The importance of venous tone in circulatory regulation is gaining increasing recognition, and it is now clear that reflexes mediated through the sympathetic nervous system are important determinants of venous tone. In characterizing the circulatory action of drugs, major emphasis has been placed on their effects on the heart and arteriolar bed, but little attention has been directed toward their influence on the reflex regulation of venous tone. The purpose of this investigation was to determine whether reserpine and guanethidine, two drugs commonly employed in the clinical management of hypertension, affect the reflex regulation of venous tone.

Methods

Twenty-two mongrel dogs, weighing 9.5 to 19 Kg., were anesthetized with intravenous pentobarbital in doses ranging from 15 to 45 mg./Kg.; lower doses were usually sufficient for reserpine-treated dogs. The technique described by Bartelstone for the demonstration of reflex vasoconstriction was employed. Through a median sternotomy incision, theazygos vein and internal mammary vessels were ligated, the vena cava sectioned in the neck, and the common carotid arteries isolated.

Pressures were measured in the abdominal aorta and inferior vena cava through catheters introduced into the femoral artery and vein, and in some experiments, internal mammary artery pressure was also recorded. Statham P23AA transducers, positioned at the level of the heart, were employed in conjunction with a multichannel direct-writing oscillograph. Respiration was maintained through an endotracheal tube with a Harvard pump. Simultaneous occlusion of the thoracic aorta distal to the left subclavian artery and of the inferior vena cava just below the right atrium resulted in isolation of the circulatory bed below the clamps, while circulation in the upper segment was maintained. This major vessel occlusion (MVO) of 30 to 60 seconds duration was performed repeatedly in each animal. The effects of MVO are discussed in detail in Bartelstone's description of his technique.

Tests to determine the presence of reflex vasoconstriction were carried out repeatedly in each experiment in the following manner: Fifteen seconds after MVO, both common carotid arteries were occluded for 45 seconds, or the central end of the cut right vagus nerve was stimulated for 30 seconds. In each experiment, the combination of frequency, voltage, and impulse duration which produced the greatest venous pressor response to central vagal stimulation (CVS) was used. The frequency ranged from 20 to 30 impulses per second, the voltage from 15 to 40, and the duration of each impulse from 1 to 2 msec.

Carotid occlusion (CO) and CVS were performed during MVO at five- to 15-minute intervals both before and after the intravenous administration of 0.5 mg./Kg. of reserpine (five dogs), 1.0 mg./Kg. of guanethidine (two dogs), 3 mg./Kg. guanethidine (two dogs), and 10 mg./Kg. guanethidine (five dogs). A similar experimental design was employed in dogs which had been pretreated with either intraperitoneal injections of 0.5 mg./Kg. of reserpine (four dogs) or intravenous injections of 10 mg./Kg. guanethidine (four dogs) on each of the two days prior to the actual experiment.

In each dog in which reserpine or guanethidine affected these venous reflexes, 5 μg./Kg./min. norepinephrine were infused for 30 minutes. Following discontinuation of this infusion and the return of heart rate and arterial pressure to control values, the responses to CO and CVS were tested again. In order to compare the effects of reserpine and guanethidine on reflex vasoconstriction and on the response to direct sympathetic nerve stimulation, the right cardioaccelerator nerve was stimulated supramaximally for 15 seconds before and after drug injection at 6 to 15 volts and at a frequency of 10 per second in 10 dogs.

Results

EFFECTS OF MAJOR VESSEL OCCLUSION

A typical response to MVO in an untreated dog is illustrated in figure 1. In all experiments, MVO produced an abrupt fall in femoral artery pressure to levels between 5...
The effects of simultaneous occlusion of the thoracic aorta and inferior vena cava, marked as MVO for major vessel occlusion, on the internal mammary artery (IMA), femoral artery (FAP), and inferior vena caval (IVC) pressures in a normal dog.

and 15 mm Hg and a rapid rise in vena caval pressure from levels of 45 to 75 mm H$_2$O to levels between 75 and 150 mm H$_2$O; femoral artery and vena caval pressures then reached a plateau at these levels. The internal mammary artery pressure rose by 10 to 50 mm Hg immediately after the onset of MVO. This elevation in arterial pressure in the cephalad portion of the animal lasted only five to 10 seconds and then fell to essentially the level existing prior to MVO. The acute and chronic administration of guanethidine and the acute administration of reserpine did not affect the venous pressure response to MVO. However, in the dogs which had been pretreated with reserpine, the control vena caval pressures were lower (5 to 40 mm H$_2$O), and MVO increased them to values ranging from 30 to 95 mm H$_2$O. The heart rate and mean arterial pressure were also lower in the reserpine-pretreated dogs.

