Reflex Changes in Systemic Arterial Pressure Arising from Changes in Mesenteric Arterial Pressure

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REFLEX CHANGES IN SYSTEMIC ARTERIAL PRESSURE ARISING FROM CHANGES IN MESENTERIC ARTERIAL PRESSURE

By John J. Pollock

It has been shown that occlusion of the mesenteric (celiac, superior and inferior mesenteric) arteries of the anesthetized dog produced a moderate elevation in the systemic arterial blood pressure. This response, although generally much smaller than the response to bilateral common carotid arterial occlusion, was nearly doubled after cervical vagotomy and carotid sinus denervation. The response in the vagotomized animal could be greatly reduced or abolished by hexamethonium or phenoxybenzamine.

To demonstrate further that the response was reflex in nature and not due solely to hemodynamic factors, cross perfusion experiments were performed. An increase in the perfusion pressure of the isolated splanchnic bed produced a depressor response in the systemic blood pressure in all animals. The response was transient in most experiments, but in several experiments, the depressor response was sustained. Both depressor and pressor responses to changes in mesenteric perfusion pressure were greatly reduced or abolished after hexamethonium, phenoxybenzamine, cervical spinal cord section and splanchnicectomy.

The experimental results confirmed the hypothesis of the existence of a baroresponsitive mechanism in the splanchnic vascular bed.

ACKNOWLEDGEMENTS

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Dedicated to my wife Phyllis, for her help, patience and understanding.

SECTION I

LITERATURE REVIEW

The control of blood pressure has held the attention of scientists ever since the demonstration of circulation by William Harvey in 1628. The study of the regulatory factors which influence the blood pressure, the manner in which they exert this influence and the relative importance of each of the factors has produced numerous and often conflicting reports in the literature. In general, the effects have fallen into two broad categories; first, those which have been explained on a hemodynamic basis, that is, on the basis of known physical laws governing the behavior of fluids through tubes and second, those which are reflex in nature. The latter are those factors which are exercised via afferent nerve endings in receptors around or near the heart and blood vessels. The hemodynamic factor commonly invoked to explain blood pressure changes is either that of the elimination of a large blood reservoir and the diversion of this blood from one vascular bed to another or the imposition of an additional resistance into the circulatory system.

The reflexogenic factors can be further subdivided into two groups according to the type of receptor which is involved. They are the chemoreceptors of the carotid and aortic bodies, and the baroreceptors of the carotid sinus and arch of the aorta. Of the chemoreceptors, the carotid body has been known and studied for a very long time. Haller was the first to note its presence in the intercarotid region in 1743. The aortic body chemoreceptors were discovered in 1906 by Wiesel. Both the carotid and aortic bodies have been extensively studied and the contribution of each has been documented in the literature.

Although there are reports from the late 1800's of investigators studying mechanical effects in the carotid sinus region, it was only the proof by Hering (13), in the early 1900's, that stimulation of the central end of the sinus nerve, a branch of the glossopharyngeal, caused reflex bradycardia and systemic hypotension that focused attention on the carotid sinus itself

as a baroreceptor area. Hering also showed that vascular reflexes aroused by mechanical stimulation of the sinus wall were entirely abolished by section of this nerve.

In the dog Hering's nerve is now known to supply at least three specialized receptor areas: a) the chemoreceptors in the carotid body; b) the pressor receptors in the carotid sinus; and c) some of the pressor receptors in the common carotid artery other than those of the carotid sinus.

Although the discovery of a reflex arising from the aorta by Cyon and Ludwig (8) in 1866 long preceded the discovery of the carotid sinus reflex, there is much less information regarding it. In 1902, Köster and Tschermak (19) localized baroreceptors in the aortic arch and its immediate thoracic branches. In man and dog, the aortic nerve which transmits the afferent impulses, is identified by its junction with the superior laryngeal nerve and is not separated from the remainder of the vagal fibers in the neck. Like the carotid sinus nerve, the aortic nerve is a mixed nerve. It carries depressor impulses arising from pressor receptors in the aorta as well as pressor impulses from the aortic body chemoreceptors.

The carotid sinuses and the aortic arch constitute baroreceptor areas through which the cardioaccelerator and vasoconstrictor centers are continuously restrained by inhibitory nerve impulses aroused in their walls by intravascular pressure.

In 1953, Green (11) described a baroreceptor area in the common carotid artery at the level of the superior thyroid artery. This area is supplied by a branch of the vagus nerve. Green (12), Neil (21) and Ross and Green (3) have also described several sites of baroreceptor endings in the wall of the common carotid artery between the superior thyroid artery and the subclavian bifurcation. These areas are supplied by nerve fibers which join the aortic

nerve. By perfusion of this area Green (11) was able to show reflex effects on circulation similar to those evocable from the carotid sinus and aortic arch.

Since a considerable measure of circulatory control is achieved by variations in the volume of the vascular bed in the splanchnic area, and, because stimulation of the central ends of splanchnic nerves profoundly influence blood pressure, it has been suggested for many years that a baroscnsitive mechanism located in the splanchnic area might be responsible to some extent for these changes (5,18). In 1935, Gammon and Bronk (10) reported recording of afferent impulses in the peripheral ends of the splanchnic and mesenteric nerves of the cat initiated by vascular distention. Identification of the Pacinian corpuscle as the source of these impulses was demonstrated by a process of eliminating the nerve supply of one after another of a small group of these corpuscles. The pulsatile discharge was consequently diminished in frequency and finally abolished as successive corpuscles were eliminated. These corpuscles lie in close proximity to the mesenteric vasculature and, in addition, have an intrinsic circulation of their own. It is presumed that a change either within the intrinsic vessels of the corpuscles or within the large vessels nearby, or in both, is capable of evoking the discharge. These receptors are little affected by changes in body temperature and the degree of oxygenation of the perfused fluid (10). The possibility of some other type of receptor being discharged has not entirely been eliminated. Gammon and Bronk (10) injected into and withdrew from the intact animal, blood to obtain increases and decreases, respectively, in the firing of these corpuscles. From this, it was concluded that one of the functions of the Pacinian corpuscle in the mesentery is to signal the degree of distention of the mesenteric vessels. A correlation between the mean systemic blood pressure and the activity of the Pacinian corpuscles was suggested. However, when the blood pressure was changed by peripherally acting agents such as

adrenaline and acetylcholine, the results were not what might have at first been expected. An increase in the blood pressure due to adrenaline gave a decrease in the frequency of the impulse discharge. Conversely, with a fall in the blood pressure due to acetylcholine, an increase in the frequency of impulse discharge was generally observed. The mesenteric bareroceptors thus differ from the bareroceptors of the carotid sinus and the arch of the aorta in that the latter respond to blood pressure changes independent of their mode of production. No significant changes in the systemic arterial pressure were noted upon changing the mesenteric perfusion pressure, although local volume changes in the mesentery itself were observed.

Heymans, Bouckaert, Farber and Hsu (14) and Heymans, Bouckaert and Wierzuchowski (15) demonstrated that increases and decreases in the mesenteric circulation in dogs induced a vasodilatation and vasoconstriction, respectively, in the spleen, kidney and in the periphery (leg) but had no effect on systemic arterial blood pressure. These authors stated that occlusion effects of the celiac and superior mesenteric arteries were insignificant even with the sino-aortic nerves cut, and the receptors were postulated to control only the local distribution of blood in the abdominal viscera.

The question of whether the effects were reflex or not and their importance in the control of circulation stimulated further research.

In 1939, Sarnoff and Yamada (22) reopened the question of the reflex regulation of systemic arterial blood pressure by bareroceptors in the mesenteric vascular bed of the cat. The combined occlusion of the celiac, superior and inferior mesenteric arteries, or, of the pancreatic arteries produced a brisk systemic pressor response. In general, the response was substantially greater than that observed after bilateral carotid occlusion. Both mesenteric arterial occlusion and carotid occlusion produced a similar pattern of response,

namely, a rapid sustained rise during the period of occlusion. Both the common carotid and the mesenteric arterial occlusion responses were greatly reduced by hexamethonium and tetraethylammonium. They concluded that the receptors in the splanchnic area, presumably the Pacinian corpuscles, make a significant contribution to cardiovascular regulation.

Later, Yamada (24) reported a similar reflex in the abdomen of the dog. In order to demonstrate the pressor effect of mesenteric arterial occlusion more clearly, it was necessary to eliminate the buffering effect of the aortic arch and the carotid sinuses by section of both vagi and the carotid sinus nerves. Thoracic splanchnicectomy and spinal cord section at C_2 considerably reduced the response, while dorsal root section from T_4 to L_3 completely or nearly completely prevented the response. Ganglionic and adrenergic blocking agents also produced a substantial reduction of the response.

Heymans, Schaepdryver and Vleeschhouwer (16) in 1960, reinvestigating this problem, used the dog as the test animal. Occlusion of the common carotid arteries resulted in a much more pronounced pressor effect than that following occlusion of the celiac, superior and inferior mesenteric arteries. They also reported that the responses differed in that during prolonged occlusion the pressor response following combined mesenteric arterial occlusion (celiac, superior and inferior mesenteric arteries) progressively decreased, whereas that following common carotid occlusion was a more sustained pressor effect. The hypertensive effect of combined occlusion of the celiac, superior and inferior mesenteric arteries was unaffected by intravenous injection of hexamethonium in doses producing depression of the carotid sinus vasomotor reflexes. These same hypertensive responses were also observed in their spinal dog, whether treated or untreated with hexamethonium. These findings led

to the conclusions that: 1) occlusion of the celiac and superior and inferior mesenteric arteries may determine minor increases of the systemic blood pressure, obviously of hemodynamic nature and not induced by baroreceptive vasomotor reflexes, 2) a pressure increase in the mesenteric arterial circulation does not decrease the systemic blood pressure, 3) the aortic and carotid sinus baroreceptors are the major means of reflex blood pressure homeostasis. The results of Bayer and Scher's (4) work tend to confirm those of Heymans', et al. (16). Although it is difficult to appraise their work because the details of their methods are not clear, they did claim that during perfusion of the aortic or of the superior mesenteric arterial system they were unable to produce any reflex changes in the systemic arterial blood pressure. After transection of the cord at C_1 or after infusion of thiopental in amounts sufficient to eliminate spontaneous respiration, the response to bilateral common carotid occlusion was obliterated. The response to splanchnic arterial occlusion, however, was reported as being the same as or greater than that observed prior to these procedures.

