GASTROINTESTINAL FUNCTION

REGULATION AND DISTURBANCES

VOLUME 3

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Preface

In recent years, research into the various factors in gastric functioning has burgeoned. At the same time, there have been advances in our understanding of the hormones of the digestive tract; in particular, of their role in the relationship between the stomach and the intestines. Knowledge of secretion and motility has grown and increased in complexity. However, research into functional aspects at present lags far behind the study of morphology, and it is here that more efforts are needed.

The situation which has prevailed in research into gastrointestinal regulation hitherto can be illustrated by the well-known story of the blindfolded men who were asked to identify an elephant simply by feeling it. Each touched only one part of the animal, and each identified it as something different as a result.

This series of symposia was designed from the outset to foster a multidisciplinary approach to gastrointestinal regulation; hence the adoption of the four themes, secretion, motility, blood flow and inflammation. The challenge of such an approach is the integration of the results obtained by different disciplines, which do not always correspond. Some progress has been made in this direction.

Despite our good intentions, it has not always been possible to have presentations on all four themes at any one meeting. On this occasion, no research papers on blood flow were presented. However, Paul C. Johnson, Professor of Physiology at the University of Arizona, who gave the special lecture, spoke on the mechanisms of autoregulation of blood flow in the intestinal tract. Each of the presentations and the discussions which followed them left a deep impression.

It is our hope and belief that the contents of this volume, the third in the series, will be very useful to researchers and clinicians working in gastroenterology, and that this series of symposia will act as a stimulus for future developments in this field.

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I. Special lecture

Mechanisms of blood flow autoregulation in the intestine

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INTRODUCTION

The phenomenon known as autoregulation of blood flow is a homeostatic mechanism which tends to maintain constant blood flow despite changes in arterial perfusion pressure. Before discussing this phenomenon in detail, however, it is appropriate that some of the special features of the intestinal circulation which are pertinent for this phenomenon be considered.

FEATURES OF INTESTINAL CIRCULATION

The intestine has not one circulation but several, serving the needs of the mucosa, submucosa and muscularis layers.[1] In addition, and important for microcirculatory studies, the mesentery comprises a fourth, parallel circuit. Major purposes of the circulation are to provide oxygen to the tissue and to remove waste products. In the case of the muscularis layer, these are perhaps the dominant missions. However, in the mucosa, absorption of foodstuff from the lumen is perhaps dominant.

Capillary wall structure is modified for the dominant local function: in muscle tissue low continuous endothelium is typically found, while in mucosa fenestrated endothelium, through which water can pass much more readily, is present.[2]

Comparison of the capillary filtration coefficient (CFC), i.e., the ease with which water moves across the capillary wall, in intestine and in skeletal muscle reveals that fluid moves much more rapidly across the intestinal capillaries; at high blood flows, the ratio may be ten times greater than in skeletal muscle.[3]

Local control mechanisms play a dominant role in regulating intestinal blood flow. Stimulation of the sympathetic nerves to the intestine causes initially a large decrease in blood flow. However, blood flow very quickly

