INFLUENCE OF INTESTINAL INHIBITORY REFLEX ON MESENTERIC BLOOD FLOW THROUGH AN INTESTINAL SEGMENT OF THE DOG

Takehiko SEMBA, Tsuyoshi MIZONISHI, Yoshihito IKEDA, and Yusho NAGAO

Department of Physiology, University of Hiroshima School of Medicine, Hiroshima, 734 Japan

Abstract The variations in both tonus and rhythmical motility of the intestinal musculature are known to affect profoundly intestinal blood flow. In the present study, the influence of marked reflex inhibition of intestinal tone on the blood flow through an intestinal segment was investigated in the dog. Experiments were performed under conditions of both normal circulation and cross-circulation. Inhibitory reflex was elicited by elevating the intraluminal pressure of a loop or by electrical stimulation of the intestinal wall. Fluctuations of blood flow during the intestinal inhibitory reflex were observed with normal circulation. Arterial and venous blood flows decreased in the initial period of intestinal relaxation, and recovered within 30 sec although reflex inhibition still remained. This is an autoregulatory escape phenomenon. In successive periods, arterial and venous blood flows decreased again due to "the venous-arteriolar response" and then recovered to the quiescent level. The decrease in venous blood flow corresponded to an increase of the degree of oxygen saturation in the venous blood. The decreases in arterial and venous blood flows were observed during the inhibitory reflex even when the intestinal circulation was maintained by the cross-circulation. Two different patterns, i.e., the parallel and reversed patterns, were distinguished in correlation with venous blood flow and oxygen saturation. The autoregulatory escape phenomenon could not be elicited in the experiments in the cross-circulation system because variation of the systemic blood pressure during inhibitory reflex was limited to ±4%.
The splanchnic vasculature has been studied extensively because of its importance in cardiovascular homeostasis with regard to both flow resistance and blood volume distribution. It is known that the intestinal musculature is subjected to wide variations in both tonus and rhythmical motility and that these variations may profoundly affect intestinal blood flow. It is a matter of prime importance to take these into consideration in any analysis of blood flow changes in the intestine. The authors (1970a, b and 1971) have studied the influence of movements of the stomach, small intestine and colon on the portal blood flow and observed that mesenteric venous outflow was affected by contraction of the bowels. It was found that venous outflow which was augmented at the initial period of contraction was reduced during the period of the maximal contraction, and that during the relaxation period there was sustained augmentation of venous outflow. These findings provoked the interest of the authors to investigate the influence of marked reflex inhibition of intestinal tone on the blood flow through this organ.

METHODS

The experiments were performed on 55 dogs anesthetized with intravenous administration of 25 mg/kg sodium pentobarbital (Nembutal, Abbott). A tracheal cannula was intubated. Arterial blood pressure was recorded from the common carotid artery by means of an electronic manometer (Nihon Kohden, MP-3A). Heparine (Wako, 300–1000 unit/kg) was given to prevent coagulation.

A section of the ileum about 120 cm in length, corresponding to about two-thirds of the entire intestine, was chosen for studying intestinal circulation. The superior mesenteric artery and vein supplying the section were cannulated and connected to the cuvettes of oxymeters (Waters 0–500, XC–350) and electromagnetic flowmeters (Nihon Kohden, MF–26), respectively. The blood flow through the mesenteric artery and vein and the degree of oxygen saturation in the venous blood were recorded continuously by an ink-writing oscillograph (Nihon Kohden, RJG–3026A). To record the changes in intestinal tone and motility, a glass cannula filled with saline was inserted into lumen of a loop 6 cm in length involved in the section. The cannula was connected to a pressure-transducer (Nihon Kohden, MP–4T). The intraluminal pressure in this loop was maintained at about 20 cm H₂O. Intestinal inhibitory reflex was produced either by distension of the intestinal wall by means of rapid injection of saline into the loop where it was not used for measuring blood flow or by electrical stimulation of the serosal surface of its loop. Square pulses were given through bipolar electrodes under the following stimulus conditions; the intensity 5–10 V, pulse width 1 msec and frequency at 10–50 Hz.