Selkurt and Rothe (23) were able to reduce the pressor effect due to mesenteric arterial occlusion with hexamethonium but not abolish it. Bonnati and Chiggino (2) on the other hand were able to abolish the response with tetraethylammonium.

Erdmann, Heye and Jungmann (9) attempting to elucidate reflexogenic zones in the abdominal aorta, found that varying the perfusion pressure in a recipient dog's abdominal aorta receiving blood from a donor dog could produce changes in arterial pressure in the supradiaphragmatic half of the recipient dog, even though this half was almost completely arterially isolated.

The present investigation was undertaken to examine and evaluate the effects of pressure variations in the splanchnic vascular bed. One of the

problems encountered with the occlusion experiments so far reviewed was the difficulty in assessing the contribution of the hemodynamic factors, involved in mere occlusion, to a pressor response. First, an increase in systemic arterial pressure occurs when kinetic energy is converted to pressure energy by the stoppage of blood flow. This pressure increase is very small because even in a vessel as large as the aorta the kinetic energy for resting cardiac output is equivalent to only 3 to 5 mm Hg, or less than 5 per cent of the mean blood pressure. In other large arteries this kinetic energy factor becomes very small and in the arterioles and capillaries it is negligible. Second, there is the factor of elimination of a large vascular reservoir and redistribution of blood by the mesenteric arterial occlusion as a contributory cause of the rise in the systemic arterial blood pressure. In order to obviate these two difficulties one technique used in this study was that of cross perfusion with donor blood of isolated splanchnic vascular beds. Systemic arterial blood pressure changes which occur during this isolated perfusion must therefore be due to factors other than changes in kinetic energy to pressure energy and redistribution of blood volumes.

SECTION II

METHODS AND MATERIALS

a. General Preparation

b. Arterial Occlusion Experiments

c. Autoperfusion Experiments

d. Cross Perfusion Experiments

General Preparation

In the following series of experiments dogs weighing 6 to 25 kilograms were used with the majority of animals around 10 kilograms. The dogs were anesthetized intravenously with 15 mg/kg of pentobarbital sodium in addition to 45 mg/kg of chloralose. Several dogs were anesthetized with 90 mg/kg of chloralose alone. The left femoral artery was exposed and cannulated for the purpose of recording systemic blood pressure. The trachea was cannulated and all animals maintained on positive pressure breathing. Dogs were given approximately 320 milliliters of air/kg/min (or 20 ml/kg at a rate of 16 respirations per minute). All animals were heparinized with 5 to 10 milliliters of a 1 per cent heparin in saline solution. A heating pad under the animals served to maintain body temperature. The vagi were exposed but not immediately cut. The common carotid arteries were prepared for reversible periarterial occlusion by encircling the artery with thread and pulling the thread through polyethylene tubing (Figure 1).

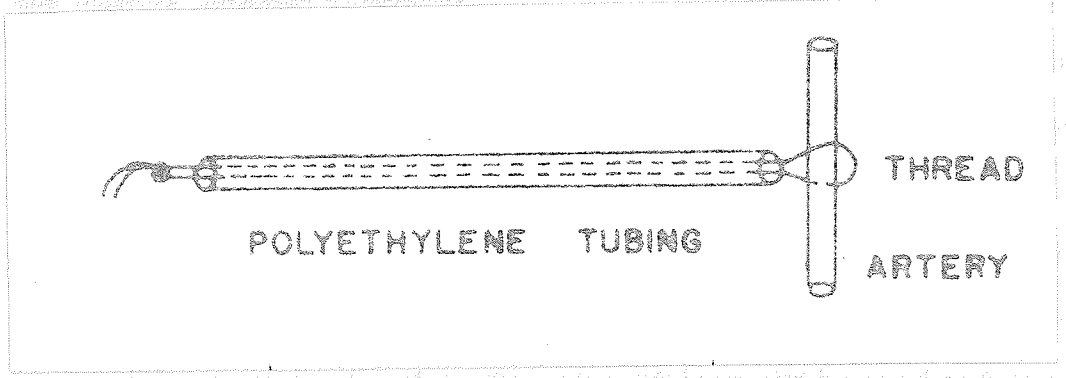

Figure 1. Arrangement for reversible occlusion of blood vessels.

Through a midline abdominal incision the celiac, superior and inferior mesenteric* arteries were very carefully dissected free of attachments and thread placed about them in the manner described in Figure 1. It was then

* The proper technical names for these arteries in the dog are the cranial and caudal mesenteric arteries respectively. However since most of the literature refers to them as the superior and inferior mesenteric arteries, they will be so called throughout this paper.

possible to occlude and release the occlusion with minimal disturbance of the abdominal viscera. Simultaneous occlusion of the celiac, superior and inferior mesenteric arteries will be referred to as mesenteric arterial occlusion. In the cross perfusion experiments (see below) the inferior mesenteric artery was permanently ligated at the time of exposure and all the preperfusion mesenteric arterial responses were obtained with the occlusion of the celiac and superior mesenteric arteries. Blood pressure responses are reported as the average of the maximum change in the systolic blood pressure.

Arterial Occlusion Experiments

The common carotid arteries and the mesenteric arteries were occluded for a period of 90 seconds. A combination of carotid and mesenteric arterial occlusion was performed in which the common carotids were occluded for 60 seconds at which time the mesenteric arteries were occluded for 60 seconds followed by release of the mesenteric arterial occlusion and 60 seconds later, release of the carotid arterial occlusion.

Duplicate tests were performed for responsiveness to bilateral common carotid arterial occlusion, mesenteric arterial occlusion, and the combined carotid and mesenteric arterial occlusion under each of the following conditions: 1) on the otherwise intact animal, 2) after high bilateral cervical vagotomy, 3) after bilateral carotid sinus denervation. The systemic blood pressure was measured from a femoral artery through a Statham strain gauge and recorded on a Grass Model 5 Polygraph.

Six experiments were performed on vagotomized dogs using either phenoxybenzamine or hexamethenium to demonstrate the effect of these agents on the carotid and mesenteric arterial occlusion procedures in animals which were not subjected to isolated mesenteric perfusion.

Autoperfusion Experiments

Five autoperfusion experiments were performed. A branched cannula from the femoral artery supplied blood to the celiac and superior mesenteric arteries. A three-way stopcock interposed in the cannula permitted interruption of the blood flow and allowed for the rapid injection of 30 to 50 milliliters of a saline or dextran solution. The portal vein was prepared for reversible occlusion in the same manner as that used for arterial occlusion. The solution was injected into the arterial vessels of the animal with and without portal vein occlusion. The portal vein was occluded in an attempt to raise the pressure in the splanchnic vascular bed more rapidly.

Cross Perfusion Experiments

After the responsiveness of the animal had been ascertained, with the carotid, mesenteric and combined carotid and mesenteric arterial occlusion tests, it was prepared for cross perfusion of the isolated splanchnic bed in the following manner (Figure 2).

Polyethylene cannulas of the largest diameter able to be inserted (P.E. 260 or 320) into the superior mesenteric and celiac arteries were filled with 1 per cent heparin solution. After the celiac artery was cannulated, arterial blood from a femoral artery was used to autoperfuse the area supplied by the celiac artery. After cannulation of the superior mesenteric artery it too was autoperfused so that at no time were the viscera allowed to become anoxic. A large cannula was inserted into the peripheral end of the ligated portal vein and connected to the central end of the ligated femoral vein until the switch to cross perfusion with blood from a donor animal was ready. This autoperfusion period was kept as short as possible. With the Sigmamotor pump apparatus filled with saline, dextran, or blood, it was quite easy to switch from auto- to cross perfusion. The donor animal was maintained

