg./min.), bradykinin (0.1 μg./min.), adenosine (10 μg./min.), or ATP (10 μg./min.) decreased both compliance and vascular resistance. Serotonin (2 μg./min.) decreased compliance but did not alter vascular resistance.

4. A single bolus injection of epinephrine (0.5 μg.) was shown to decrease

or increase vascular resistance depending on the contractile state of the ileum. One microgram of acetylcholine decreased vascular resistance with minimal change in ileal lumen pressure. Ten micrograms of acetylcholine produced concurrent rise and fluctuation in the vascular resistance and ileal luminal pressure.

5. It is concluded that changing local blood flow for short periods does not affect ileal wall tension, whereas ileal wall tension can affect local blood flow. The direct vascular effect of a vasoactive agent on the intestinal vasculature can be modified by its effect on intestinal wall tension. Since the responses of visceral and vascular muscles are often opposite in direction, the net vascular effect is usually less than its direct vascular effect.

Department of Physiology
Giltner Hall
Michigan State University
East Lansing, Mich. 48823

REFERENCES

1. DABNEY, J. M., SCOTT, J. B., and CHOU, C. C. Effects of cations on ileal compliance and blood flow. *Amer J Physiol 212*:835, 1967.
2. SIDKY, M., and BEAN, J. W. Influence of rhythmic and tonic contraction of intestinal muscle on blood flow and blood reservoir capacity in dog intestine. *Amer J Physiol 193*:386, 1958.
3. SCOTT, J. B., and DABNEY, J. M. Relation of gut motility to blood flow in the ileum of the dog. *Circ Res 14* (Suppl.):234, 1964.
4. BOATMAN, D. L., and BRODY, M. J. Effects of acetylcholine on the intestinal vasculature of the dog. *J Pharmacol Exp Therap 142*:185, 1963.
5. CHOU, C. C., FROHLICH, E. D., and TEXTER, E. C., JR. A comparative study of the effects of bradykinin, kallidin II and eledoisin on segmental superior mesenteric resistance. *J Physiol 176*:1, 1965.
6. CHOU, C. C., and DABNEY, J. M. Intestinal compliance. *Amer J Dig Dis 12*:1189–1197, 1967.
7. ZFASS, A. M., HOROWITZ, L., and FARRAR, J. T. Effect of vascular occlusion on small-bowel intraluminal pressures in dogs. *Amer J Dig Dis 12*:154, 1967.
8. CODE, C. F., HIGHTOWER, N. C., and MORLOCK, C. G. Motility of the alimentary canal in man. *Amer J Med 13*:328, 1952.
9. TEXTER, E. C., JR., CHOU, C. C., MERRILL, S. L., LAURETA, H. C., and FROHLICH, E. D. Direct effects of vasoactive agents on segmental resistance of the mesenteric and portal circulation. *J Lab Clin Med 64*:624, 1964.
10. SCOTT, J. B., DAUGHERTY, R. M., JR., DABNEY, J. M., and HADDY, F. J. Role of chemical factors in regulation of flow through kidney, hindlimb, and heart. *Amer J Physiol 208:* 813, 1965.
11. BUEDING, E., and BÜLBRING, E. Relationship between energy metabolism of intestinal smooth muscle and the physiological actions of epinephrine. *Ann NY Acad Sci 139*:758, 1967.