As undulatory changes of blood pressure during intestinal inhibition were unavoidable, cross-circulation experiments were attempted in order to maintain blood pressure constant. In such experiments, the femoral artery of the donor
INTESTINAL INHIBITORY REFLEX AND MESENTERIC BLOOD FLOW

was connected to the superior mesenteric artery of the recipient and the venous
blood from the mesenteric vein of the recipient was returned to the femoral vein
of the donor.

RESULTS

1. Experiments on animals with normal circulation

The blood pressure of the common carotid artery in 26 experiments ranged
between 90 and 200 mmHg, the average value being 140 mmHg. Mesenteric
blood flow was 42.3 ml/min. The average blood flows of the mesenteric artery
and vein were 25.9 and 25.1 ml/min/100 g of the intestine, respectively. The
calculated vascular resistance was 4.5 mmHg/ml/min/100 g of the intestine.

As shown in Fig. 1, a few seconds after the onset of stimulation, the intestinal
tone began to decrease and rhythmical motility was lost. Twenty seconds after
the onset of stimulation, the tone decreased to the minimal level and this level was
maintained for 7.5 sec after cessation of the stimulation. About 20 sec after the
end of stimulation, the tone elevated beyond the initial level and rhythmical
motility reappeared and then recovered to the quiescent level.

The undulatory changes of the systemic blood pressure produced during the
inhibitory reflex were within 30% of the value in the quiescent one. The arterial
blood flow was reduced from 37.8 ml/min in the quiescent gut to 31.5 ml/min
within 7 sec after the onset of stimulation. However, arterial blood flow began
to recover to reach 42.0 ml/min within 30 sec though the inhibitory reflex still
persisted (autoregulatory escape phenomenon). Then arterial blood flow de-
creased and at the end of maximal inhibition it reached 32.0 ml/min. During
the recovery period of inhibitory reflex arterial blood flow increased to 41.1 ml/
min, thereafter returned to the control level. Hyperemia of the intestinal wall
could be observed with the naked eye during this period.

Venous blood flow changed almost in parallel with changes in arterial blood
flow. Venous flow of 39.5 ml/min in the quiescent gut decreased to 34.5 ml/min
at the initial period of the inhibitory reflex, thereafter it began to increase to reach
44.5 ml/min (the period of the escape). Before recovery to the control level, ve-
nous blood flow decreased and reached 35.2 ml/min at the end of the maximal
inhibition.

The oxygen saturation of the arterial blood was 94.0% with no fluctuation
during inhibitory reflex. In contrast, the oxygen saturation of the venous blood
showed a remarkable fluctuation, the changes being reciprocal in phase to the
fluctuation of the venous outflow. The degree of oxygen saturation was 76.5%
in the quiescent gut, and 7 sec after stimulation it increased to 77.0%. During
the period of the escape, it was reduced to 75.4% and thereafter increased until
the end of stimulation to 77.6%. At the end of the period of the maximal in-
hibition, oxygen saturation decreased to 77.0% and then it gradually returned to
quiescent level.
Fig. 1. Changes in blood pressure of the common carotid artery (BP), intraluminal pressure of loop (IM), blood flow of the superior mesenteric artery (AF), blood flow of the superior mesenteric vein (VF) and degree of oxygen saturation in venous blood (VO₂) during and after the inhibitory reflex under normal circulation. At the time indicated by a signal, electrical stimulation was applied to the serosal surface of the loop where it was not used for measuring blood flow. Time mark: 20 sec. (The same abbreviations apply also to the following figures and tables.)

