Effect of the Autonomic Nervous System on Arteriolar Tone in the Experimental Animal

By Lloyd Beck, Ph.D.

Evidence obtained from experiments involving perfusion of vascular beds and cardiac output studies with controlled filling pressure of the right heart before and during ganglionic blockade support the view that the heart of the dog is tonically stimulated by its sympathetic innervation. The blockade of this tonic stimulation to the heart permits a reduction in cardiac output. The fall in cardiac output results in a decrease in passive stretch of the arterial system which permits a passive rise in peripheral resistance thus compensating for the loss of arteriolar tone so that the peripheral resistance may be unchanged during ganglionic blockade despite a reduction in neurogenic arteriolar tone.

Upon administration of ganglionic blocking agents to anesthetized animals, the blood pressure and the cardiac output fall considerably.\(^1\),\(^2\) Calculation of the total peripheral resistance disclose that the resistance remains essentially unchanged. Similar results have been found in the hypertensive patient.\(^3\) The failure of the peripheral resistance to fall after the administration of ganglionic blocking agents has raised the following questions: 1. Is significant arteriolar tone of sympathetic origin tonically present? 2. If present, do the ganglionic blocking agents fail to block such activity? 3. Is the fall in cardiac output accomplished by a decrease in venomotor tone which causes peripheral venous pooling resulting in a reduction in central venous pressure? 4. Is there another mechanism whereby the ganglionic blocking agents exert their activity?

Because the blood vessel is essentially an elastic tissue, the fall in blood pressure produced by ganglionic blocking agents should cause a rise in resistance when the stretch on the blood vessel is reduced as a result of the passive narrowing of the vessels. The effect of changes in perfusion pressure on vessel distensibility was tested by perfusing vascular beds in the dog before and during ganglionic blockade. The perfusion experiments explained why the peripheral resistance failed to decrease after ganglionic blockade, but did not elucidate the mechanism whereby the reduction in cardiac output was accomplished. A second set of experiments was devised to investigate whether venous pooling was responsible for the decrease in cardiac output.

Perfusion Experiments

In the perfusion experiments a special pump* with tubing of suitable size to permit variation in blood flow over a wide range was employed. Perfusion was carried out either on the vascular bed supplied by the femoral artery or on the vascular bed below the kidney supplied by the descending aorta. In the case of the femoral bed a large polyethylene catheter leading to the pump was introduced into the proximal end of the divided femoral artery and pushed retrograde into the descending aorta. To reduce collateral circulation, the aorta was then approached retroperitoneally through the inguinal area to reduce trauma to the animal and its sympathetic innervation. A ligature was placed around the aorta containing the catheter and tied tightly to prevent bypass of blood. The catheter leading from the pump was introduced into the distal end of the severed fem-

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2. From the Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Mich.

oral artery. By this means blood reached the leg only through the pump. In the case of the vascular bed supplied by the entire descending aorta, a retroperitoneal approach was made through a transverse incision in the flank. A large polyethylene catheter leading to the pump was introduced into the proximal portion of the divided aorta. A catheter leading from the pump was introduced into the distal aorta. The pump therefore supplied all of the blood to the hind part of the animal below the kidneys.

When the blood flow is at low levels as in the determination of the lower portion of the pressure-flow curves, reactive hyperemia is prone to develop. To circumvent hyperemia a shunt was employed to bypass the pump during the interval when determinations were not being made.

A test for integrity of sympathetic innervation was made by utilizing a delay system. The delay consisted simply of a glass coil interposed in the pump circuit and placed in a thermos bottle to prevent heat loss. Thus when a drug was administered intravenously to the body, several minutes passed before the drug would reach the leg. In the meantime reflex changes occurring in the limb could be observed. The test consisted of injecting epinephrine or histamine into the body of the dog. When the systemic blood pressure rises a reflex dilation occurs in the perfused limb and when the systemic blood pressure falls a reflex constriction occurs in the perfused limb if the sympathetic nerves are functionally intact.

All animals were anesthetized with sodium pentobarbital and heparin was used as the anticoagulant. Resistance values were calculated by dividing the perfusion pressure in millimeters of mercury by the blood flow in milliliters per minute.