REFLEX VENOCONSTRICTION DURING CAROTID OCCLUSION

In the 14 untreated dogs studied, following the sustained rise in vena caval pressure produced by MVO, a further rise in venous pressure ranging between 25 and 50 mm H$_2$O was produced by CO. An example of this response is shown in figure 2. This reflex venoconstrictor response to CO was demonstrated repeatedly during periods of observation up to four hours. The response of venous pressure to CO was abolished in five dogs by the intravenous injection of reserpine, in five dogs by the intravenous injection of 10 mg./Kg. guanethidine (fig. 2), and in two dogs by the intravenous administration of 3 mg./Kg. guanethidine. It was reduced in two dogs given 1 mg./Kg. of this drug. In the four dogs pretreated with guanethidine, the reflex venopressor response to CO during MVO was also eliminated. The norepinephrine infusion failed to restore the venopressor response to CO in each experiment in which this reflex had been blocked by reserpine or guanethidine.

REFLEX VENOCONSTRICTION DURING CENTRAL VAGAL STIMULATION

In 14 untreated dogs, CVS during MVO resulted in an elevation of femoral artery, internal mammary artery, and inferior vena caval pressures. Vena caval pressure increased by 25 to 160 mm H$_2$O during CVS. A typical response to CVS during MVO is shown in the left panel of figure 3. These effects of CVS were abolished within three minutes (the shortest time interval tested) following an injection of 10 mg./Kg. of guanethidine in
The effects of central vagal stimulation (CVS) on internal mammary artery (IMA), femoral artery (FAP), and inferior vena caval (IVC) pressures during major vessel occlusion (MVO) before (left) and after (right) intravenous guanethidine, 10 mg./Kg.

five dogs and did not return for three hours (the longest period of observation) following the injection (fig. 3). The pressor response to CVS observed in the internal mammary artery during MVO was markedly reduced in three of these dogs and abolished in the other two. In these experiments, the arterial pressor response to CVS alone, performed without MVO, was reduced but not abolished.

In five dogs, the responses to CVS during MVO were measured at frequent intervals before and after an intravenous injection of 0.5 mg./Kg. of reserpine. In each dog, a gradual reduction of the venous, internal mammary, and femoral arterial pressor responses to CVS occurred, and finally, the responses disappeared completely between 50 and 110 minutes after the reserpine injection (fig. 4). Pretreatment with reserpine (four dogs) or guanethidine (four dogs) eliminated the venopressor response to CVS during MVO. The norepinephrine infusion failed to restore the venopressor response to CVS in each experiment in which this reflex had been blocked by reserpine or guanethidine.

The effects of central vagal stimulation (CVS) on internal mammary artery (IMA), femoral artery (FAP), and inferior vena caval (IVC) pressures before (left panel), 22 minutes (center panel), and 105 minutes (right panel) after the intravenous injection of 0.5 mg./Kg. reserpine.

HEART RATE RESPONSES TO CARDIOACCELERATOR NERVE STIMULATION

In five dogs, the heart rate response to stimulation of the cardioaccelerator nerve was tested both before and at 15-minute intervals after the intravenous injection of 0.5 mg./Kg. of reserpine. In these five dogs, the heart rate response to accelerator nerve stimulation was reduced but not abolished at the time that the venopressor response to CVS had disappeared (fig. 5). The response to cardioaccelerator nerve stimulation was not abolished by reserpine in any of these experiments during the two and a half hours following its injection (the longest time interval observed). However, guanethidine, 3 or 10 mg./Kg. administered intravenously, eliminated the heart rate response to cardioaccelerator nerve stimulation within the first hour after injection. The exact time of onset of this blockade to cardioaccelerator nerve stimulation by guanethidine could not be tested because of the marked increase in heart rate produced by guanethidine during the first 15 to 45 minutes after its injection. In the dogs which had been pretreated with reserpine or guanethidine, the effect of cardioaccelerator nerve stimulation on heart rate...
The effect of right cardioaccelerator nerve stimulation (CAN) at a frequency of 10 per second on heart rate (HR), as determined from the femoral artery pressure (FAP), before (top panel), 25 minutes (center panel), and 108 minutes (bottom panel) after the intravenous injection of 0.5 mg./Kg. reserpine.

FIGURE 5

The effect of right cardioaccelerator nerve stimulation (CAN) at a frequency of 10 per second on heart rate (HR), as determined from the femoral artery pressure (FAP), before (top panel), 25 minutes (center panel), and 108 minutes (bottom panel) after the intravenous injection of 0.5 mg./Kg. reserpine.

was found to be abolished at the time of study.

EFFECT OF ARTERIAL PRESSURE ON VENOPRESSOR RESPONSE TO CENTRAL VAGAL STIMULATION

In three dogs, the aspiration of blood from the abdominal aorta during simultaneous MVO and CVS completely prevented the increase in femoral artery pressure without preventing the caval pressor response to CVS (fig. 6).

Discussion

The reliability of the major vessel occlusion technique for the demonstration of venoconstrictor reflexes has been critically examined by Bartelstone. He concluded that the venopressor response to CO is not dependent on a rise in proximal arterial pressure. This conclusion was based on the observation that aspiration of arterial blood during simultaneous CO and MVO prevented the arterial pressor response to CO in the lower half of the animal without preventing the venopressor response. In our studies on the contribution of the arterial pressor response to the venopressor effect of CVS, the aspiration of blood from the abdominal aorta during simultaneous CVS and MVO completely prevented the femoral arterial pressor response and reduced femoral artery pressure to zero without preventing the venopressor response to CVS (fig. 6). Hence, the response of the venous pressure to CVS occurs without a rise in proximal arterial pressure and appears, therefore, to result primarily from venoconstriction.