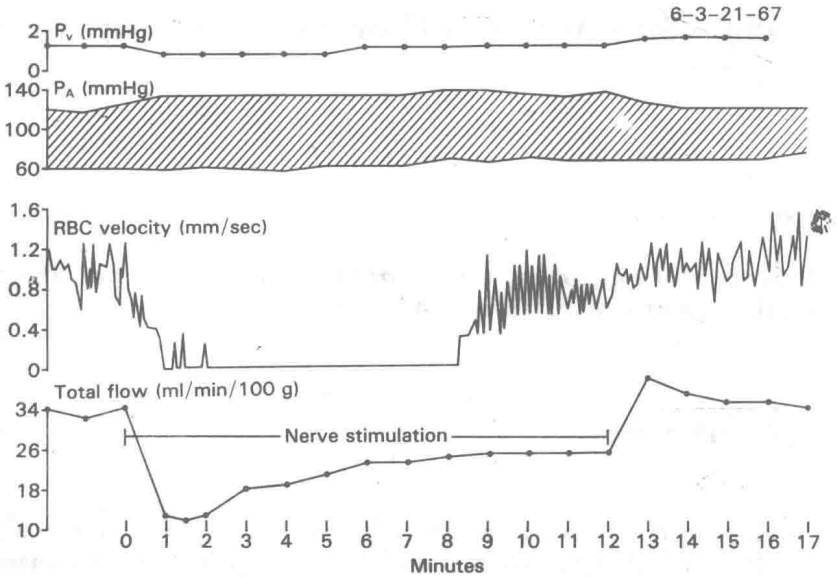

Fig. 1 Total intestinal blood flow and red-cell velocity in a mesenteric capillary during sympathetic nerve stimulation at 15 V and 7 Hz. (D. R. Richardson and P. C. Johnson, unpublished data).

returns toward initial levels, due to the action of local mechanisms.[4]

Initially, it was thought that this "escape" of blood flow was due to a shunt mechanism whereby flow to the submucosa increased while that in other areas remained low. However, further studies showed that capillary flow fell initially but then returned as total blood flow to the intestine was restored.[5] The experiment shown in Fig. 1 was performed by measuring red-cell velocity in a single capillary of the mesentery while simultaneously measuring flow through the adjacent loop of intestine. This experiment showed that it was likely that the same arterioles which contracted in response to nerve stimulation, subsequently relaxed. Thus, it appears that no shunt mechanism is involved, and that local control mechanisms can override the central nervous system when the two are in competition.

BLOOD FLOW AUTOREGULATION

Blood flow to an isolated loop of intestine can be well regulated despite changes in arterial perfusion pressure[6] (Fig. 2). As arterial pressure is reduced, the vascular resistance falls. As a consequence of the changes in resistance, blood flow is maintained. One explanation for this phenomenon is that blood flow is controlled by the tissues according to metabolic need.

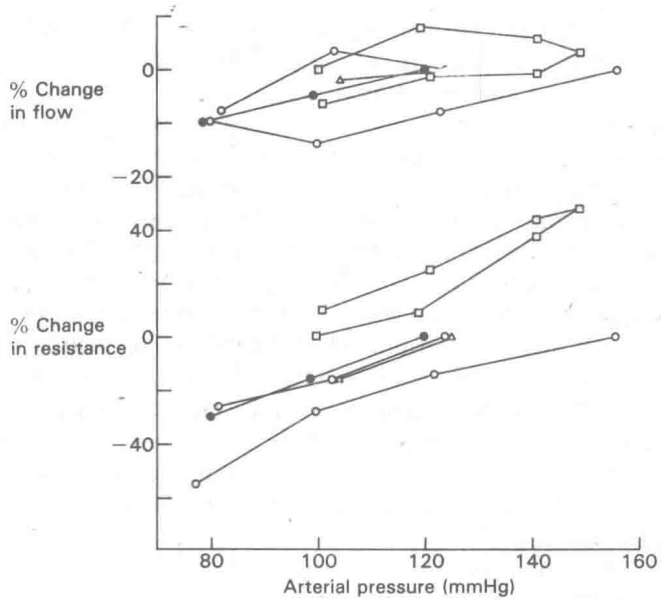

Fig. 2 Autoregulation of total blood flow to a loop of small intestine (ileum) with alteration in perfusion pressure. Selected experiments are shown in which autoregulatory response was especially strong.

According to the metabolic hypothesis, vasodilator substances are constantly produced by the tissue. If blood flow falls, the concentration of these substances will rise and cause relaxation of the arterioles, returning blood flow toward control level.

A second explanation is the myogenic hypothesis, which states that the arterioles are sensitive to intravascular pressure and contract when that pressure is elevated, or relax when the pressure falls. The mechanism for this response is not known at this time.

METABOLIC MECHANISM

To investigate the metabolic hypothesis further the author has performed experiments on a skeletal muscle preparation, the cat sartorius muscle.[7] The findings in this muscle may be applicable to the muscularis layer of the intestine as well, although that has not yet been shown. The sartorius muscle is about 6 cm long and 4 cm wide, and has a thin central region which can be transilluminated to study the response of the microcirculation in detail.

