Activity of the Vasomotor Centers

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The hind limb of the cat connected to the body by its nerves alone, and perfused with Krebs' solution is a simple method of studying the reactions of the vasomotor mechanisms. The central action of epinephrine and a failure of the center as a result of prolonged hemorrhage or anoxia have been shown.

Our knowledge of the vasomotor mechanism in the past has for the most part been obtained by studying the blood pressure and blood flow in the peripheral vessels by means of plethysmography or flow meters before and after section of the vasomotor nerves. A small number of workers have perfused isolated organs connected only by nerves. More recently a number of workers have perfused various parts of the body from another animal or by pumps. These methods are obviously very costly and although possible for special projects are not suitable for the routine studies such as the action of drugs.

In the present investigations, the innervated hind-limb perfused with Krebs' solution at 37 C. gives identical results to those obtained by other more complicated and expensive methods. It offers also a simple method for the study of the action of the central vasomotor mechanisms.

In this paper a number of the classical experiments are reported to show the general value of the method, and in doing so several new points have been brought out and detail added. For simplicity the term "vasomotor centers" is used, but it is to be understood that these include all the central mechanisms including synapses in sympathetic ganglia.

Methods

The observations were made on cats anesthetized with chloralose (60 mg./Kg. body weight), the blood pressure being recorded in the carotid artery. One hind leg was perfused through the femoral or the iliac artery, or more commonly through the abdominal aorta because of its convenient size. All branches below the cannula and down to the femoral artery were tied. All veins were also tied off and the femoral vein was opened. In critical experiments, especially those involving drugs, the muscles and bone were divided so as to leave the sciatic and femoral nerves as the sole connection with the body. This procedure was liable to cause shock and therefore was not used in all experiments. Krebs' solution, equilibrated with 5 per cent CO₂ and O₂ was used for perfusion. Krebs' solution produces much less edema and thus enables the reaction of the hind legs' blood vessels to continue for much longer than does Ringer-Locke's solution.

The reactions of the higher centers and those of the spinal cord and sympathetic ganglia can be differentiated by section of the spinal cord at the first cervical segment.

The perfusion system was previously described.1 It consists essentially of perfusion from a large bottle at a height of about 5 feet, a record being made of the perfusion pressure by means of a side tube. The actual perfusion pressure is adjusted to about 50 cm. H₂O by means of a clip between the heating coil and the cannula.

Results

Response of the Baroreceptors. The method demonstrates particularly well the effect of a fall in pressure in the carotid artery; indeed, the response to occlusion of one artery, blood pressure being recorded in the other, is the simplest way of testing the sensitivity of the preparation. If, however, the procedure is repeated at the beginning of an experiment, a progressive increase in the vasomotor response is seen, indicating a facilitation of the baroreceptor reflex. This is so little evident in the blood pressure that it has not hitherto been described (fig. 1).

Decrease in blood pressure produced by direct depression of the heart's activity or by vasodilator agents cause an increased vasomotor response. Providing that the fall in blood pressure is not so severe as to produce asphyxia, the vasoconstriction is absent after inactivating the baroreceptors by dividing both...
Fig. 1-14. 1. Upper record (PP), perfusion pressure to hind limb, in cms. of water. Lower record, (B.P.), carotid arterial pressure. Between each pair of arrows, opposite carotid artery occluded. 2 and 5. Heart rate (HR) measured from the electrocardiogram, below blood pressure (B.P.) At arrow, 10 ml. and 30 ml. Krebs' solution injected rapidly intravenously. 4. Stepwise decline of arterial pressure by successive 10 ml. bleedings. 6. Effect of breathing 10 per cent O₂ and N (arrows). Both vagus nerves cut and carotid artery occluded. 7. Overventilation with the pump (arrows). 8. Stimulation of central contralateral sciatic nerve (arrow). 9. Compression of left atrium (arrow). 10. Compression of pulmonary artery. 11. One blast from the pump to lungs (arrow). 12. Both vagi divided at first arrow; carotid artery occluded at second arrow; 100 μg. epinephrine at third arrow. 13. Upper record (SP), perfusion pressure to the skinned limb; middle record (NL), perfusion pressure to the normal limb. At arrow 100 μg. epinephrine injected intravenously. 14. Upper record (SL) from the skinned limb. Between the arrows 20 μg. norepinephrine.
vagus nerves and clipping the other carotid artery, indicating that there is no direct stimulation of the vasomotor center as described for histamine and acetylcholine in the dog (Taylor and Page); nor do they seem to be any impulses from the abdomen such as those described in the dog by Heymans and co-workers.