Average values of 13 examples belonging to this pattern are shown in Table 1. Blood flow was expressed in term of ml of blood/min/100 g of the intestine. Relative values of blood pressure, blood flow, oxygen saturation and intraluminal pressure in each phase during the inhibitory reflex were given in percent with respect to quiescent values. Period I is the time when the motility was in the first half way to the maximal inhibition (period II), namely, 6.2 sec after the onset of the inhibitory reflex. Period II is the time of the maximal inhibition, 24.5 sec after the beginning of the stimulation. The intraluminal pressure during the maximal inhibition was 58.2% of the quiescent level. Period III is the first half way of the recovery period, 13.7 sec after cessation of the stimulation. Period IV is the second half way of the recovery period, i.e., 36.4 sec after cessation of the
Table 1. Changes in blood pressure (BP), arterial blood flow (AF), venous blood flow (VF), oxygen saturation (VO₂) and intraluminal pressure (IM) during and after the inhibitory reflex in normal circulation. Figures in parentheses indicate relative values in percentage with respect to quiescent values.

<table>
<thead>
<tr>
<th></th>
<th>Quiescent</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong> (mmHg)</td>
<td>113.0</td>
<td>109.9</td>
<td>120.6</td>
<td>107.9</td>
<td>113.3</td>
</tr>
<tr>
<td>(100)</td>
<td></td>
<td>(97.2)</td>
<td>(106.7)</td>
<td>(95.4)</td>
<td>(100.2)</td>
</tr>
<tr>
<td><strong>AF</strong> (ml/min/100 g)</td>
<td>25.9</td>
<td>23.3</td>
<td>27.1</td>
<td>22.8</td>
<td>25.0</td>
</tr>
<tr>
<td>(100)</td>
<td></td>
<td>(89.9)</td>
<td>(104.6)</td>
<td>(88.0)</td>
<td>(96.5)</td>
</tr>
<tr>
<td><strong>VF</strong> (ml/min/100 g)</td>
<td>25.1</td>
<td>21.3</td>
<td>26.3</td>
<td>21.5</td>
<td>24.6</td>
</tr>
<tr>
<td>(100)</td>
<td></td>
<td>(84.8)</td>
<td>(104.7)</td>
<td>(85.6)</td>
<td>(98.6)</td>
</tr>
<tr>
<td><strong>VO₂</strong> (%)</td>
<td>75.9</td>
<td>77.3</td>
<td>74.6</td>
<td>74.0</td>
<td>75.8</td>
</tr>
<tr>
<td>(100)</td>
<td></td>
<td>(101.8)</td>
<td>(98.2)</td>
<td>(97.4)</td>
<td>(99.8)</td>
</tr>
<tr>
<td><strong>IM</strong> (mmHg)</td>
<td>122.4</td>
<td>85.0</td>
<td>71.3</td>
<td>104.5</td>
<td>126.6</td>
</tr>
<tr>
<td>(100)</td>
<td></td>
<td>(69.4)</td>
<td>(58.2)</td>
<td>(85.3)</td>
<td>(103.4)</td>
</tr>
</tbody>
</table>

stimulation when the tone was elevated more than the quiescent level.

Blood pressure decreased by 2.8% at period I and by 4.6% at period III and it increased by 6.7% and 0.2% at period II and IV, respectively. Arterial blood flow dropped by 10.1% at period I, increased by 4.6% at period II, again dropped by 12.0% at period III and it gradually recovered to the quiescent level at period IV. Venous blood flow changed in parallel with arterial blood flow, namely, it decreased by 15.2% at period I, increased by 4.7% at period II, again dropped by 14.4% at period III and it recovered almost to the quiescent level at period IV.

The increase of oxygen saturation in the venous blood synchronized with diminution of venous blood flow at period I and an augmentation of venous blood flow was accompanied by a reduction of oxygen saturation at period II. In the recovery period (III and IV), they ran parallel with each other. Oxygen saturation increased by 1.8% at period I, decreased by 1.8% at period II, again decreased by 2.6% and 0.2% at period III and IV, respectively. The relationship among changes in BP, AF, VF, VO₂, and IM are graphically shown in Fig. 2.

2. Experiments on the cross-circulation system

In the cross-circulation systems, the undulation of the systemic blood pressure produced by the inhibitory reflex was unavoidable in the donor. However, the undulation was within ±4% of the quiescent level. During the inhibitory reflex arterial and venous blood flows constantly decreased, and both decreased temporarily beyond the quiescent level in the recovery period.