The muscle was isolated surgically and mounted on the stage of a

microscope. It was continuously perfused with blood by way of the femoral artery and a length of polyethylene tubing inserted into the arterial system of the cat. Blood was returned to the animal via the femoral vein and another circuit of tubing. Arterial pressure to the muscle could be reduced in a stepwise fashion with a clamp on the arterial tubing. The image of an arteriole of interest was formed by the microscope optics and projected onto a spherical mirror with slits cut into it, and also projected to a television camera. Photodiodes were placed behind the slits, and by monitoring light intensity at two points along the arteriole, red-cell velocity could be determined with a correlator system. The diameter of the arteriole could also be determined and the video information recorded on tape. To perform a study of autoregulation, arterial pressure was reduced in a stepwise fashion by tightening the screw clamp on the arterial circuit.

Figure 3 shows an example of how the arterioles responded when arterial pressure was reduced. The arteriole dilated and red-cell velocity fell, but generally did not decrease much while arterial pressure remained in the autoregulatory range.

If the metabolic hypothesis is correct, the arteriolar dilation was due to the accumulation of vasodilator substances in the tissue. To test this hypothesis, the tissue oxygen level was elevated artifically by placing a tent around the muscle. The muscle was covered with a thin layer of silicone oil, which permits the oxygen to diffuse easily to the muscle surface. The behavior of arterioles at the muscle surface was then examined with dif-

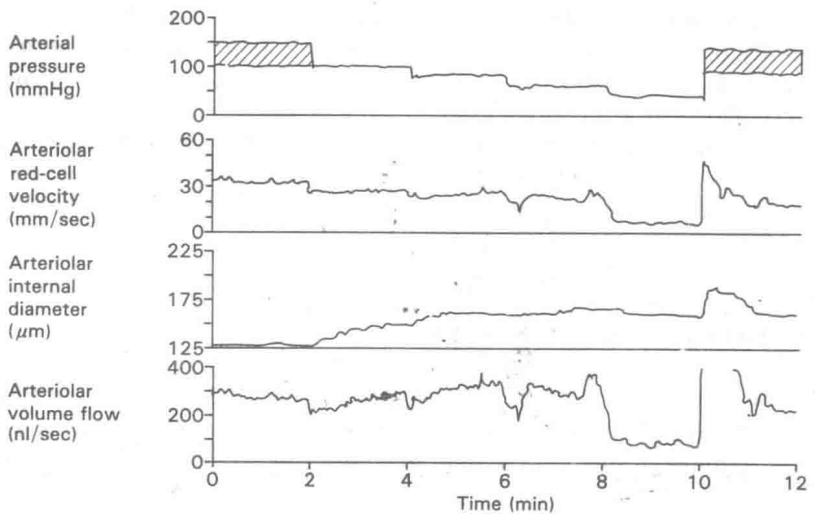

Fig. 3 Example of response of arteriole in cat sartorius muscle to reduction of arterial pressure. Volume flow is calculated from red-cell velocity and diameter. Note that this arteriole shows very good autoregulation.

ferent concentrations of oxygen in the tent.

Figure 4 shows the behavior of six orders or sizes of arterioles on the muscle surface. When there was no oxygen in the tent, i.e., 100% nitrogen, the arterioles dilated with pressure reduction. When either 10% or 20% oxygen in nitrogen was introduced into the tent, the arterioles constricted and no longer dilated when arterial pressure was reduced. This behavior was seen in the various orders of arterioles.

From these observations, it was concluded that when oxygen is supplied from an external source, the normal mechanism for controlling blood flow is interrupted and autoregulation no longer occurs. It appears, therefore, that oxygen plays an essential role in autoregulation in skeletal muscle. While this experiment has not been repeated in the muscularis layer of the intestine, it is predicted that similar results would be seen there.