Figure 1 illustrates the changes in resistance which occur when the stretch on the vessel is changed by varying the perfusion pressure. This pressure-flow curve was obtained by perfusion of the descending aortic bed below the kidney. This figure was chosen because it demonstrates particularly well the

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**Fig. 1** Top. Pressure-flow curve obtained by perfusion of aorta below the kidney. **PP**, perfusion pressure in mm. Hg; **Flow**, blood flow in ml. per minute; peripheral resistance (**PR**) calculated by dividing the perfusion pressure in mm. Hg by blood flow in ml. per minute; vessel radius (**R**) assigned an arbitrary value of unity when peripheral resistance is 10.0.

**Fig. 2** Bottom. Pressure-flow curve obtained by perfusion of femoral bed. **PP**, perfusion pressure in mm. Hg; **Flow**, blood flow in ml. per minute; -X-, curve obtained before administration of hexamethonium; -O-, curve obtained after administration of 5 mg. per Kg. of hexamethonium intravenously; *arrows*, level of systemic arterial pressure before and after ganglionic blockade; *dotted lines*, predicted pressure-flow curves for rigid tube system. Deviation of actual curves from predicted curves due to vessel distension as perfusion pressure is increased.

ability of the blood vessels to distend when the perfusion pressure is elevated to high levels. Before determination of the pressure-flow curve a test for integrity of the sympathetic innervation was carried out in the manner indicated. No reflex response occurred and it was concluded that a complete sympathectomy had been accomplished. It is therefore unlikely that the decrease in peripheral resistance which occurs upon elevation of the
perfusion pressure can be accounted for by reflex changes, unless they are of local origin. Assuming that changes in resistance are the result of vessel distention, we can calculate from Poiseuille's law the change in radius necessary to account for the decrease in resistance. Thus, when the resistance drops from 10.0 to 1.17 the radius increases from unity to 1.71 (fig. 1). These results indicate that if the perfusion pressure is increased, the resulting increase in vessel stretch causes a decrease in the peripheral resistance by a passive distention of the arteriolar bed.

Figure 2 illustrates the situation before and after blockade of sympathetic tone. The upper curve is a plot of pressure against flow before blockade and the lower curve the same plot after the administration of 5 mg. per Kg. of hexamethonium. Before blockade the mean systemic arterial pressure was 120 mm. Hg; after blockade the pressure fell to 80 mm. Hg. If we compare the resistance at a perfusion pressure of 120 mm. and 80 mm. Hg on the unblocked curve we can calculate that the resistance would have been expected to increase from 7.89 to 10.2 had there been no blockade of sympathetic activity. If, on the other hand, the resistance at 120 mm. Hg on the unblocked curve is compared to the resistance at 80 mm. Hg on the blocked curve we can calculate that the resistance is almost identical. The failure of the resistance to fall even though the sympathetic tone is lost is due to the passive decrease in vessel radius when the perfusion pressure is reduced, for if we determine the resistance at the same perfusion pressure as before blockade we find the resistance has fallen to approximately 65 per cent of control. Similarly, a fall in resistance is seen if the determination is made at the same blood flow level before and after blockade. In this instance the resistance in the blocked state is approximately 80 per cent of the resistance in the unblocked state. The fact that the resistance after ganglionic blockade is decreased when the blood flow is maintained constant demonstrates that a reduction in blood flow is a prerequisite if the resistance is to remain unchanged. It is the reduction in blood flow which allows the perfusion pressure and thus the distending force to decrease, which in turn permits a passive increase in vascular resistance. We can conclude then that reduction in blood flow must occur if the vascular resistance is to remain unchanged during ganglionic blockade.