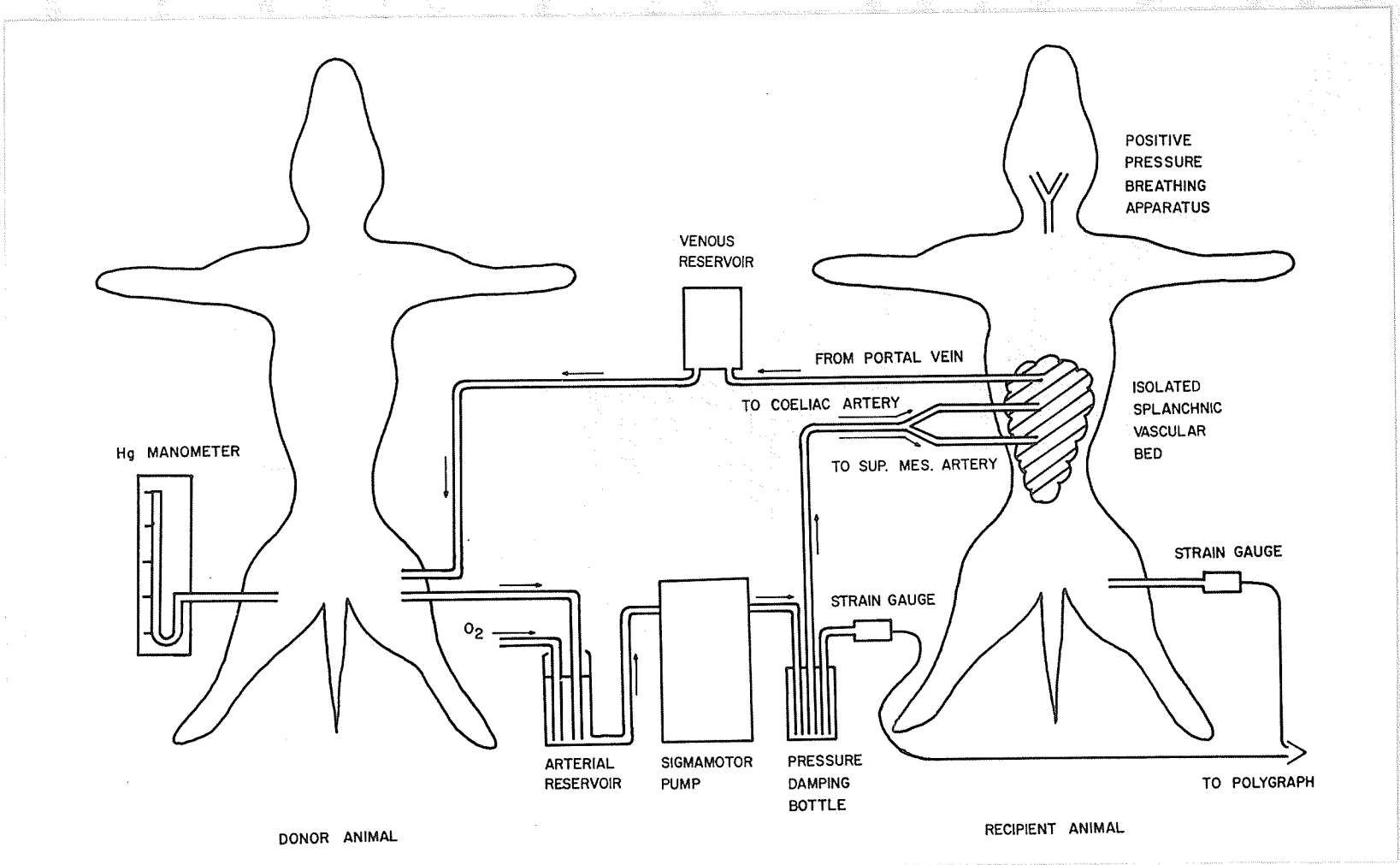

Figure 2. Schematic representation to illustrate the perfusion of the isolated splanchnic vascular bed.

at a level slightly lower than the recipient animal to allow venous blood to flow passively from the recipient to a venous reservoir and thence to the donor animal via the femoral vein. A clamp was sometimes put on the portal venous return line between the animal and the venous reservoir, simultaneously with the increased perfusion in order to increase rapidly the pressure in the isolated splanchnic vascular bed.

After passing through the pump the blood went to a damping bottle which made it possible to have some control of the pulse pressure by simply changing the volume of air above the blood in the bottle. A strain gauge was connected to the bottle in order to record the pressure presented to the perfused arteries. A mercury manometer was connected to the right femoral artery of the donor dog to monitor its blood pressure.

The pump was calibrated such that at any given perfusion pump speed (expressed in pulses per minute) and pressure, the blood flow could be determined.

The superior hemorrhoidal artery and vein, branches of the portal vein central to the point of cannulation and gastric arteries were ligated in an attempt to isolate the perfused area as completely as possible. Blood volume increases in the systemic circulation through leaks during increased perfusion of the splanchnic bed did occasionally occur. These volume changes manifested themselves by an increase in the systemic arterial pressure during the increased perfusion period. Further careful inspection and ligation of the blood vessels of the area usually resulted in a more complete isolation such that, on increased perfusion, a depressor response resulted.

After a response of the systemic blood pressure of the recipient animal had been obtained by varying the perfusion rate and pressure, attempts

to inhibit the response were made with phenoxybenzamine, an adrenergic blocking agent (5 to 10 mg/kg), hexamethonium, a ganglionic blocking agent (2 to 7.5 mg/kg), cervical spinal cord section and splanchnicectomy.

SECTION III

EXPERIMENTAL RESULTS

a. Arterial Occlusion Experiments

b. Autoperfusion Experiments

c. Cross Perfusion Experiments

Arterial occlusion experiments

The carotid, mesenteric and combined carotid and mesenteric arterial occlusions were successively performed before vagotomy, after vagotomy and after vagotomy and carotid sinus denervation on each animal. After vagotomy and after carotid sinus denervation, the systemic blood pressure rose but it gradually returned to a level approximating that before these procedures were performed.

In forty-four intact dogs bilateral occlusion of the common carotid arteries resulted in an average of 39 (0 to 103) mm Hg rise in systolic blood pressure. Occlusion of the mesenteric arteries resulted in an average of 21 (3 to 75) mm Hg rise in blood pressure. In five of these animals in which the control response to carotid occlusion was small, the response to mesenteric occlusion was larger than usual. The baseline blood pressure in these five cases was in the same range as the other experiments. With the combined (carotid and mesenteric arterial) occlusion procedure, the pressor response to carotid occlusion was 37 (0 to 70) mm Hg and that of mesenteric arterial occlusion was a further 23 (0 to 70) mm Hg increase.

Following vagotomy the average carotid occlusion pressor response increased to 54 (5 to 120) mm Hg; ten animals exhibited no change or a decrease in the response, and the abdominal response remained relatively unchanged at 22 (0 to 65) mm Hg. The carotid occlusion portion of the combination response increased to 49 (5 to 180) mm Hg, while the abdominal portion decreased very slightly to 18 (0 to 70)mm Hg.

After carotid sinus denervation in the above vagotomized animals, the common carotid occlusion response was reduced to 8 (-23 to 45) mm Hg with three depressor responses and only seven pressor responses greater than 20 mm Hg. In all except two of the forty-four dogs the response had been considerably reduced as compared with the response before denervation. Even in the animal with a 45 mm Hg pressor response to bilateral common carotid occlusion the average response

was reduced by more than 50 per cent. The residual response was attributed to either incomplete denervation, baroreceptor activity located in other parts of the common carotid artery, or to a hemodynamic effect. The response at this time to mesenteric arterial occlusion was significantly increased in thirty-five out of the forty-four dogs from 22 (0 to 65) mm Hg before denervation to 38 (-36 to 190) mm Hg after denervation ($P < .001$), with only one depressor response occurring.

In all experiments, the diastolic pressure changes were qualitatively similar to the systolic pressure changes. Systolic pressure changes were therefore considered as changes in the systemic arterial pressure.

Table I summarizes the above results.

Table I

The average increase in systolic blood pressure (mm Hg) of the intact, vagotomized and carotid sinus denervated animals following carotid, mesenteric and combined carotid and mesenteric arterial occlusion.

	INTACT	VAGOTOMIZED	VAGOTOMIZED AND CAROTID SINUS DENERVATED
Carotid Arterial Occlusion	39 (0 to 103)	54 (5 to 120)	8 (-23* to 45)
Mesenteric Arterial Occlusion	21 (3 to 75)	22 (0 to 65)	38 (-36* to 190)
Combined Carotid and Mesenteric Arterial Occlusion	37 (0 to 70) 23 (0 to 70)	49 (5 to 180) 18 (0 to 70)	8 (-3* to 25) 27 (-7* to 76)

* Negative sign indicates a depressor response.

The distribution of the responses can be seen in Figures 3 and 4.

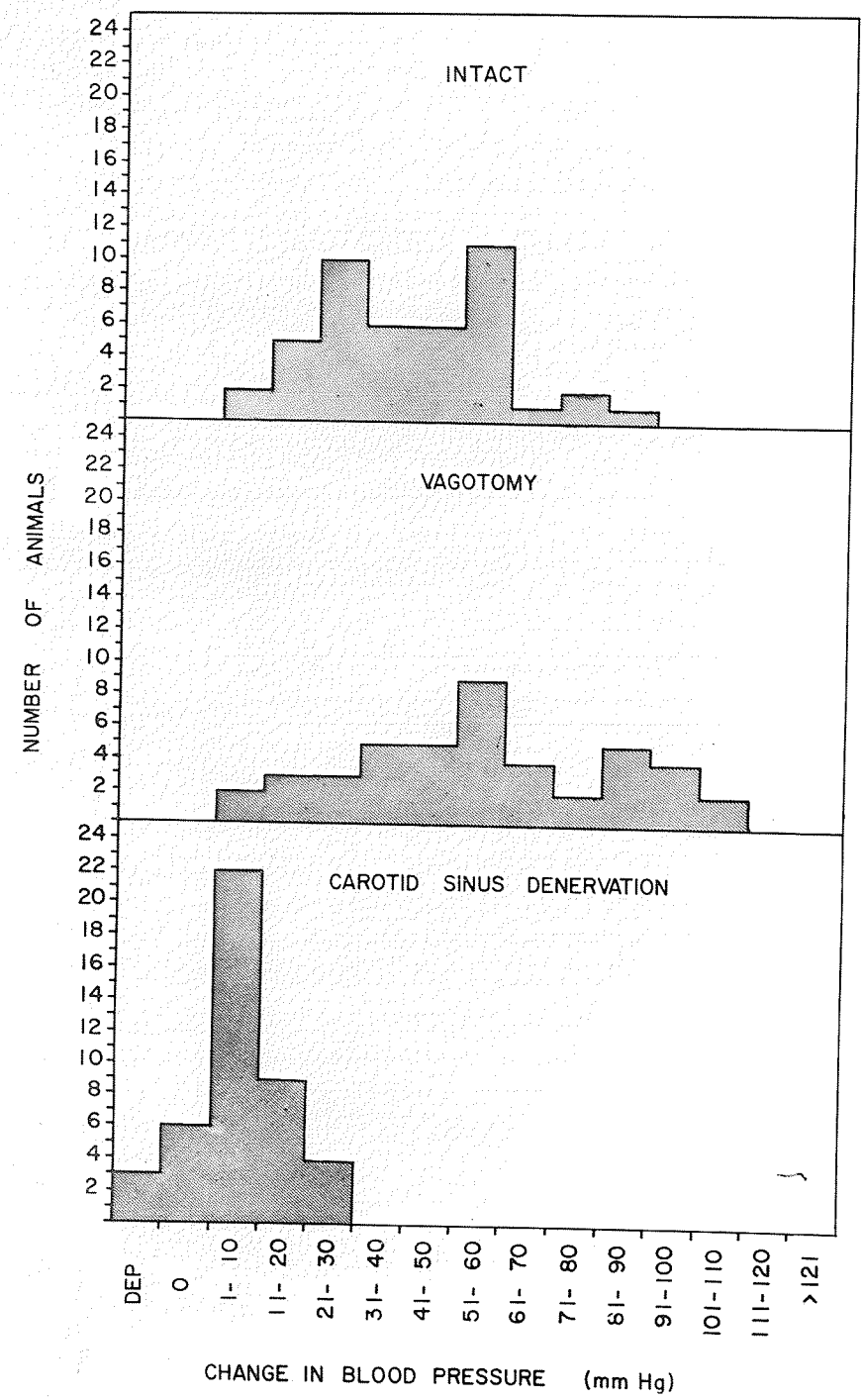

Figure 3. The distribution of the blood pressure responses after carotid occlusion on the intact, vagotomized and carotid sinus denervated animals. DEP indicates depressor response. (forty-four dogs).