Bartelstone has also considered the effect of changes in arterial pressure in the cephalad portion of the animal on pressure in the lower, essentially isolated portion of the ani-
mal. He has observed that MVO produces essentially the same venopressor response in the lower portion of the animal whether the arterial pressure in the cephalad segment of the circulation is elevated as a result of the infusion of norepinephrine or depressed as a result of cessation of the cardiac output.

It is now well established that a sudden reduction of carotid sinus pressure or CVS results in reflex venoconstriction. In this investigation, the effects of reserpine and guanethidine on reflex venoconstriction were investigated, and single intravenous injections of these drugs, as well as treatment during a two-day period, were found to abolish these reflexes. The venopressor response to CO and CVS was blocked by guanethidine within the first five minutes after injection during the initial arterial depressor response. The time of onset of this blockade fits well with the observations of McCubbin et al. that during stimulation of the lumbar sympathetic chain, the arteriolar constrictor response in the leg is blocked within five minutes after guanethidine injection. In the present experiments, it was not possible to determine the exact time of onset of the blockade of the positive chronotropic response to cardioaccelerator nerve stimulation following the administration of guanethidine, because of the tachycardia produced by the release of myocardial catecholamines by this drug. However, the effects of cardioaccelerator nerve stimulation were found to be blocked between 20 and 50 minutes following guanethidine injection, at a time when the heart rate had returned to control values.

Reserpine eliminated reflex venoconstriction secondary to CO and CVS within 90 minutes after its intravenous administration, at a time when the heart rate response to cardioaccelerator nerve stimulation was only reduced. This difference in the degree of blockade of the venoconstriction and of cardiac acceleration suggests that different dose-response relationships may exist for these two responses. An alternate possibility is that the blockade of reflex venoconstriction induced by reserpine resulted, at least in part, from the action of this drug on the central nervous system.

The observation that the infusion of norepinephrine did not restore the venopressor responses to CO or CVS at a time when these responses were blocked by reserpine or guanethidine is consistent with the observation of McCubbin et al. who reported that the infusion of norepinephrine did not restore the arteriolar constrictor response to sympathetic nerve stimulation in dogs treated with guanethidine. Our studies are also consonant with those of Cass and Spriggs, who found that the antiadrenergic effects of guanethidine were not dependent on depletion of the adrenergic transmitter store. The failure of the norepinephrine infusion to overcome the block produced by reserpine is interesting in view of the report by Burn and Rand that the abolition of the arteriolar constrictor response to direct sympathetic nerve stimulation in the reserpine-pretreated animal could be reversed by the administration of norepinephrine.

The blockade of reflex venous constriction by reserpine and guanethidine suggests that the hypotensive effects observed in patients undergoing treatment with these drugs may be mediated, in part, by a decline in venous return which, in turn, would tend to reduce the cardiac output. These effects would be expected to be most pronounced when patients assume the erect position, and indeed, postural hypotension is frequently observed. This hypothesis is supported by the observations that in patients receiving guanethidine and studied in the semierect position, the cardiac output tends to be low while the calculated systemic vascular resistance is normal or even elevated.

Summary

The effects of reserpine and guanethidine on reflex venoconstriction were studied in a group of open-chest anesthetized dogs by the major vessel occlusion technique described by Bartelstone. Guanethidine (10 mg./Kg. intravenously) blocked reflex venous constriction following carotid occlusion and central
vagal stimulation within five minutes after injection in five dogs. Reserpine (0.5 mg/Kg intravenously) required 50 to 110 minutes to abolish these venopressor reflexes in five animals. Pretreatment with either reserpine (0.5 mg./Kg. intraperitoneally on two consecutive days in four dogs) or guanethidine (10 mg./Kg. intravenously on two days in four dogs) also abolished reflex venoconstriction. These results indicate that reserpine and guanethidine are capable of blocking reflex venoconstriction, and it is suggested that this action may contribute to their effects in the treatment of hypertension.

References

Book Reviews


After opening with a brief coverage of the pathology and clinical features, the authors devote most of the monograph to therapy. The operation of lumbar sympathectomy is discussed in terms of technique, surgical anatomy, physiological effects on vaso-motor and sudomotor activities, and clinical effects. The chapter on vaso-dilator drugs is adequately documented by responses of the limbs to chlorpromazine, promazine, tolazone, and dibenzylzine.


This is a detailed analysis of 44 different grafts and synthetic prostheses, including a comparison of their porosity, tissue reaction, functional behavior, and ultimate fate in the body. The pig has been used by the author as the ideal laboratory animal to determine the long-term fate of grafts within a relatively short period. The concluding chapter on the search for better graft material effectively outlines the necessity for future investigation.
Effects of Reserpine and Guanethidine on Venous Reflexes
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