Figures 1 and 2 illustrate the expected changes in resistance when the vascular tone is not excessively high. Would we expect to find the same increase in resistance upon lowering the blood pressure if the animal were hypertensive? We have tried to answer this question by creating a condition of excessive tone in blood vessels by the administration of barium acetate (fig. 3). After obtaining a control pressure-flow curve 3 mg. per Kg. of barium acetate was administered intravenously. When a new steady state was reached a second pressure-flow curve was obtained. We can see that the increase in resistance is much greater after barium if we compare the resistance changes on the 2 curves for equivalent decrements in perfusion pressure. For example, at 100 mm. and 50 mm. Hg we can calculate that before barium the resistance rose from 1.00 to 1.67; after barium the resistance rose from 3.74 to 7.14. Similarly, we can conclude that the greater the smooth muscle tone the greater the increase in re-
arteriolar tone for a given decrement in perfusion pressure or in blood flow. Thus we can assume that a greater passive increase in resistance will occur in the hypertensive state for a given reduction in either blood pressure or in blood flow than in the normotensive state. Certainly, however, until more is known regarding the factors which contribute to the elevated resistance in hypertension, care must be exercised in extrapolating to essential hypertension.

Experiments Involving Filling Pressure of Right Atrium

It is evident from the foregoing that the sympathetic tone can be reduced without decreasing peripheral resistance if the pressure distending the blood vessels is sufficiently decreased by a reduction in blood flow. If no decrease in blood flow occurs, the peripheral resistance is decreased when arteriolar tone of sympathetic origin is blocked by the administration of ganglionic blocking agents. Let us now consider the events occurring in the intact animal when ganglionic blocking agents are administered. Here we see a reduction in blood pressure and in cardiac output, but little change in peripheral resistance. The reduction in cardiac output and blood pressure have been assumed to result from blockade of vasomotor tone and it has been shown above that the peripheral resistance need not decrease when neurogenic arteriolar tone is lost, providing a simultaneous reduction in blood flow takes place. Since a reduction in blood flow is necessary to prevent a decrease in resistance when sympathetic tone is abolished, it appears that a decrease in cardiac output must be the primary event leading to the sequential changes observed upon administration of a ganglionic blocking agent.

In an attempt to explain the reduction in cardiac output the hypothesis has been advanced that ganglionic blocking agents result in a peripheral venous pooling by reducing venomotor tone. The venous pooling is assumed to reduce the filling pressure of the heart resulting in a reduction in cardiac output and consequently in a reduction in systemic blood pressure. We first attempted to examine this hypothesis by measuring the central venous pressure before and during ganglionic blockade. Unanesthetized dogs were immobilized by either decamethonium or gallamine. After the administration of the neuromuscular blocking agent the dogs were intubated and artificially respired. The pump was fitted with neoprene bushings to prevent leakage of gas. Oxygen consumption was measured by connecting a Benedict Roth Metabulator to the respirator. Cardiac outputs were determined by the direct Fick method. The central venous pressure was measured by a strain gage connected to a catheter introduced into the right atrium. Half of the animals received 50 mg. per Kg. of hexamethonium while the remainder received 10 mg. per Kg. The dose appeared to have little effect on the results (table 1).

The cardiac output fell to approximately one half of the control output and the total peripheral resistance rose to approximately

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<th>TABLE 1.—Cardiac Output and Total Peripheral Resistance Change Following Ganglionic Blockade</th>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Control</td>
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<tr>
<td>Decamethonium</td>
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<td>3.91</td>
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<td>2.91</td>
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<td>Mean</td>
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*Chlorisondamine 5 mg. per Kg.
in the previous set of experiments. It was advantageous to ventilate with either pure oxygen or with air throughout any given experiment when measuring oxygen consumption. Some of the animals were immobilized with decamethonium to maintain the intrathoracic pressure constant; others were mildly hyperventilated to inhibit voluntary respiration.

The results illustrated in figure 4 were obtained from a dog under pentobarbital anesthesia and immobilized with decamethonium. After the cardiac output and central venous pressure had become stable, 10 mg. per Kg. of hexamethonium was administered slowly by intravenous route over a 10-minute period. During the administration of hexamethonium the volume of blood in the reservoir increased indicating a tendency for the central venous pressure to rise (which is offset by the uptake of blood by the reservoir). Determinations 42 and 77 minutes after hexamethonium show that the cardiac output fell to approximately one half of the output in the 40-minute period preceding blockade, despite a constantly maintained right atrial pressure. To show that the heart was still responsive to an increase in filling pressure and not undergoing spontaneous deterioration, right atrial pressure was elevated by 2.5 cm. of water. During the next 24 minutes 710 ml. of blood returned to the animal. The cardiac output at this time was above the control level. The catheters were then removed, the incisions repaired and the animal returned to his cage. The dog showed no ill effects other than an infection at the site of the incisions and was sacrificed 1 week later. We can conclude that the reduction in cardiac output was not due to deterioration of the animal, nor to a reduction in filling pressure of the right heart.