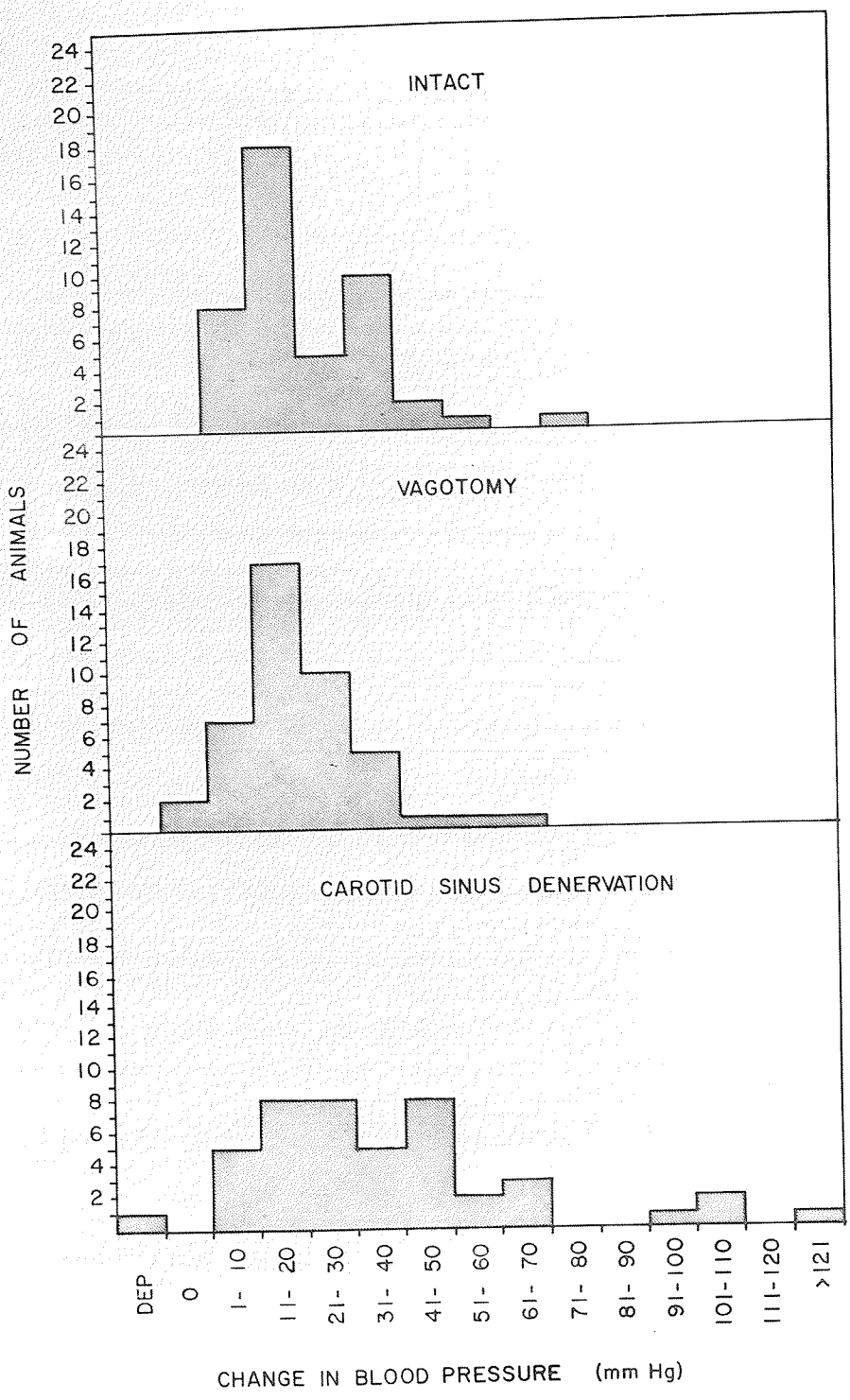

Figure 4. The distribution of the change in blood pressure after mesenteric arterial occlusion on the intact, vagotomized and carotid sinus denervated animals. DEP indicates depressor response. (forty-four dogs)

Although the magnitude of the carotid and mesenteric arterial occlusion responses differed, the pattern of the response was essentially the same, that is, a relatively sharp rise, with the pressor response being sustained until the occluded vessels were desoccluded, at which time the systemic blood pressure fell to or below the control blood pressure level.

In three out of three experiments it was possible to reduce greatly or abolish the pressor response to carotid and mesenteric arterial occlusion with phenoxybenzamine. In the first experiment, a single 5 mg/kg dose greatly reduced the pressor response after approximately 30 minutes. A second 5 mg/kg dose abolished the response about 50 minutes after the first dose or about 20 minutes after the second dose. Following administration of the drug the blood pressure at the time of testing averaged about 70 mm Hg and was never lower than 60 mm Hg. In the second experiment (Figure 5) 2 mg/kg was administered and reduced the response after approximately 25 minutes. After 160 minutes and with the response to both carotid and mesenteric arterial occlusion still reduced, a second 2 mg/kg dose was administered. This further reduced both responses but did not abolish them. A third and fourth dose administered some 35 and 45 minutes, respectively, after the second dose, almost completely abolished both responses. At the time of testing the blood pressure was 130 mm Hg. A cumulative dose of 8 mg/kg had been administered. Two mg/kg doses, in a third experiment, abolished the response after a total cumulative dose of 6 mg/kg.

The effectiveness of the phenoxybenzamine blockade was also tested with noradrenaline and the changes paralleled those seen with occlusion, that is with increasing blockade, the response to injected noradrenaline and to carotid and mesenteric arterial occlusion progressively decreased.

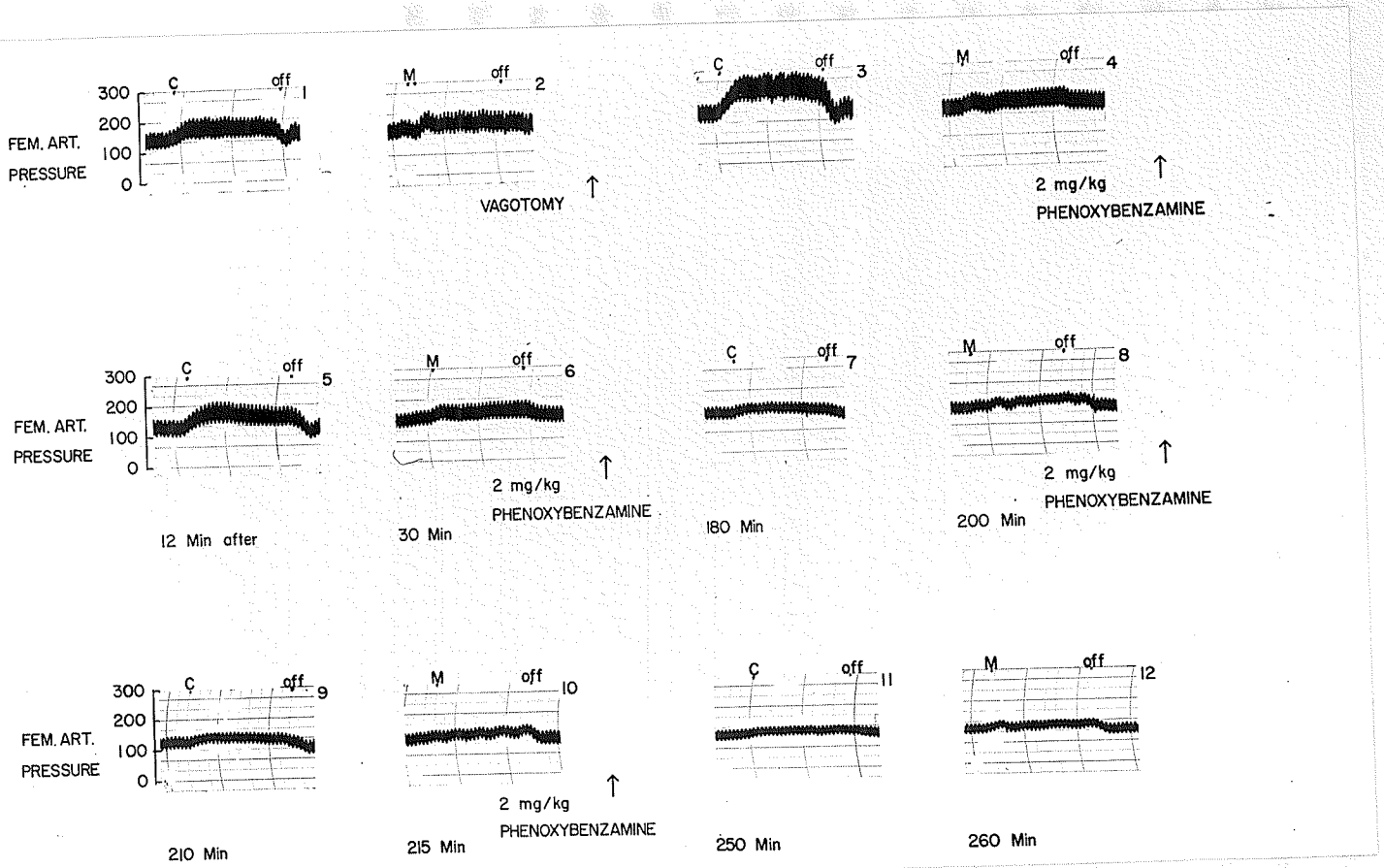

Figure 5. The effect of phenoxybenzamine on the femoral arterial blood pressure in the vagotomized animal during bilateral common carotid (C) arterial occlusion and mesenteric (M) arterial occlusion.