**Injection of Fluid.** The intravenous injection of fluids has been described as producing variable effects on the vasomotor system. Both vasodilatation and vasoconstriction have been described by various authors. In our preparation both effects are seen.

In a sensitive preparation the intravenous injection of 10 ml. of Krebs' solution or Ringer-Locke's solution or saline produces a marked depression lasting a few minutes (fig. 2). This depression is associated with a brief rise in arterial pressure which is probably the cause of the response, since it does not occur after cutting the vagus nerves and occluding the other carotid artery. This fact suggests that there are no baroreceptors in the cerebral circulation supplied by the vertebral arteries. A slowing of the heart accompanies the vasomotor depression. A further injection of 10 ml. immediately after recovery may fail to produce a response, but a depression can be obtained if 10 min. or so is allowed for recovery. It must be remarked that 10 ml. does not raise the venous pressure.

If more than 30 ml. are injected rapidly so as to raise the venous pressure, there is usually no increase in vasomotor activity (fig. 3) often accompanied by cardiotachycardia. While the venous pressure remains high the response to carotid occlusion may be lost, as described by McDowall.

It is commonly possible to obtain the inhibitory effects of small amounts of fluid such as Krebs' solution and the stimulating effects of large amounts on the vasomotor and cardiac responses in the same animal. After a varying interval to permit fluid to pass into the tissues, the procedure can be repeated.

**Hemorrhage.** When a fresh animal is severely and rapidly bled, there is an intense vasoconstriction. Since the response is present in the spinal preparation the hemorrhage must also stimulate centers below the medulla.

If an amount of blood just sufficient to lower the blood pressure is removed, there may be no vasomotor response, which suggests that the recovery of the blood pressure after a small hemorrhage does not involve the baroreceptors. This confirms the observations of Edholm and McDowall and Edholm. Another possible explanation of the apparent vasomotor inactivity may be the loss of the activity of the skin vessels in such a perfused limb.

On the other hand, after the center has been impaired by several slow hemorrhages, a point is reached when further bleeding leads to a failure of the vasomotor mechanism (fig. 4). This vasodilatation is then, not entirely a peripheral dilatation due to tissue asphyxia, as has been suggested by Remington and his colleagues.

When the center is impaired by hemorrhage, section of the vagus leads to a further depression of the central mechanism. The circumstances of its occurrence suggest that the failure is due, in part at least, to loss of impulses from aortic chemoreceptors. Occasionally, if the hemorrhage is very severe, a dual effect is obtained: an initial depression is followed by an increased vasomotor response which, however, is never so intense as in an unbled animal.

**Oxygen Lack.** Administration of nitrogen leads to an initial stimulation of the vasomotor mechanism. Since the stimulating effect occurs after inactivation of the chemoreceptors by section of both vagus nerves, by carotid occlusion (fig. 5) and in the spinal preparation, it may be considered to act on both the brain and the spinal cord. It is possible that this apparent direct stimulation by anoxia is due, in part at least, to the heart failure with consequent ischemic asphyxia of the center.

Even though the administration is not prolonged until there is a failure of respiration, there is subsequently a progressive failure of the vasomotor mechanism which is irreversible. The administration of 5–10 per cent oxygen with the nitrogen prevents this progressive failure. This progressive failure after oxygen lack might be considered unexpected, but we are familiar with its occurrence in relation to isolated cardiac muscle in which it has been
shown to be due to the uptake of sodium (Hercus, McDowall and Mendel20).

**Carbon Dioxide.** The central stimulating action of carbon dioxide can be demonstrated in amounts which do not affect the blood pressure, no doubt because of its peripheral dilator action. Similar results are produced by asphyxia by causing the animal to rebreathe its own expired air (fig. 6).

On the other hand, loss of carbon dioxide produced by overventilation (fig. 7) or by simply opening the chest widely leads to a failure of the vasomotor mechanism. This failure can be prevented by using 5 per cent carbon dioxide with oxygen for the artificial respiration. The vasomotor failure precedes the fall in blood pressure, no doubt because the loss of carbon dioxide leads to peripheral vasoconstriction (McDowall21).

The spinal centers are relatively insensitive to carbon dioxide, thus after administering oxygen and 5 per cent carbon dioxide to the spinal animal the onset of vasoconstriction on stopping the pump is far slower than after repairing with air.