The autoregulatory escape phenomenon which was observed in the experiments on animals with normal circulation could not be observed. Two different patterns could be distinguished in the relationship between the changes of venous blood flow and undulation of oxygen saturation of the venous blood, i.e., a parallel and a reversed patterns. In the parallel patterns (P-pattern), a decrease of venous
blood flow in the inhibitory period ran parallel with a reduction of the degree of oxygen saturation and during the recovery period an increase of venous blood flow was accompanied by an augmentation of oxygen saturation. In the reversed pattern (R-pattern), the oxygen saturation of the venous blood changed reciprocally to the fluctuation of venous blood flow. A decrease of venous blood flow corresponded to an augmentation of oxygen saturation during the inhibitory period and an increase of the venous blood flow was accompanied by a reduction of oxygen saturation during the recovery period.

P-pattern: The fluctuation of the venous blood flow ran parallel with the fluctuation of the oxygen saturation of the venous blood. The average values of nine examples belonging to this pattern are shown in Table 2, and the phasic changes in all parameters are shown in Fig. 3.

The systemic blood pressure of the donor changed by 2.1% during the inhibitory reflex. In the intestinal motility, period I was 3 sec after the onset of the stimulation, and its tone decreased by 17.1%. Period II, the maximal inhibitory period, appeared 14 sec after the onset of the stimulation. The tone decreased by 35.9%. Period III, the first half of the recovery period, was 20 sec after cessation of stimulation when the tone decreased by 17.4%. At period IV, the second half of recovery period, the tone increased temporarily more than the quiescent level.
Table 2. Changes in BP (donor’s blood pressure), AF, VF, VO₂ and IM during and after the inhibitory reflex under cross-circulation. P-pattern. Figures in parentheses indicate relative values in percentage with respect to quiescent values.

<table>
<thead>
<tr>
<th></th>
<th>Quiescent</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
<td>124.2 mmHg</td>
<td>121.8</td>
<td>121.7</td>
<td>123.2</td>
<td>126.1</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(98.0)</td>
<td>(97.9)</td>
<td>(99.1)</td>
<td>(101.5)</td>
</tr>
<tr>
<td><strong>AF</strong></td>
<td>20.0 ml/min/100 g</td>
<td>19.1</td>
<td>15.7</td>
<td>20.4</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(95.8)</td>
<td>(78.4)</td>
<td>(102.0)</td>
<td>(109.0)</td>
</tr>
<tr>
<td><strong>VF</strong></td>
<td>20.0 ml/min/100 g</td>
<td>19.5</td>
<td>16.0</td>
<td>20.6</td>
<td>21.9</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(97.5)</td>
<td>(80.0)</td>
<td>(103.0)</td>
<td>(109.5)</td>
</tr>
<tr>
<td><strong>VO₂</strong></td>
<td>74.7%</td>
<td>74.0</td>
<td>73.0</td>
<td>74.5</td>
<td>75.5</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(99.0)</td>
<td>(97.7)</td>
<td>(99.7)</td>
<td>(101.0)</td>
</tr>
<tr>
<td><strong>IM</strong></td>
<td>145.2 mmH₂O</td>
<td>120.5</td>
<td>93.1</td>
<td>120.0</td>
<td>152.7</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(82.9)</td>
<td>(64.1)</td>
<td>(82.6)</td>
<td>(105.1)</td>
</tr>
</tbody>
</table>

* donor's blood pressure

Table 3. Changes in BP (donor’s blood pressure), AF, VF, VO₂ and IM during and after the inhibitory reflex under cross-circulation. R-pattern. Figures in parentheses indicate relative values in percentage with respect to quiescent values.