With hexamethonium the carotid response disappeared after an initial dose of 2.5 mg/kg (Figure 6). In two out of the three experiments performed using hexamethonium, the pressor response to mesenteric arterial occlusion was abolished with cumulative doses of 5 and 7.5 mg/kg. It was noted however, that after the initial dose, as the carotid occlusion response was decreasing, the mesenteric arterial occlusion response increased slightly. In both animals the blood pressure varied around a relatively steady level not too different from the control blood pressure. One animal was tested until the carotid and mesenteric arterial occlusion procedures again started to elicit the pressor response, indicating that the effect of the drug was diminishing. At this time the experiment was terminated. In the third animal, after 2.5 mg/kg of hexamethonium, the response to carotid occlusion was almost completely abolished, while the response to mesenteric arterial occlusion was only slightly decreased. Subsequent 2.5 mg/kg doses caused the response to become slightly greater than the responses before hexamethonium. A total cumulative dose of 20 mg/kg had finally been administered.

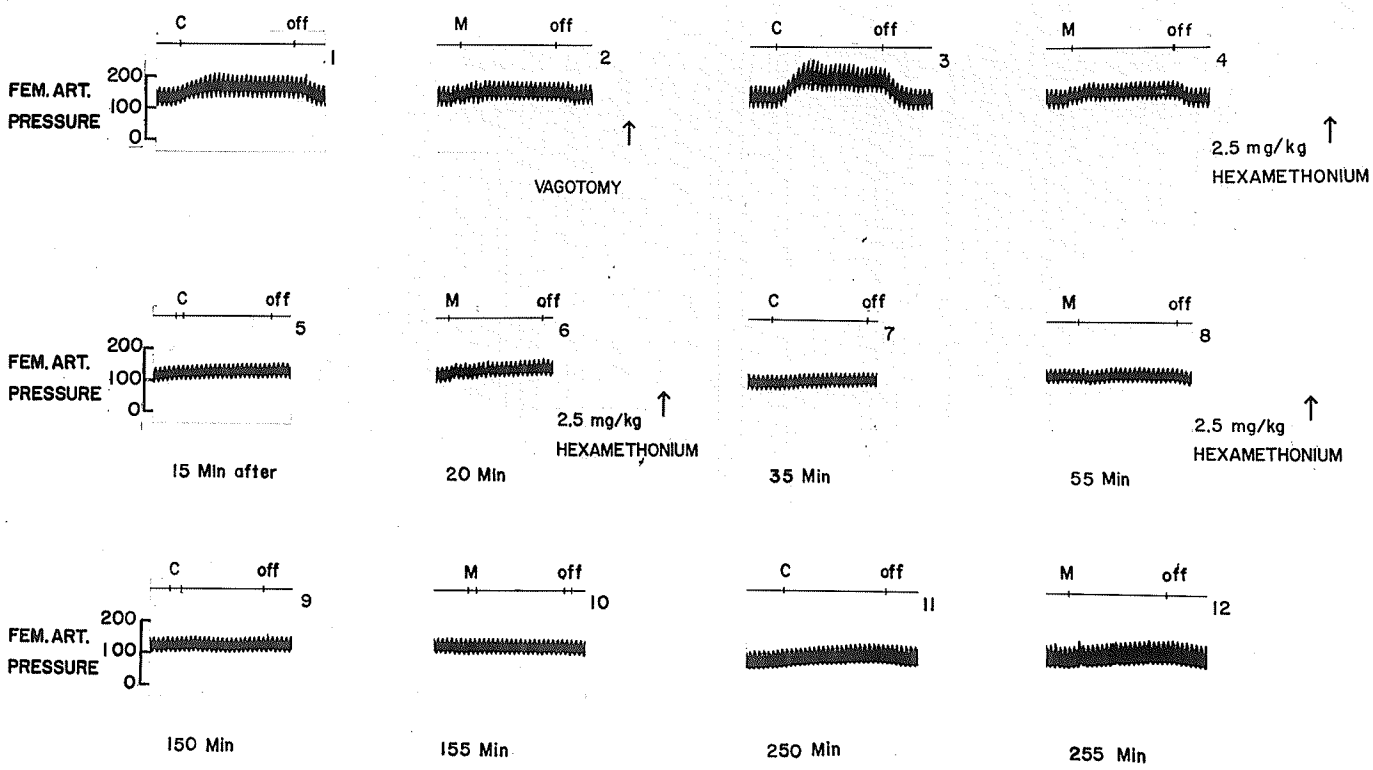

Figure 6. The effect of hexamethonium on the femoral arterial blood pressure in the vagotomized animal during bilateral common carotid (C) arterial occlusion and mesenteric (M) arterial occlusion.

Autoperfusion Experiments

In five experiments, autoperfusion of the celiac and superior mesenteric arteries with blood from the femoral artery produced, on occlusion of the portal vein, an average decrease in the systemic blood pressure of 25 mm Hg. It was possible to increase the depressor response from 10 to 40 mm Hg in one animal by tying off several small hemorrhoidal veins and a small vein proximal to the point of portal occlusion. The injection of 30 ml of saline under high pressure into the superior mesenteric artery with no portal vein occlusion produced a depressor response of 18 mm Hg. in one animal. In the other animals the effect was much smaller with a slight pressor effect following very shortly afterwards.

Injection of a 30 to 50 ml of saline or Dextran along with portal vein occlusion produced results which varied unaccountably even within the same animal from a depressor response to a pressor response.

Cross Perfusion Experiments

In all thirty-eight cross perfusion experiments it was possible to produce a fall in systemic arterial blood pressure by increasing the perfusion rate and pressure. In only seven experiments was the depressor response to increased perfusion 15 mm Hg or less. The onset of the effect usually began 5 to 10 seconds after the increase in the perfusion pressure, with the peak effect occurring around 20 to 35 seconds later.

Figure 7 presents a complete series of tests performed on one animal. Panel 1 indicates a pressor response of 25 mm Hg upon bilateral common carotid (C) arterial occlusion for 90 seconds. Panel 2 depicts a 30 mm Hg pressor response to mesenteric (M) arterial occlusion. After vagotomy a slight increase in both responses occurred (Panels 4,5). Following carotid sinus denervation, the carotid occlusion response was abolished (Panel 7) and

Figure 7. The change in the femoral arterial blood pressure following bilateral common carotid (C) and mesenteric (M) arterial occlusion in the intact, vagotomized and carotid sinus denervated animal (Panels 1-9) and following cross perfusion of the isolated splanchnic bed (Panels 10-13). Separate bilateral common carotid (C) and mesenteric (M) arterial occlusion responses obtained during a 90 second occlusion as indicated by the signal marker (top line). The combination of carotid and mesenteric arterial occlusion responses obtained at 60 second intervals.
In the cross perfusion panels, from top to bottom; mesenteric perfusion pressure, signal marker, and femoral arterial pressure. Panels 10,11,12; perfusion rate of 86 pulses per minute. Panel 10; no portal venous clamp applied, Panels 11,12; portal venous clamp applied. Panel 13; slower perfusion rate of 45 pulses per minute with the portal clamp applied.
Note: The discontinuity of mesenteric perfusion pressure in panel 10 caused by repair of polyethylene connection with strain gauge.

