
By JOSEPH H. TRAPOLD, PH.D.

With the technical assistance of Joan G. Sullivan, B.S.

The response of the mesenteric vascular circuit of anesthetized dogs to a group of ganglionic blocking agents has been studied. The results demonstrate that these agents produce a decrease in blood pressure, blood flow and vasomotor activity of the mesenteric bed and either no change or a decrease in mesenteric resistance. When the perfusing pressure to the mesenteric artery was maintained at control levels an increase in flow with a concomitant decrease in mesenteric resistance followed the injection of the blocking agents. The present report presents experimental evidence that our preliminary report was in error.

The ability of ganglionic blocking agents such as hexamethonium, pentolinium and chlorisondamine to lower blood pressure in man and in laboratory animals is well known. Accompanying the fall in blood pressure induced by such agents there is an increase in blood flow to certain areas, especially in the extremities and usually a reduction in cardiac output. On the basis of the effectiveness of these agents in interrupting the transmission of impulses across the ganglia of the autonomic nervous system and the relatively weak activity of this group of drugs directly upon smooth muscle, it is felt that their cardiovascular effects are due primarily to a reduction in neurogenic control over the peripheral vascular system. In spite of peripheral vasodilatation in certain areas of the body following the administration of ganglionic blocking agents, total peripheral resistance frequently fails to change significantly from control values. Plummer and associates have reported that the injection of chlorisondamine, a recently introduced ganglionic blocking agent, in anesthetized dogs produces a decrease in blood pressure without a significant change in total peripheral resistance. Concomitantly with this fall in blood pressure, resistance in the femoral artery was temporarily decreased and a sustained significant increase in mesenteric resistance occurred. Employing the same method as Plummer and associates, we concluded in a previous report that hexamethonium and pentolinium produced an increase in mesenteric resistance. Recently, however, we have obtained experimental evidence that the conclusion of our preliminary report was in error. The following report presents this evidence and indicates once again that false conclusions regarding the vasomotor effects of drugs can arise from the failure to appreciate technical errors which may be introduced by the use of flow recorders.

In view of this error we have conducted a series of experiments designed to evaluate more critically the effect of ganglionic blocking agents upon the mesenteric bed of the anesthetized dog.

METHODS

Animals. Fifty-seven mongrel dogs of both sexes weighing 12 to 17 Kg. were employed and were fasted for at least 12 hours prior to each acute experiment. Anesthesia was obtained with ether.
Inflow from carotid artery

Pressure recording

Cranial mesenteric artery

Aorta

Maisch metering pump

Funnel with heating jacket (38°C)

Rotameter

Inflow from carotid artery

Fig. 1. Schematic representation of arrangement employed to perfuse the mesenteric artery in situ with the aid of a Maisch metering pump.

barbital sodium, 250 mg./Kg. intravenously or Dial-urethane (Ciba) 0.5 ml./Kg. intravenously.

Recording. All events measured were recorded optically; respiration was recorded with the aid of a modified Anderson respiratory manometer and blood pressure by Hamilton manometers via polyethylene catheters from the aortic arch and the outflow limb of the flow system. Mesenteric blood flow was measured with the aid of a Shipley-Wilson rotameter. The outflow tube of the rotameter was connected via a glass cannula inserted into the superior mesenteric artery as close to the origin of this vessel from the abdominal aorta as possible. Inflow to the rotameter was obtained from 1 of 3 sources, from the superior mesenteric artery via a glass cannula inserted cephalad to the outflow cannula (double cannulation method), from a carotid or femoral artery via a glass cannula of maximal tolerated diameter (single cannulation method), or from a Maisch variable-control metering pump as illustrated (Fig. 1). In this arrangement inflow to the pump was obtained from a carotid artery via a reservoir, the temperature of which was maintained at 38°C. The output of the Maisch metering pump was found to be constant against a constant peripheral resistance.

Clotting was prevented by the intravenous injection of 5 mg./Kg. of heparin sodium supplemented by injections of 0.5 mg./Kg. at approximately 20 min. intervals. As an additional precaution, the rotameter was rinsed with distilled water at 15 to 20 min. intervals during the period of the experiment. Frequent base-line checks were made. The system was calibrated before and after each experiment.

Mesenteric resistance was calculated in

\[ PRU = \frac{\text{mm. Hg}}{\text{ml./min.}} \]

using the blood pressure values obtained from the outflow end of the rotameter.

Drugs. The following ganglionic blocking agents were employed in this study, chlorisondamine dimethochloride (Ecolid-Ciba), pentolinium tartrate (Ansolysien-Wyeth), and hexamethonium chloride (Hexameton-Burroughs Wellcome). All drugs were diluted in distilled water and injected intravenously. Doses were calculated as mg./Kg. of body weight unless otherwise stated.