The significance of this observation is twofold. First, the coupling between tissue oxygen levels and the diameter of the arterioles provides a con-

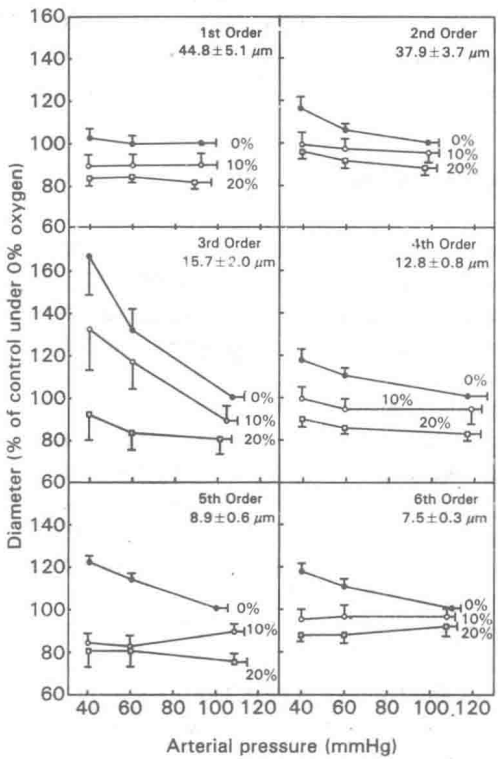

Fig. 4 Diameter changes in six orders of arterioles in cat sartorius muscle during arterial pressure reduction while the muscle is exposed to 0%, 10% and 20% O_2. Values are means ± SE. Reproduced from Ref. 7 by permission.

stant blood flow. Second, the maintenance of normal blood flow also holds capillary hydrostatic pressure constant. Capillary pressure (P_c) depends upon venous pressure (P_v). The latter depends on blood flow (F) and venous vascular resistace (R_v). This is simply expressed in the equation:

$$P_c = P_v + F \cdot R_v.$$

When arterial pressure is reduced, flow falls and capillary pressure is reduced. However, when vasodilator metabolites are released, flow returns to normal levels and capillary pressure is restored. This observation is important since, as noted above, the capillaries of the intestine allow water to pass between blood and tissue very easily and reduction of capillary pressure could cause tissue dehydration.

In summary, reduction of arterial pressure causes a reduction of blood flow, leading to a lowering of capillary pressure. However, this effect is offset by production of vasodilator metabolites and dilation of the arterioles.

There is a second mechanism which also acts to keep blood flow constant in these circumstances. When arteriolar pressure falls, the stimulation for myogenic contraction is reduced, causing relaxation of the arterioles. This also tends to restore blood flow and capillary pressure.

MYOGENIC MECHANISM

To study the myogenic mechanism, the author and his colleagues examined the microcirculation of the cat mesentery. The experimental arrangement was similar to that used for the sartorius muscle. The tissue was covered with polyvinyl film so that oxygen from the atmosphere could not reach it.

When the arterial pressure was reduced, the arterioles dilated and volume flow, as calculated from red-cell velocity and arteriolar diameter, was maintained until arterial pressure fell to 40 mm Hg. To determine whether this response was due to production of vasodilator metabolites, studies have been begun in which a tent was again fixed around the tissue, which was exposed to nitrogen gas containing no oxygen and to a mixture of 90% nitrogen and 10% oxygen.

In studies to date, the behavior of the arterioles appears not to be influenced by elevated oxygen around the tissue (D. G. Lang and P. C. Johnson, unpublished data). These findings indicate that metabolic factors are not important in the autoregulatory response in the mesentery.