**DISCUSSION**

It has been shown by Waud et al., Trapold and Sullivan, and Fries and Rose that the total peripheral resistance decreases when ganglionic blocking agents are administered if cardiac output is maintained constant by
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a mechanical heart. Their observations demonstrate the ability of the ganglionic blocking agents to decrease vasomotor tone in the open-chest animal. In this preparation the cardiac output is usually below normal and sympathetic tone is elevated to maintain the blood pressure. Thus, events occurring in the open-chest preparation need not parallel those occurring in the close-chest animal. By examining the changes taking place in perfused vascular beds we have avoided the problem of the open chest. The results obtained, however, confirm the conclusions of these investigators.

Neither type of experiment accounts for the fall in cardiac output which occurs upon administration of ganglionic blocking agents. We have seen that the blocking agents decrease the cardiac output but usually do not decrease or may even increase the peripheral resistance. These changes are in marked contrast to those occurring upon administration of agents which cause direct vascular relaxation. Starr et al. have shown that nitrates and carbachol markedly reduce the total peripheral resistance, but do not decrease, and often increase, cardiac output. The divergent actions of the 2 groups of drugs in the intact animal render untenable the view that the fall in cardiac output can be accounted for by passive vascular dilatation resulting from blockade of sympathetic activity. These observations have led some investigators to believe that the blocking agents act by reducing venomotor tone and not arteriolar tone. They suggest that if the venomotor tone is reduced, a peripheral venous pooling of blood would result in a decrease in effective filling pressure of the heart and consequently in a reduction in cardiac output. The fall in cardiac output would cause a secondary fall in blood pressure. Crumpton et al. in 1954 hinted at a direct depressant action of the ganglionic blocking agents upon the heart, but stated: "Our studies do not permit conclusions as to whether the reduction in output is due entirely to a decrease in venous return or is associated with a specific action of the drug upon the myocardium." In a later paper they suggested that the reduction in cardiac output could be wholly explained on the basis of venous pooling.

Our first attempts to determine whether peripheral venous pooling following hexamethonium led to a reduction in cardiac output were equivocal. A marked fall in unanesthetized animals immobilized with neuromuscular blocking agents was associated with a slight but insignificant reduction in effective filling pressure. Because the relationship between cardiac output and effective filling pressure in the intact animal is still an unsettled question and since even less is known about the relationship when homeostatic mechanisms are partially abrogated by the administration of ganglionic blocking agents, an experiment was devised in which the effective filling pressure was maintained constant by means of a pressure-stabilizing device. The results obtained indicate that the fall in cardiac output cannot be attributed to a reduction in either venous or arteriolar tone. It must be concluded that the ganglionic blocking agents exert their action at least in part by a direct depression of cardiac function.

There seems to be no evidence in the literature that ganglionic blocking agents directly depress the myocardium. Acheson and Moe showed that tetraethyl ammonium (TEA) increases the cardiac output in the heart-lung preparation; and Lee and Shideman have shown that pentobarbital-induced failure can be reversed by chlorisondamine in the cat papillary and the dog heart-lung preparations. It seems more likely that the reduction in cardiac output produced by ganglionic blocking agents is indirect in nature. The low cardiac output observed in isolated hearts and in heart-lung preparations suggests that the heart, even under basal conditions, is in a state of low tonic stimulation. Rushmer's observation that the heart of the sleeping dog is smaller than that of the waking dog indicates that significant alterations in cardiology occur with minimal change in the state of activity. Several other observations
in the literature support the view that the "ganglionic blocking agents might decrease the cardiac output by an indirect action on the heart. Shipley and Gregg14 observed an increase in cardiac output upon stimulation of the stellate ganglion. Anzola and Rushmer15 have shown an elevation in the diastolic pressure following stimulation of the peripheral end of the severed inferior cardiac nerve. They believe that this increase is the result of epinephrine release from the heart. Bronk et al.,16 demonstrated rhythmic action potentials in the inferior cardiac nerve alternating with the pulse. If ganglionic blocking agents were capable of blocking such activity to the heart, reduction in output might be explained. Pardo et al.17 have shown that tetraethylammonium will block the positive chronotropic effect of preganglionic sympathetic stimulation to the heart when the impulses arise normally from the sinus node. While they state that the accompanying pressor response is not prevented, their illustration demonstrates a reduction in the pressor response. Thus it appears that TEA is also capable of blocking in part the positive inotropic response to sympathetic stimulation.