<table>
<thead>
<tr>
<th></th>
<th>Quiescent</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
<td>152.8 mmHg</td>
<td>147.0</td>
<td>149.7</td>
<td>151.5</td>
<td>152.7</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(96.2)</td>
<td>(97.9)</td>
<td>(99.1)</td>
<td>(99.9)</td>
</tr>
<tr>
<td><strong>AF</strong></td>
<td>28.5 ml/min/100 g</td>
<td>28.3</td>
<td>25.9</td>
<td>28.8</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(99.3)</td>
<td>(90.9)</td>
<td>(101.2)</td>
<td>(105.2)</td>
</tr>
<tr>
<td><strong>VF</strong></td>
<td>28.6 ml/min/100 g</td>
<td>27.4</td>
<td>24.8</td>
<td>31.6</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(95.8)</td>
<td>(86.7)</td>
<td>(110.4)</td>
<td>(104.8)</td>
</tr>
<tr>
<td><strong>VO₂</strong></td>
<td>75.9%</td>
<td>76.3</td>
<td>76.9</td>
<td>75.5</td>
<td>75.8</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(100.5)</td>
<td>(101.3)</td>
<td>(99.4)</td>
<td>(99.8)</td>
</tr>
<tr>
<td><strong>IM</strong></td>
<td>211.8 mmH₂O</td>
<td>161.8</td>
<td>130.0</td>
<td>197.2</td>
<td>225.2</td>
</tr>
<tr>
<td></td>
<td>(100)</td>
<td>(76.3)</td>
<td>(61.3)</td>
<td>(93.1)</td>
<td>(106.3)</td>
</tr>
</tbody>
</table>

* donor’s blood pressure

Both arterial and venous blood flows began to decrease 3 sec after the stimulation at period I and they reached the minimal level at period II. At period III, they were increased more than the quiescent level and they increased by 9% and 9.5%, respectively, at period IV. The oxygen saturation of the venous blood decreased to the minimal level at period II, and it recovered to the initial level in period IV.

R-pattern: In this case, the fluctuation of venous blood flow ran reversely with that of oxygen saturation of the venous blood. The average values of 11 examples belonging to this pattern are shown in Table 3, and the phasic changes in all parameters are shown in Fig. 4.

The undulation of the systemic blood pressure of the donor was within ±3.8% during the inhibitory reflex. The changes in the intraluminal pressure indicated
that the inhibitory reflex was produced 3 sec after the stimulation (period I) and reached the minimal level after 11 sec (period II), then the tone recovered gradually at period III and at period IV, the tone elevated more than the quiescent level temporarily and then recovered the initial level. The arterial blood flow changed in parallel with the venous blood flow during the reflex inhibition, and in the maximal inhibition (period II) the arterial and venous blood flows decreased by 9.1% and 13.3%, respectively. In the recovery period, both the arterial and venous blood flows increased more than the quiescent level. The oxygen saturation in venous blood increased by 0.5–1.3% during the inhibitory period (period I and II) in spite of the venous blood flow decrease. In the recovery period (period III and IV), it increased by 0.6% and 0.2%, respectively, while on the contrary, the venous blood flow increased.
DISCUSSION

Previously, we observed that mechanical changes in the intestinal loop interfered with mesenteric blood flow when vagal stimulation or hypertonic saline infusion were used to induce almost maximal intestinal motor responses (Sembá et al., 1973). However, the influence of reflex inhibition of intestinal tone and rhythmical motility on the mesenteric blood flow have not yet been investigated. Either the distension of the intestinal wall or electrical stimulation of the serosal surface of the intestinal loop produced an inhibition of intestinal tone and motility with reduction of arterial and venous blood flows through the intestinal segment. The reduction of mesenteric blood flow during the inhibitory reflex was seen not only in animals having normal circulation but also in recipient animals of the cross-circulation system. The efferent pathways in the intestinal inhibitory reflex were mainly splanchnic nerves and partially vagal nerves (Sembá et al., 1964). As the vasomotor supply to the mesenteric blood vessels from the vagal nerve had been denied by Kewenter (1965), a reduction of mesenteric blood flow during the intestinal inhibitory reflex may be ascribable to the stimulation of vasocon-
T. SEMBA, T. MIZONISHI, Y. IKEDA, and Y. NAGAO

strictor. Stimulation of the splanchnic nerve immediately induced an inhibition of ileal motor activity. Simultaneously, vasoconstrictor responses were observed in the gut (DRESEL and WALLENTIN, 1966; SEMBA et al., 1973). JOHANSSON and LANGSTON (1964) also observed that stimulation of afferents in the mesenteric nerves caused a reflex inhibition of the ileum and also constriction of the intestinal vessels. In the experiments in cross-circulation, reduction of arterial and venous blood flows was induced in parallel with a profound inhibition of tone and rhythmicity. Influence of the reduction of tone on the arterial and venous blood flows has not been observed. It may be concluded that the reduction of mesenteric blood flow during the inhibitory reflex was induced by the action of vasoconstrictor which was admixed in the splanchnic nerve.