Further evidence that the myogenic factor is important in the mesentery was obtained in an experiment in which the arterial and venous connections to the animal were clamped, stopping blood flow to the tissue under study. Then a reservoir was connected to both circuits and the reservoir

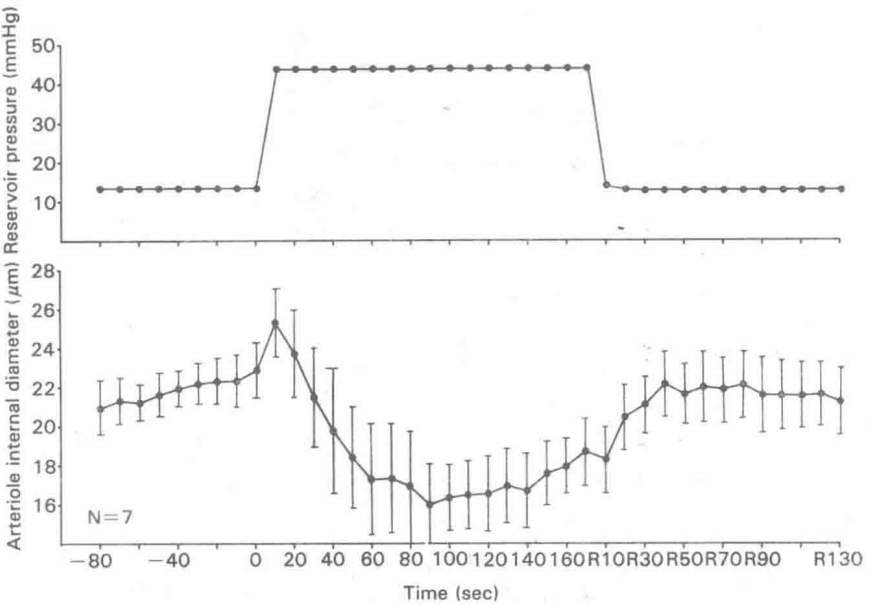

Fig. 5 Constriction of mesenteric arterioles with simultaneous arterial and venous pressure elevation under conditions of no flow in the mesentery. Times preceded by R indicate recovery period.

raised to provide an elevated, static pressure in the mesentery.[8] No blood flow occurred at this time.

Elevation of static pressure under conditions of no blood flow caused the arterioles to constrict for as long as the pressure was elevated (Fig. 5). There was some secondary dilation during the third minute, when oxygen levels in the tissue may have become inadequate to support contraction of the vascular smooth muscle.

SERIES-COUPLED EFFECTOR HYPOTHESIS

As noted above, blood flow in the mesentery is maintained rather constant when arterial pressure is reduced. It is surprising and unexpected that a mechanism which is sensitive to pressure can maintain a constant blood flow. The author and his colleagues have developed a theory which explains how this can occur.[9]

The explanation supposes that the individual branches of the arteriolar network are myogenically controlled, and each branch responds only to the pressure within it. Under control conditions the pressure in the network would be as shown in Curve 1 in Fig. 6, and the diameter of the

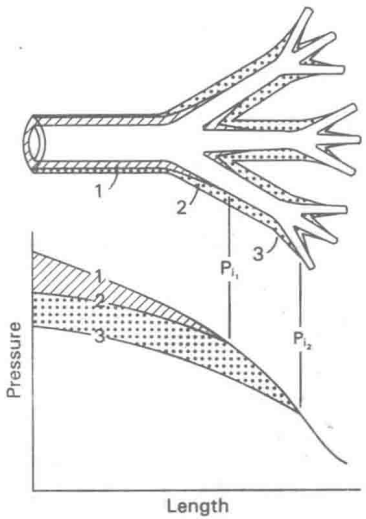

Fig. 6 Schematic diagram illustrating the behavior of a series-coupled network of myogenic effectors. Upper panel shows consecutive vascular segments and lower panel shows hypothetical pressure gradients in control state (1), after a 20% arterial pressure reduction (2), and following a 40% arterial pressure reduction (3). Reproduced from Ref. 9 by permission.

vessels as shown in Network 1. If the arterial pressure is reduced moderately, the large arterioles will dilate, and in so doing return pressure in the small arterioles downstream to its original level. When this happens, the flow will also return to its initial level. If pressure is reduced further, the large arterioles will have exhausted their capacity to respond and now the smaller vessels downstream will dilate.

To test this hypothesis, the response of various-sized arterioles in the mesentery was compared: the large arterioles dilated with pressure reduction from 120 to 100 mm Hg, while the smallest arterioles did not change diameter. However, when pressure was reduced from 80 to 60 mm Hg, the large arterioles lost their capacity to respond and the smallest arterioles dilated substantially. Such a mechanism would cause flow to remain constant over a range of arterial pressure, although flow is not controlled.