RESULTS

The effects of the intravenous injections of chlorisondamine, pentolinium and hexamethonium, upon canine mesenteric blood pressure, blood flow and calculated resistance are presented in Table 1. These results represent the averaged values and standard deviations obtained in 38 dogs.

Double Mesenteric Cannulation. The intravenous injection of chlorisondamine, pentolinium or hexamethonium in 17 dogs produced a decrease in systemic and mesenteric pressure and mesenteric flow with a concomittant increase in mesenteric resistance. The response to hexamethonium differed from that to chlorisondamine and pentolinium in that flow and pressure showed a partial return toward control values within 1 hour. Bilateral renal ligation prior to the injection of the above blocking agents in 4 additional animals did not observably alter the response of the mesenteric bed from the response of the other animals of this series. Acute bilateral adrenal ligation in 3 animals and the prior injection of 2.5 mg./Kg. of the adrenergic blocking agent phentolamine in 5 dogs greatly reduced, or prevented, the increase in mesenteric resistance induced by ganglionic blocking agents in this series. Repositioning of the outflow cannula after injection of the ganglionic blocking agents frequently elevated blood flow toward control values. The most probable explanation of this
### Table 1—The Effect of Ganglionic Blocking Agents Upon Blood Flow and Resistance in the Superior Mesenteric Artery

<table>
<thead>
<tr>
<th>Method</th>
<th>Agents*</th>
<th>Dose mg/Kg.</th>
<th>No. of dogs</th>
<th>Mesenteric pressure mm.Hg(S/D)$_{\text{t}}$±σ</th>
<th>Mesenteric blood flow ml/min.±σ</th>
<th>Calculated mesenteric resistance PRU±σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double mesenteric</td>
<td>C</td>
<td>0.3</td>
<td>8</td>
<td>118±34.5, 87±27.6</td>
<td>21.5±17.1, 9.3±7.9</td>
<td>8.73±7.5, 13.86±14.0</td>
</tr>
<tr>
<td>cannulation</td>
<td>P</td>
<td>0.38</td>
<td>5</td>
<td>92±28.6, 65±28.9</td>
<td>21.7±9.6, 7.4±4.1</td>
<td>5.12±3.8, 11.91±11.7</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>1.5</td>
<td>4</td>
<td>127±19.9, 98±18.1</td>
<td>9.5±8.4, 2.6±3.7</td>
<td>20.36±9.7, 50.77±28.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to 5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single mesenteric</td>
<td>C</td>
<td>0.3</td>
<td>6</td>
<td>105±44.7, 65±23.7</td>
<td>23.3±12.4, 13.5±6.3</td>
<td>4.05±1.9, 3.82±1.46</td>
</tr>
<tr>
<td>cannulation</td>
<td>P</td>
<td>0.38</td>
<td>5</td>
<td>86±7.4, 60±6.0</td>
<td>45.3±33.6, 25.5±17.1</td>
<td>2.45±1.14, 1.76±0.87</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfused in situ</td>
<td>C</td>
<td>0.3</td>
<td>7</td>
<td>124±26.4, 60±6.0</td>
<td>43.3±9.6, 57.8±18.5</td>
<td>2.90±0.54, 2.06±0.40</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.38</td>
<td>1</td>
<td>93‡, 91‡</td>
<td>47.3, 51.2</td>
<td>1.97, 1.78</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>1.5</td>
<td>2</td>
<td>86±5.5‡, 68±1.0</td>
<td>54.5±28.0, 57.7±32.0</td>
<td>2.68±1.68, 1.69±0.92</td>
</tr>
</tbody>
</table>

* C = chlorisondamine dimethochloride
P = pentolinium tartrate
H = hexamethonium chloride

Table 1

- Observation is that the cannula was moved from its proper alignment in the vessel by an increased descent of the diaphragm during inspiration which occurred in most experiments following the injection of the blocking agents.
- Single Mesenteric Cannulation. The intravenous injection of either chlorisondamine or pentolinium in 11 dogs produced a decrease in systemic and mesenteric blood pressure with either no change or a slight decrease in mesenteric resistance.
- Difference in the Resistance of the "Single" and "Double" Cannula Flow Systems. The difference between the resistance of the "single" and the "double" cannula flow systems per se was evaluated with whole blood maintained at 37°C over a flow range of 5 to 65 ml./min. Inflow was obtained from and varied by a Maisch metering pump. The resistance of the rubber tubing through which the blood was returned via a reservoir to the pump and into which the blood flowed from the out-flow cannula was maintained as constant as possible with a screw clamp. Inflow and outflow pressure for both systems was measured with the aid of Hamilton optical manometers. The results of this evaluation demonstrated that the resistance of the double cannulation system was 13 to 20 per cent greater than the resistance of the single cannulation system at flow rates of 40 to 65 ml./min. and 40 to 50 per cent greater at flow rates of 5 to 20 ml./min.