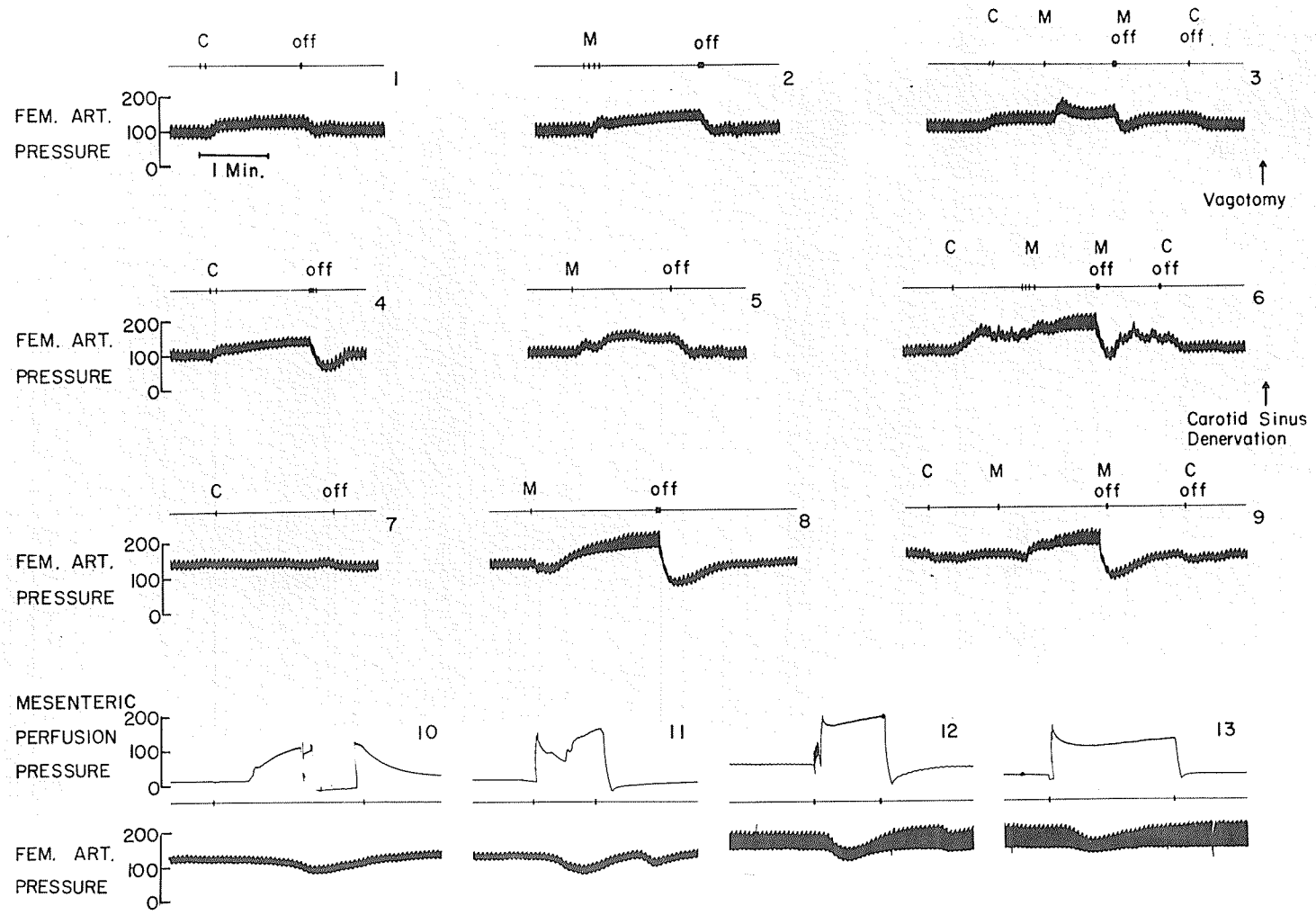

Figure 7. The change in the femoral arterial blood pressure following bilateral common carotid (C) and mesenteric (M) arterial occlusion in the intact, vagotomized and carotid sinus denervated animal (Panels 1-9) and following cross perfusion of the isolated splanchnic bed (Panels 10-13).

the mesenteric arterial occlusion response was increased (Panel 8). During cross perfusion of the isolated splanchnic bed, increasing the perfusion pump rate from 24 to 86 pulses per minute, with perfusion pressures of 115, 150, and 180 mm Hg, caused a fall in femoral arterial blood pressure of 23, 38 and 46 mm Hg respectively (Panels 10,11,12). The response to a slower rate of perfusion (45 pulses per minute) and a perfusion pressure of 110 mm Hg is indicated in Panel 13. The depressor response was 35 mm Hg. The portal venous clamp was not applied during the increased perfusion in Panel 10. The slower development of the depressor response as compared to Panels 11,12, 13, in which the portal venous clamp was applied, can be readily seen in this animal. The discontinuity of the mesenteric perfusion pressure tracing in Panel 10 was caused during repair of the polyethylene connection to the strain gauge.

The maximum depressor response obtained for the thirty-eight experiments ranged from 3 to 135 mm Hg with an average of 47 mm Hg. Included in the above figures is the maximum response obtained from individual animals whether it was obtained with or without portal venous occlusion. Of the thirty-eight animals, twenty-eight had a portal venous occlusion test performed. The average of the depressor responses was 40 mm Hg, with a range from 3 to 85 mm Hg. Twenty-nine animals with no occlusion of the portal venous system had an average response of 33 mm Hg with a range from 6 to 135 mm Hg. Of the nineteen animals that had been tested both with and without the portal venous clamp, the average response with the clamp on was 37 mm Hg, while without the clamp the response was 36 mm Hg (see Discussion).

The depressor response once obtained was generally unable to be maintained except in three experiments. In these cases, a very long perfusion or slowly increased perfusion pump speed caused a gradual and a sustained

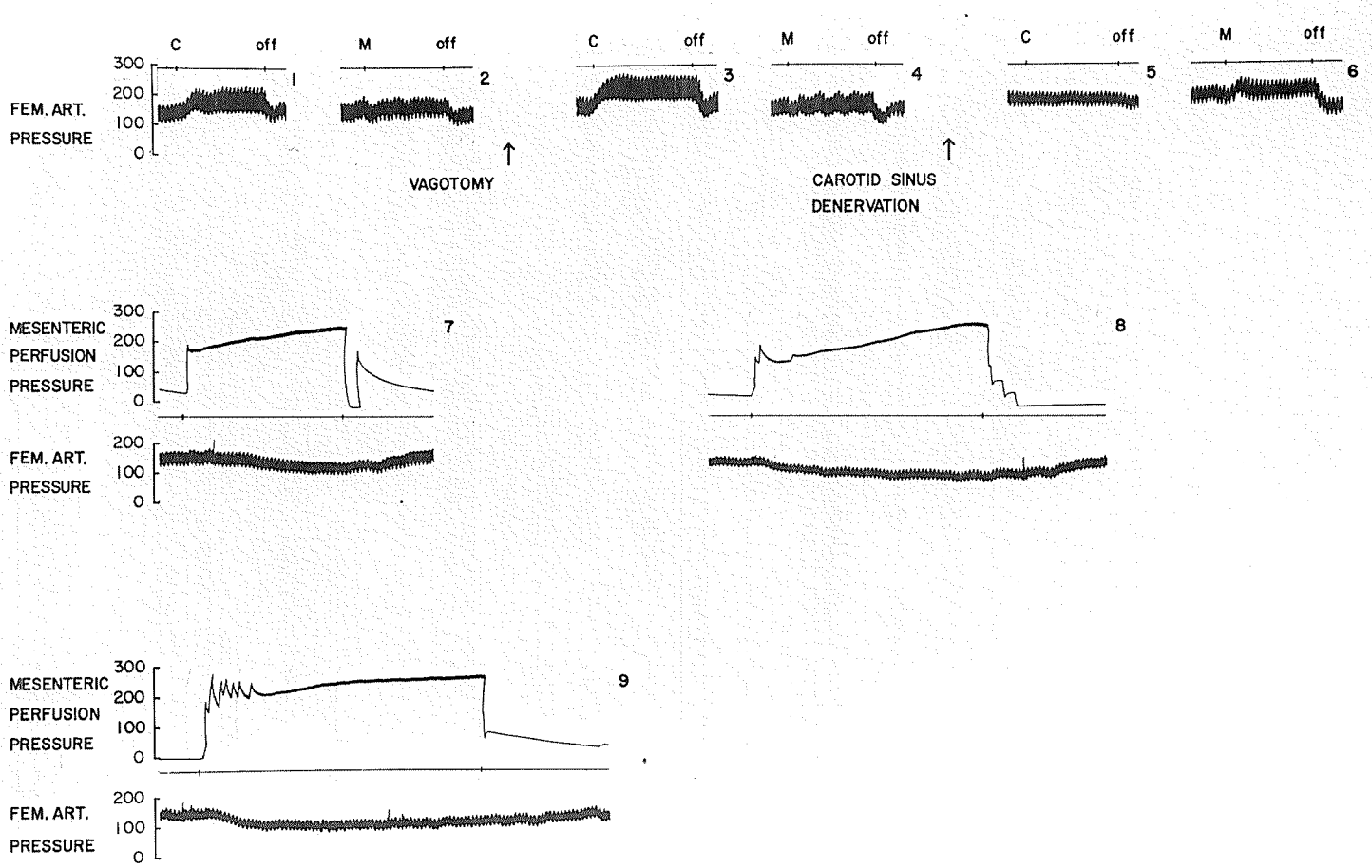

Figure 8. The sustained depressor response of the femoral arterial blood pressure during prolonged perfusion of the isolated splanchnic bed. Panels 1-6; responses to carotid (C) and mesenteric (M) arterial occlusion before and after vagotomy and carotid sinus denervation. Panels 7,8,9; slow perfusion pump rate of 45 pulses per minute. Panels 7,8; with portal venous clamp on. Panel 9; without portal venous clamp.

depressor response in the systemic blood pressure. One such experiment is illustrated in Figure 8.

The change in the systemic blood pressure due to a decrease in the perfusion pressure was more difficult to demonstrate. A slight pressor response can be seen in Figure 10 (Panels 7 to 10). After decreasing the perfusion pressure, the rise in the systemic blood pressure occurred in only eight experiments.

Because of the changing resistance of the isolated splanchnic bed it was difficult to reproduce exactly the development of a given mesenteric perfusion pressure for any given pump rate. However, a range of pump rates was found for each individual animal within which an increased pump rate generally resulted in a higher perfusion pressure and a greater depressor response. No response was obtained below this range. Above this range, a diminished or a very erratic response to continued perfusion was obtained. The mesenteric perfusion pressure in these cases was over 300 mm Hg.

Figure 9 illustrates the effects of hexamethonium on the cross perfusion responses. Two different perfusion pump rates were employed. Panels 6,9,11,13 belong to the slower perfusion pump rate of 43 pulses per minute and Panels 7,10,12,14 belong to the faster perfusion pump rate of 86 pulses per minute. To obtain a large change in the mesenteric perfusion pressure, the perfusion pump was sometimes stopped for a very short period of time preceeding the increased perfusion rate. The negative perfusion pressure which occurred during this period as seen in Panels 6,11 was due to a siphon effect of the column of blood between the strain gauge and the arterial reservoir which was at a slightly lower level than the strain gauge.