In the experiments in normal circulation, the reduced arterial and venous blood flows began to recover in the first half period of the inhibitory reflex, and finally reached more than the quiescent level within 24.5 sec (see Table 1, Fig. 2, period II). FOLKOW et al. (1964 a,b) have pointed out a similar decline in resistance following a peak response and named it “autoregulatory escape” from constrictor fiber influence. In the experiments in which animals had normal circulation, the inhibitory reflex was followed by undulation of the arterial blood pressure. Therefore, in order to preserve the independence of any concomitant change in the arterial blood pressure, cross-circulation experiments were attempted. In such experiments, the escape phenomenon was never observed as shown in Figs. 3 and 4. It may be expected that the escape phenomenon is related to the baroceptor reflex induced by a change in the arterial blood pressure. In the experiment of FOLKOW et al. (1964 a, b), the escape phenomenon was followed by a decline in resistance to a steady state level within 1 or 2 min, but in the present experiment the decline occurred within 30 sec. This difference between the escape period suggests that the former is concerned with the blood flow resistance and blood volume distribution in the gut, while the latter is involved the mechanisms of the central nervous effects.

In the subsequent periods of the escape phenomenon, the arterial and venous blood flows again decreased though the intestinal inhibition was well maintained (Fig. 2, period III). During this period, the arterial blood pressure was also depressed. This reduction of blood flow might be responsible for the increase in vascular resistance which was observed at the end of the escape period in association with venous blood pressure elevation. JOHNSON (1959) named this phenomenon the “venous-arteriolar response.” It is suggested that the elevation of venous blood pressure sufficient enough to increase arteriolar pressure would induced a myogenic response of the resistance vessels.

The correlation between venous blood flow and the degree of oxygen saturation of the venous blood has been described in a previous paper (SEMBA et al., 1973). The fluctuation of the degree of oxygen saturation changed reciprocally to the fluctuation of venous blood flow during the period of inhibition. In the
In the experiment in which animals had normal circulation, the oxygen saturation increased in spite of the decrease in venous blood flow in the first half of inhibitory period (Fig. 2, period I). During this period, blood flow may be maintained only through the anastomotic shunting of minute blood vessels. In the successive period (Fig. 2, period II), an increase of venous blood flow was followed by a remarkable reduction of oxygen saturation. This shows that the congested blood in the previous period may be flowed out and the reduction in oxygen saturation is induced. In this period, oxygen consumption has been reported either to increase (Baker and Mendel, 1967) or to decrease (Shepherd et al., 1973). In the next successive period (Fig. 2, period III), a reduction of oxygen saturation was followed by a decrease of venous blood flow. This may be induced by vasoconstriction of the intestinal blood vessels. In the recovery period (Fig. 2, period IV), venous blood flow recovered and the oxygen saturation also increased. This may be induced by vasodilatation (Selkurt, 1962). In the experiments in cross-circulation, two patterns were distinguished in regard to changes of venous blood flow and changes of oxygen saturation in the venous blood. P-pattern (Fig. 3) may be produced by the vasoconstrictor effect of the gut. In R-patterns (Fig. 4), the blood flow may be maintained through the anastomotic channel only during the inhibitory period. In both patterns, vasodilatation and hyperemia were observed in the recovery period. Anastomosis has been mainly found in the submucosal layer (Barlow et al., 1951). Therefore, the mechanisms of blood re-distribution may play a role in this layer of the intestine.

This work was supported by research grants from the Ministry of Education, Science and Culture of Japan (No. 937002 and 137006).

REFERENCES