Perfusion by "Maisch" Metering Pump. In view of the reduction of perfusion pressure and flow to the mesenteric bed of the intact animal following the administration of ganglionic blocking agents, 10 experiments were conducted in which the perfusion pressure and flow was held constant by means of a Maisch metering pump. The effects of the intravenous administration of chlorisondamine, pentolinium and hexamethonium are presented in Table 1. All of these agents caused a pronounced fall in systemic pressure, a slight fall in mesenteric perfusion pressure and a definite increase in mesenteric blood flow. Calculated mesenteric resistance decreased in each experi-
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Fig. 2. Top, effect of intravenous injection of ganglionic blocking agents to anesthetized dogs upon blood pressure-flow relationship in the superior mesenteric artery. (Average of 6 experiments.) Bottom, effect of ganglionic blocking agents upon blood pressure-calculated resistance relationship in the mesenteric artery. Flow was varied by a Maisch variable control metering pump. G.B.A. = ganglionic blocking agent. PRU = Mesenteric blood pressure (mm. Hg)/mesenteric blood flow (ml./min.).

The slight decrease following chlorisondamine was statistically significant ($p < 0.02 > 0.01$).

Pressure-Flow Relationship Before and After the Injection of Ganglionic Blocking Agents. The possibility that the decrease in mesenteric resistance was true only when the perfusion pressure to the mesenteric bed was high led to a study of the effect of ganglionic blocking agents upon the pressure-flow relationship in this vascular bed. Figure 2 illustrates the effect of 0.3 mg./Kg. chlorisondamine upon the pressure-flow relationship in the mesenteric bed of 6 dogs. Mechanically lowering the perfusion pressure below 60 mm. Hg during the control period produced a progressive increase in mesenteric resistance. The injection of chlorisondamine shifted the pressure-flow curve to the right of the control curve and mechanically lowering the perfusion pressure to this area produced a progressive increase in mesenteric resistance only when this pressure was reduced below 35 mm. of Hg. In 2 additional experiments, 1 in which 0.25 mg./Kg. of hexamethonium was injected and the other in which 0.35 mg./Kg. of pentolinium was administered, essentially the same results were obtained.


discussion

The results of this study indicate that the intravenous administration of the ganglionic blocking agents chlorisondamine, pentolinium and hexamethonium to the anesthetized dog produces a decrease in calculated mesenteric resistance. The contradiction between the results of this study and former studies is apparently due to the relatively high resistance of the flow system employed in earlier studies.

In order to evaluate the effect of ganglionic blocking agents upon the vasomotor activity of the mesenteric bed we employed the method suggested by Green and associates and determined the effect of these agents upon the pressure-flow relationship in the superior mesenteric artery. These studies demonstrated that the control pressure-flow relationship in this area is similar to that reported for the total systemic vascular bed of the anesthetized dog and vascular areas such as the coronary system, the pulmonary bed and the skin. The observation that calculated resistance in the mesenteric bed varies inversely to flow and pressure particularly at pressures below 60 mm. Hg also has been reported for other vascular beds, and agrees with the pressure-resistance relationship “uncorrected for yield pressure” reported by Selkurt for the kidney of the dog. Furthermore, our studies demonstrated that the injection of ganglionic blocking agents consistently produced a shift of the mesenteric pressure-flow curve away from the pressure axis thereby indicating that these agents produced a reduction in vasomotor activity in the mesenteric bed.