The mesenteric perfusion pressure was only slightly higher, 10 to 20 mm Hg, with the faster perfusion rate. The systemic arterial depressor response showed a steeper and greater response with the faster perfusion (Panel 7) as

compared to the slower perfusion rate (Panel 6). After the administration of hexamethonium 5 mg/kg, the depressor responses were immediately eliminated and remained abolished, even though the blood pressure did return to the pre-hexamethonium levels within approximately 35 minutes. It was possible to abolish almost completely the depressor response in the six such experiments performed. In one experiment, a 65 mm Hg depressor response was reduced to no response with 5 mg/kg of hexamethonium. In another experiment, an additional 2.5 mg/kg of hexamethonium to the original 5 mg/kg (7.5 mg/kg cumulative total) dose failed to reduce any further the already greatly diminished response.

In two experiments, immediately after the decrease in blood pressure following hexamethonium injection, the blood pressure was returned to the pre-hexamethonium levels with a constant infusion of noradrenaline. Even under these conditions the depressor response was abolished.

The results of the experiments with phenoxybenzamine were essentially the same as those obtained after hexamethonium administration. That is, the systemic depressor response to increased perfusion pressure was abolished in the six experiments in which it was tried. The results of one such experiment can be seen in Figure 10. Perfusion pump rates of 43 and 86 pulses per minute were used. Panels 7,9,11, and 13 show the slower perfusion rate, Panels 8,10, 12, and 14 the fast rate. The depressor response to the fast perfusion rate was greater than that of the slower perfusion rate. The steepness of the fall however was not as apparent as in Figure 9. The depressor response could not be maintained. However, when the perfusion was stopped, a slight pressor response was apparent as shown in Panels 7,9, and 10. The perfusion was continued until the blood pressure was near the preperfusion level (Panels 7,10). The perfusion was stopped at the point of greatest response (Panel 8) or just as it was beginning to return to the baseline blood pressure level (Panel 9).

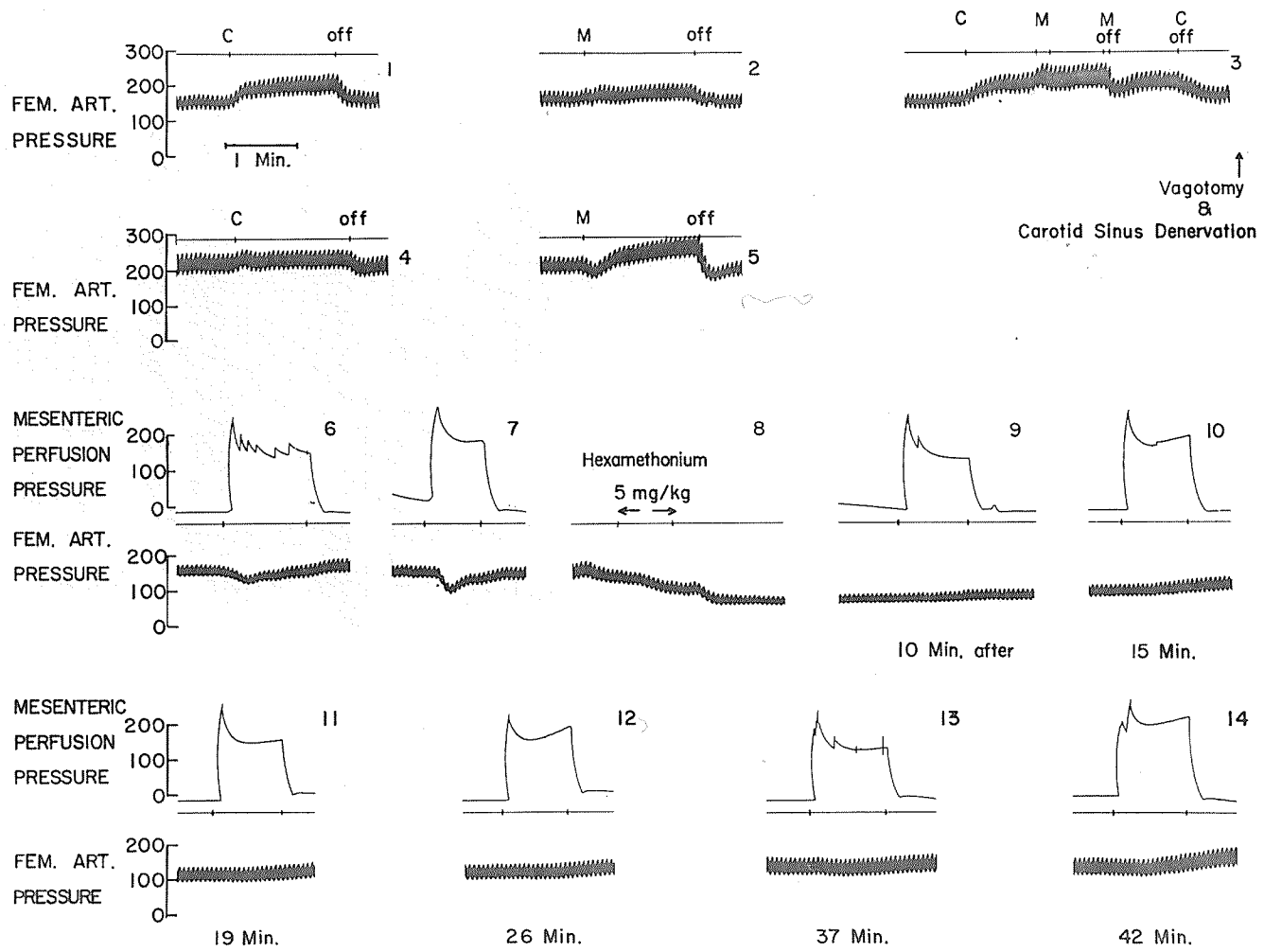

Figure 9. The effect of hexamethonium on the femoral arterial blood pressure during increased perfusion of the isolated splanchnic bed. Panels 1-5; responses to carotid (C) and mesenteric (M) arterial occlusion before and after vagotomy and carotid sinus denervation. Panels 6,9,11, 13; responses to a perfusion pump rate of 45 pulses per minute, Panels 7,10,12,14; responses to a perfusion pump rate of 86 pulses per minute. Portal venous clamp applied in all perfusion panels shown. Time indicates minutes after administration of hexamethonium.

The difference in the recovery pattern of the slopes was quite apparent. When the perfusion pressure was decreased near the peak of the systemic depressor response the systemic blood pressure more quickly returned to the baseline blood pressure level.

After phenoxybenzamine, the depressor responses were considerably reduced after thirty-five minutes and were completely abolished at forty-five minutes.

A small, delayed pressor response was sometimes observed during increased perfusion after hexamethonium (e.g., Figure 9, Panel 14) and phenoxybenzamine (e.g., Figure 10, Panel 14). Although the cause is not definitely known, this phenomenon could be due to small collateral vessels opening up following the administration of these agents.

Splanchnicectomy and spinal cord section at C_3 to C_4 in two animals each were able to abolish almost completely the depressor response. In one animal with splanchnicectomy, cutting the nerves around the coeliac and superior mesenteric ganglia resulted in a greater inhibition of the depressor response possibly because of an incomplete splanchnicectomy. In all four animals however the systolic blood pressure, although 60 mm Hg or greater, was considerably reduced as compared to the blood pressure before these procedures were performed.

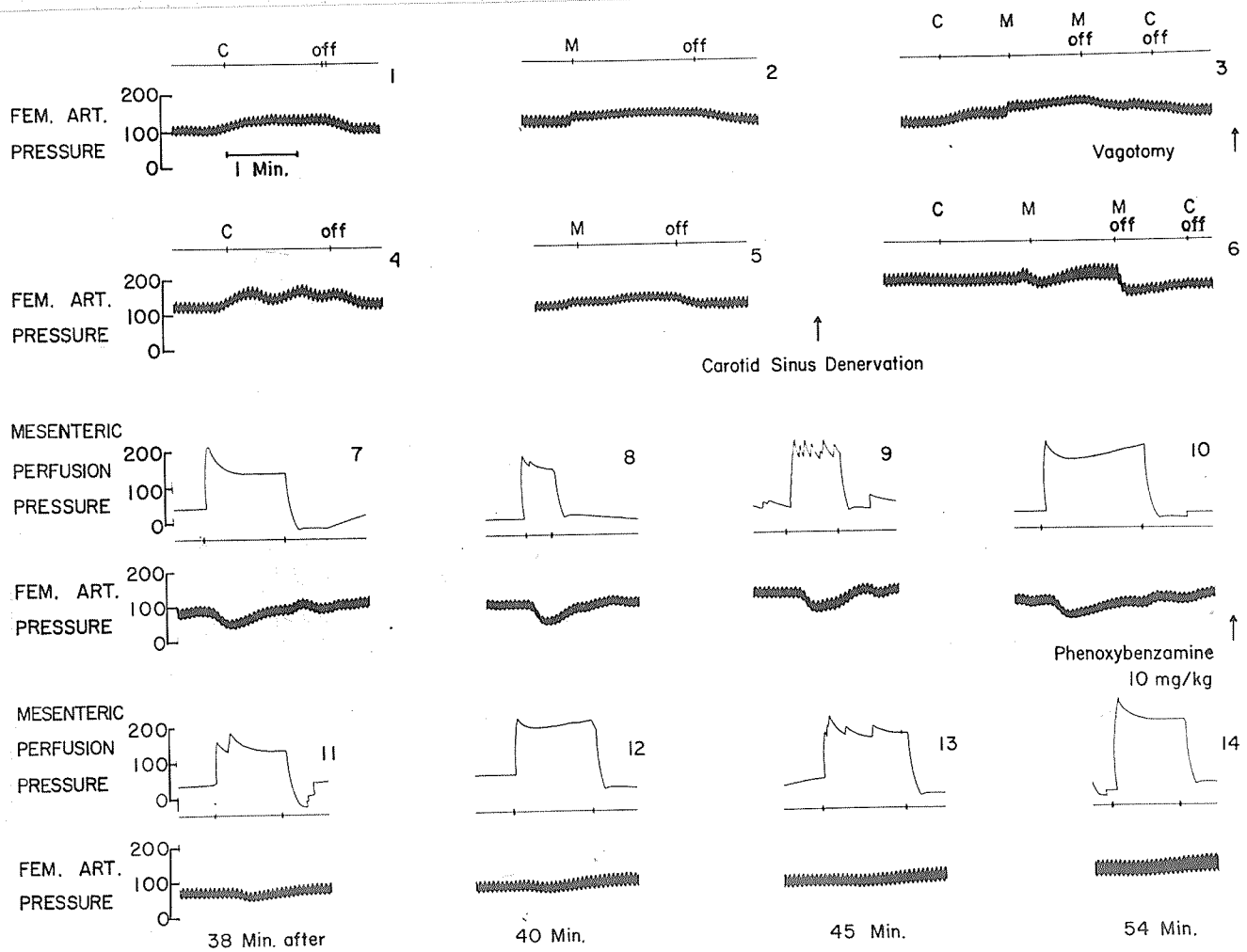

Figure 10. The effect of phenoxybenzamine on the femoral arterial blood pressure during increased perfusion of the isolated splanchnic bed. Panels 1-6; responses to carotid (C) and mesenteric (M) arterial occlusion before and after vagotomy and carotid sinus denervation. Panels 7,9,11,13; responses to a perfusion pump rate of 45 pulses per minute, panels 8,10,12,14; responses to a perfusion pump rate of 85 pulses per minute. Partal venous clamp applied in all perfusion panel shown. Time indicates minutes after administration of phenoxybenzamine.