A reduction in either epinephrine or norepinephrine acting upon the heart could explain the decrease in cardiac output and might help to explain why we have observed in some animals an accumulation of blood in the reservoir after ganglionic blockade. Wiggers in 192718 and Rushmer in 194519 showed that epinephrine could increase the diastolic size of the heart without elevating the diastolic pressure. During exercise or epinephrine infusion the end-systolic volume of the heart decreases20 and, conversely, the end-systolic volume would be expected to increase when catechol secretion decreases. If the ganglionic blocking agents reduced the amount of catechol amines acting upon the heart, a decrease in end-diastolic and an increase in end-systolic size would be expected. This would explain both the reduction in cardiac output and the tendency for the central filling pressure to rise in some animals. The tendency of the filling pressure to rise would be offset by an accumulation of blood in the reservoir.

If the ganglionic blocking agents do effect a decrease in blood pressure by an indirect depression of cardiac function, they still must be considered better therapeutic agents than a myocardial depressant such as quinidine. An agent causing direct myocardial depression would allow a reflex vasoconstriction when the blood pressure fell. The ganglionic blocking agents would prevent a reflex increase in peripheral resistance by blockade of sympathetic vasoconstrictor impulses to the arterioles, and thus diminish the work requirements of the heart.

The above experiments with ganglionic blocking agents and evidence from other types of experiments cited in the literature indicate that the heart is tonically stimulated by the sympathetic system under basal conditions. The reduction in blood pressure with little associated change in total peripheral resistance following ganglionic blockade is believed to be occasioned by blockade of this sympathetic activity to the heart in the anesthetized dog. Caution must be exercised, however, in extrapolating the results to the unanesthetized animal or to the human. With large doses of ganglionic blocking agents in the recumbent human, hemodynamic changes analogous to those occurring in the dog are seen, but small doses which do not lower the blood pressure in the recumbent patient may lower the standing blood pressure. The difference in the small and large dose effect might indicate a different mechanism of action in the 2 situations. If little venomotor tone exists in the recumbent human but is normally present in the standing human, evidence of venomotor blockade would not become apparent until the patient assumed the standing position. Thus, in the human being, if ganglionic blocking agents blocked venomotor tone in low doses and sympathetic activity to the heart in high doses, we could explain the reduction in standing blood pressure after a small dose of the drug and the reduction in recumbent blood pressure after a larger dose. Because of the more profound alterations in venous
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pressure produced by a change from the recumbent to the standing position in man, it would seem that an evaluation of changes in veno-motor tone produced by ganglionic blocking agents should be carried out in the human.

SUMMARY

Results of perfusion experiments show that: (1) peripheral resistance is a function of the perfusion pressure in the absence of sympathetic tone; (2) tonic sympathetic activity to the blood vessels is blocked by hexamethonium; (3) the peripheral resistance may increase after hexamethonium in spite of the blockade of sympathetic activity if the perfusion pressure is reduced sufficiently.

In the unanesthetized animal immobilized with neuromuscular blocking agents, the cardiac output can be reduced markedly and the total peripheral resistance increased without a significant fall in the filling pressure of the heart.

In the anesthetized animal the fall in cardiac output is not entirely due to a loss of vascular tone.

Evidence is presented that the heart, under basal conditions, is receiving stimulation from the sympathetic system and that the reduction in cardiac output following administration of ganglionic blocking agents is the result of the removal of the tonic stimulation.

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