The progressive increase in mesenteric resistance which occurred in the control period when the perfusion pressure was mechanically reduced below 60 mm. Hg is consistent with a number of rheologic concepts but does not necessarily prove the correctness of any of these proposed explanations. However, for the purpose of discussion, we have chosen...
to refer to this phenomena as a manifestation of "critical closing pressure" as defined by Burton. After the administration of the ganglionic blocking agents of this study, the effects of "critical closing pressure" upon mesenteric resistance became apparent only after the perfusion pressure to this area had been mechanically reduced to 35 mm. Hg or less. The possibility that these results might have been due to back-pressure from an area of higher pressure, such as from the aorta via collateral circulation, was not supported by the absence of any consistent effect of aortic clamping upon the mesenteric pressure-flow relationship before or after the injection of ganglionic blocking agents. We feel, rather, that the agents tested decreased but did not abolish the "critical closing pressure" of the mesenteric bed by reducing the influence of the autonomic nervous system over this area. This continued existence of a "closing pressure" may be the primary cause of the former findings, previously mentioned, wherein it was concluded that ganglionic blocking agents produce an increase rather than a decrease in mesenteric resistance. When the double cannula system is used, it is an effective device for reducing the mesenteric pressure below the "critical closing pressure," thereby leading to a physical increase in mesenteric resistance erroneously attributed to the action of ganglionic blocking agents. The antagonism of this increased resistance following either the injection of phentolamine or bilateral adrenal ligation is unexplained, but possibly might be due to a further reduction of the "critical closing pressure" by these procedures. The continued presence of a "critical closing pressure" of blood vessels in even one vascular area, such as the mesenteric bed, after the administration of ganglionic blocking agents is of importance in relation to the effect of these agents upon total peripheral resistance. When the perfusion pressure falls below the "critical closing pressure" of such an area, the resistance of the area to blood flow will increase. On the other hand, if perfusion pressure is kept at the control level or increased to an area, such as the mesenteric bed, a reduction in resistance occurs following ganglionic blockade.

These findings are consistent with the observations of Grob and associates, that in patients whose cardiac output increased following hexamethonium, total peripheral resistance decreased whereas in patients whose output decreased total peripheral resistance either was unchanged or increased.

The effect of ganglionic blocking agents upon peripheral resistance can be readily explained by the following sequence of probable events: A reduction in neurogenic influence on the arterial system leads to a reduction in "vasomotor tone" and subsequently a decrease in peripheral resistance; a reduction in neurogenic influence on the venous system leads to a reduction in "venomotor tone." Thus, if the pooling of venous blood and the subsequent decrease in venous return is not great enough to materially reduce cardiac output, a sustained decrease in peripheral resistance is obtained; if the reduction in venous return is sufficient to produce a reduction in cardiac output, arteriolar-capillary pressure falls below the "critical closing" level of various vascular beds hence total peripheral resistance either remains unchanged or increases.

SUMMARY

Intravenous injection of the ganglionic blocking agents chlorisondamine dimetho-chloride, pentolinium tartrate and hexamethonium chloride to intact, barbiturate anesthetized dogs resulted in a pronounced decrease in aortic pressure, mesenteric pressure and mesenteric blood flow with either no change or a slight decrease in calculated mesenteric resistance.

The discrepancy between the results of this study and former studies in which it was reported that mesenteric resistance was increased by the administration of ganglionic blocking agents to the dog has been shown to be due to the relatively high resistance of the system used to measure flow in these earlier studies. This observation indicates once again that false conclusions regarding the vasmotor effect of drugs can arise from the failure to appreciate technical errors introduced by use of flow recorders.

Chlorisondamine chloride produced an increase in mesenteric blood flow with a concomitant significant decrease in mesenteric re-
sistance when the perfusion pressure to this area was held relatively constant with the aid of a Maisch metering pump.

Following the injection of ganglionic blocking agents the mesenteric pressure-flow curve which was demonstrated to be similar to that reported for other vascular areas was shifted away from the pressure axis indicating a decrease in vasomotor activity.

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SUMMARY IN INTERLINGUA
Le injection intravenose de agentes de blocage ganglionic—dimethochlorido de chlorisondamina, tartrato de pentolinium, e chlorido de hexamethonium—in canes intacte e anesthesiate per barbituratos resultava in un pronunciate reduction del pression aortic, del pression mesenteric, e del fluxo sanguine mesenteric, accompaniate per nulle alteration o per un leve reduction del calculate resistencia mesenteric.

Le discrepancia inter le resultatos de iste studio e le reportos de previe studios (secundo le quales le resistencia eseva augmentate per le administration de agentes de blocage ganglionic a canes) se ha monstrate como debite al relativamente alte resistencia del sistema que ille previes studios empleava pro mesurar le fluxo. Iste observation signalia de novo que conclusiones erronee in re le efecto vasomotori de drogas pote resultar del non-recognition del influentia technic de registra-tores de fluxo.

Chlorido de chlorisondamina produceva un augmento del fluxo sanguine mesenteric e un concomitante reduction de grados significative in le resistencia mesenteric quando le pression perfusional a iste area eseva mantenite a un nivello relativamente constanteper medio de un pumpa mesurante de Maisch.

Post le injection del agentes de blocage ganglionic, le curva de pression-fluxo mesenteric—que eseva demonstratamente simile al curva correspondent reportate pro altere areas vascular—manifestava un disviation ab le axe pressional. Isto indicava un reducite activitate vasomotori.

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JOSEPH H. TRAPOLD and Joan G. Sullivan

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