VENOUS PRESSURE ELEVATION

When venous pressure is increased, capillary pressure will rise by a similar amount, provided flow and venous resistance do not change.

However, venous resistance falls and arterial resistance increases.[10] The

latter causes a large increase in total resistance and reduction of blood flow.

This resistance increase can be attributed to constriction of the arterioles. The constriction of these vessels and dilation of the venous vessels will attenuate the rise in capillary hydrostatic pressure. At the same time, elevation of venous pressure causes a fall in capillary filtration coefficient. This is also due to constriction of pre-capillary vessels. In some instances, flow stops in individual capillaries in the mesentery.

To summarize, elevation of venous pressure would be expected to cause capillary pressure to rise by an equivalent amount if flow does not change. However, venous distension reduces venous resistance. Also, the rise in arteriolar resistance causes myogenic arteriolar constriction and reduces blood flow. Both of these mechanisms will attenuate the rise in capillary pressure. At the same time, constriction of precapillary vessels stops flow in some capillaries and reduces the capillary filtration coefficient. These responses will reduce the outpouring of fluid from blood to tissue when venous pressure is elevated.

CONCLUSION

Both metabolic and myogenic factors in the arterioles play an important role in tissue homeostasis. When arterial pressure is lowered, these two mechanisms act together to maintain normal blood flow. When venous pressure is elevated, the two would be put into opposition since blood flow falls and arteriolar pressure rises. It appears that, under these conditions, the myogenic mechanism dominates and capillary hydrostatic pressure is controlled at the expense of blood flow, again illustrating the importance of maintaining normal tissue fluid volume at the expense of oxygen supply to the tissue.

ACKNOWLEDGEMENT

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REFERENCES

1. Folkow, B. and Neil, E. (1971): Gastrointestinal and Liver Circulation. In: *Circulation*, Chapter 26. Oxford University Press, New York.
2. Majno, G. (1963): Ultrastructure of the vascular membrane, In: *Handbook of Physiology, Sec. 2, Vol. 3, Chapter 64*. Editors: W.F. Hamilton and P. Dow. American Physiological Society, Washington, D.C.
3. Folkow, B., Lundgren, O. and Wallentin, I. (1963): Studies on the relationship

between flow resistance, capillary filtration coefficient and regional blood volume in the intestine of the cat. *Acta Physiol. Scand.* 57, 270–283.
4. Folkow, B. W., Lewis, D. H., Lundgren, O., Mellander, S. and Wallentin, I. (1964): The effect of graded vasoconstrictor fibre stimulation on the intestinal resistance and capacitance vessels. *Acta Physiol. Scand.* 61, 445–457.
5. Richardson, D. R. and Johnson, P. C. (1970): Changes in mesenteric capillary flow during norepinephrine infusion. *Am. J. Physiol.* 219(5), 1317–1323.
6. Johnson, P. C. (1960): Autoregulation of intestinal blood flow. *Am. J. Physiol.* 199(2), 311–318.
7. Sullivan, S. M. and Johnson, P. C. (1981): Effect of oxygen on blood flow autoregulation in cat sartorius muscle. *Am. J. Physiol.* 241 (*Heart Circ. Physiol.* 10): H807–H815.
8. Johnson, P. C. and Intaglietta, M. (1976): Contributions of pressure and flow sensitivity to autoregulation in mesenteric arterioles. *Am. J. Physiol.* 231, 1686–1698.
9. Johnson, P. C. (1980): The myogenic response. In: *Physiology Handbook*, pp. 409–442. Editors: D. F. Bohr, A. P. Somlyo and H. V. Sparks. American Physiological Society, Bethesda.
10. Johnson, P. C. (1984): Myogenic and venous-arteriolar responses in intestinal circulation. In: *Physiology of the Intestinal Circulation*, pp. 49–60. Editors: A. P. Shepherd and D. N. Granger. Raven Press, New York.