SECTION IV

GENERAL DISCUSSION

Gannon and Bronk in 1939, demonstrated that afferent impulses in the cat's splanchnic nerve apparently originated from Pacinian corpuscles and that these impulses were altered by changes in pressure. These receptors discharged rhythmically during the cardiac cycle with some firing only during systole and others firing throughout the cardiac cycle. Vigorous bursts of impulses could be observed from these receptors accompanying pulsatile increases in the pressure of the perfused superior mesenteric artery. They were unable to demonstrate significant changes in the systemic blood pressure to wide variations of the perfusion pressure in their 'isolated' mesenteric perfusion experiment. However, from the details of their methods it is not easily seen that the splanchnic bed was completely isolated. Without complete isolation, perfusion fluid could enter the systemic circulation and negate or mask the effects of the bareceptors on the systemic pressure.

Since then, evidence has been put forth attempting to elucidate and evaluate the nature of the role of the mesenteric vasculature and its relationship to the control of the systemic blood pressure. Reports in the literature ascribe the changes in the various vascular areas as being caused either by hemodynamic factors, or by a reflex, or by a combination of both.

Heymans et al, in 1936, showed that spinal vasomotor reflexes associated with variations in the general blood pressure caused local alteration in the blood volume of the spleen and hind limbs of dogs. They were unable to produce any augmentation of the general blood pressure by occlusion of the aorta, above the celiac and superior mesenteric arteries, even in animals with the sino-aortic nerves cut.

The present work is in accord with that of Yamada (24), Sarnoff and Yamada (22), Heymans et al (16) and Selkurt and Rothe who produced ar-

terial pressor responses by the occlusion of various mesenteric arteries, particularly the superior mesenteric artery. Vagotomy in the above experiments resulted in no appreciable alteration of the response following mesenteric arterial occlusion, while the response following carotid occlusion was generally greatly augmented (Figures 3,4,5,6,8). This suggests the elimination of the buffering capacity of the aortic arch baroreceptors and also that the afferent pathway mediating the mesenteric arterial response is not vagal. However, the results differ from those of Heymans et al (1960) in two respects. First, the contour of the mesenteric arterial response, unlike that found in Heymans' study, closely resembles that observed following bilateral common carotid occlusion. In general, a sustained response to prolonged occlusion was produced. Occasionally the mesenteric arterial occlusion response did progressively decrease during prolonged occlusion, but this occurred no more frequently nor at any faster rate than it did with some bilateral common carotid occlusion responses. Second, the results obtained with hexamethonium and phenoxybenzamine (Figures 5,6) which are in accord with those of Yamada (24), Selkurt and Rothe (23) and Hemmati and Chiggins (2), who were able either to reduce or abolish the response with either hexamethonium or tetraethylammonium chloride, indicate that the response possessed a reflex component. The dose of hexamethonium used (5 to 7.5 mg/kg) was comparable to that used by Heymans (6 mg/kg). The reason for the difference is not evident.

The carotid sinus denervation resulted in an abolition of the pressor response due to carotid occlusion. After carotid sinus denervation, the mesenteric arterial occlusion response became larger than that which occurred in either the intact or in the vagotomized animal. A larger response might be expected in the sino-aortic denervated preparation on a hemodynamic basis, that

is, the exclusion of a large arterial reservoir. The reason is that now whatever hemodynamic effects take place, do so unopposed by this buffer system.

The possibility of a simple hemodynamic effect of the imposed arterial occlusion accounting for the pressor response was considered in cats by Barnoff and Yamada (23) and in dogs by Yamada (24) and Selkurt and Rothe (23). In the bilateral renal occlusion experiments (22,24) and in the right renal occlusion experiments (23), the systemic arterial responses were small or absent. Thus, the change from kinetic energy to pressure energy in an organ having a blood flow similar to that of the splanchnic bed was negligible. These data in addition to those of the hexamethonium and phenoxybenzamine experiments in both the vagotomized and cross perfused animals made it difficult to attribute the pressor response solely to hemodynamic factors.

The results obtained from the cross perfusion experiments of the isolated splanchnic bed are directly opposed to the results obtained by Meyer and Scher (4) who were unable to obtain any reflex response in the systemic arterial pressure on perfusion of the abdominal aorta or a branch of the superior mesenteric arterial system.

In the autoperfusion experiments the response to the injection of saline under high pressure into the superior mesenteric artery was small and undoubtedly masked by the slight pressor response which followed very shortly afterwards. This slight pressor response could have been caused by the blood volume increase in the systemic circulation after the saline injection. In the isolated splanchnic bed cross perfusion experiments however, very little or no blood volume changes occurred in the systemic circulation. Thus the changes in the systemic arterial pressure in the cross perfusion technique were a reflection of the changes occurring in the isolated splanchnic bed itself and not a composite of splanchnic and systemic blood volume changes and blood redistribution.

In the present cross perfusion experiments it was thought that the rate of development of the pressure in the isolated splanchnic bed was a factor in the degree of vasodepression produced. In order to increase the rate of development of the mesenteric pressure a portal venous clamp was used. After it was shown in the first few animals that there was an increase in the depressor response with the clamp on, it was therefore routinely used for several experiments. To assess the magnitude of the increased response, nineteen experiments were then performed with and without the clamp. In a few animals there was an appreciable increase in the depressor response, with the portal venous clamp, but in most of the animals this increase was very small (see cross perfusion results).

The inability to maintain the depressor response to increased mesenteric arterial perfusion can be compared to the perfusion of the carotid sinus. Bronk found that a characteristic feature of the reflex response of the carotid sinus perfused at high pressure was that after an initial depressor response the blood pressure tends to return to normal levels, despite the maintainance of the high perfusion pressure in the sinus (5,6). Recording efferent impulses, Bronk also observed that as the pressure in the sinus is increased, the pulses decrease and finally cease completely. While maintained at this given high level of pressure, there is frequently an escape from the complete inhibition after some seconds.

In the present study, evidence has been presented showing changes in the systemic blood pressure following changes in the local splanchnic blood pressure. Except for an exact definition of the baroreceptor, the evidence meets the criteria for a reflex phenomenon. Surgical interruption of nervous links between the isolated splanchnic vascular bed and the central nervous

system prevent these changes in the systemic blood pressure. Further, pharmacological interruption of those nervous links which are classically known to partake in the control of systemic blood pressure also prevent these changes.

The Pacinian corpuscles have been implicated by Gamman and Brunk and by Sarnoff and Yamada to exert a regulatory influence on the vascular system of the cat. Functionally, these corpuscles would appear to be well adapted for this purpose (20). Anatomical examination has shown the cat to contain numerous Pacinian corpuscles distributed throughout its mesentery, whereas the mesentery of the dog contains few of these corpuscles. The greater response of the cat to mesenteric arterial occlusion (22,23) could be attributed to a greater number of these receptors. However, considering the present results, the existence of another baroreceptor in the mesentery (of the dog) cannot be discounted.

SECTION V

SUMMARY AND CONCLUSION

SUMMARY

1. Experiments performed in anesthetized dogs have shown that occlusion of the mesenteric arteries produced an increase in the systemic arterial blood pressure.

2. The pattern of the mesenteric arterial occlusion response was the same as that produced by bilateral common carotid arterial occlusion.

3. Hexamethonium and phenoxybenzamine greatly reduced or abolished the pressor response to carotid arterial occlusion and to mesenteric arterial occlusion in the vagotomized animals. The ability to reduce or abolish these pressor responses suggested that the response was a reflex in nature and with only a small hemodynamic component.

4. The fact that the pressor response to mesenteric arterial occlusion greatly increased after vagotomy and carotid sinus denervation indicated that in the dog the sino-aortic reflexes are dominant.

5. In animals in which the carotid occlusion reflex was small, the mesenteric arterial occlusion reflex response was relatively large.

6. Cross perfusion of the isolated splanchnic bed eliminated the hemodynamic factors encountered in the occlusion experiments. An increased perfusion pressure decreased the systemic blood pressure in all experiments. This decreased blood pressure was generally transitory, except in a few cases. The pressor response to a decreased perfusion pressure was less frequently observed.

7. Both the depressor response, and whenever observed, the pressor response following changes in the isolated splanchnic bed perfusion pressure could be greatly reduced or abolished with hexamethonium, phenoxybenzamine, spinal cord section and splanchnicectomy.

CONCLUSION

The experiments reported here confirm the hypothesis of the existence of a barosensitive mechanism in the splanchnic vascular bed. Surgical interruption of the afferent pathways and pharmacological interruption of the efferent pathways indicate that this mechanism is a reflex.

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