**Sensory Stimulation.** Stimulation of the central end of the sciatic nerve produces vasoconstriction (fig. 8). This may occur even when the sensory stimulation has produced a fall of blood pressure, indicating that a vasodilatation occurs elsewhere in the body. Later in the experiment, after frequent repetition, dilatation of the perfused limb occurs. A depression of the vasomotor center may also be produced by piercing the forelimb. In one experiment a pull on the tracheal cannula frequently caused a vasodilatation.

**Pulmonary Pressure.** A rise in pulmonary pressure by compressing the left atrium (fig. 9) or by a single blast from the pump (fig. 11) causes vasodilatation, whereas a fall in pulmonary pressure by compressing the pulmonary artery causes a vasoconstriction (fig. 10). The fact that a rise in pulmonary pressure produces a reflex systemic vasodilatation has already been described22-26; but this method beyond doubt shows the inhibition of the center.

**Epinephrine and Norepinephrine.** Epinephrine dilatation is, in part at least, produced by inhibition of central mechanisms. It occurs whether the drug is injected rapidly, e.g., in ⅓ ml. (fig. 12) or infused slowly; indeed, in the latter case there is additional baroreceptor activity as a result of the increased cardiac output. This dilatation is as great in the skinned as in the intact limb, indicating that it is the muscle vessels which dilate (fig. 13). This muscle vasodilatation cannot be due to adrenalin reaching the limb via the bone vessels as it occurs after division of the muscle and bone.

The vasodilatation occurs in the absence of a rise in blood pressure and with ⅓ µg. and ether anesthesia; after section of both vagus nerves and carotid occlusion the dilatation still occurs (fig. 12).

In many experiments the central inhibition is interrupted by a central stimulation which was again succeeded by a depression. Norepinephrine has the same central action (fig. 14).

Several workers have put forward evidence that the dilatation is due to an inhibition of the vasomotor center as a result of the rise in blood pressure produced,27-29 while later, Heymans and Heuvel-Heymans30, 31 showed that some inhibition might be brought about by a direct action on the baroreceptors.

In our experiments it is clear that the baroreceptors are not wholly responsible for the inhibition for it occurs when they are inactivated in the cat, and indeed may be shown to occur in the etherized animal in which small doses of epinephrine are well known to produce a fall in blood pressure. However, there is no doubt that the effect on the center is greater when the baroreceptors are operating. Our experiments do not exclude the possibility that epinephrine may block transmission in the sympathetic nervous pathway, for it has been shown that it can produce ganglionic block (Marazzi,22 Bübring and Burn,23 Lundberg,24 Malmejac25).

**DISCUSSION**

It is seen that all the well-known reactions of the vasomotor center may be demonstrated by the method described, but a number of new points appear. Thus it is evident that the response of the carotid baroreceptors to a simple fall of pressure in the carotid is very variable and may be facilitated by use or reduced by a
rise of venous pressure. The latter point may indicate at least one way in which the response of the baroreceptors may be thrown out of action, for it is well known that in emotions and in physical exercise the blood pressure and heart rate may rise sometimes to double its rest value in spite of the baroreceptors reflexes.

The inhibition of the center by the injection of fluid supports the work of many observers, showing that the so-called right atrial reflex described by Bainbridge is far from established; it must be recalled that under chloralose anesthesia the baroreceptor reflexes are highly active. The absence of the inhibition after the carotid arteries have been occluded and the vagi cut is clear indication that, in the cat at least, impulses passing up from a region other than that served by the vagus and from the carotids are of negligible importance. It also shows that the pressure transmitted to the carotid sinus through the external carotid artery is negligible. It will be recalled that in the cat the internal carotid artery is minute.

The demonstration by means of hemorrhage and by the administration of nitrogen that the centers are particularly and progressively affected by oxygen lack suggests that progressive failure of the circulation which commonly follows hypotension produced in a variety of ways may be of a similar nature.

How far the observations on epinephrine and norepinephrine explain the dilator action of those substances on the muscle vessels of the cat is difficult to decide. The latter has always been difficult to explain in view of the fact that section of the sympathetic which is now held to liberate norepinephrine certainly causes a dilatation of the same vessels. Such an inhibition of central mechanisms has already been described by Bülbbring and Burn who have suggested that the excessive outpouring of epinephrine may in this way be responsible for emotional fainting, although, if this were so, a flushing of the skin would be expected at least prior to the syncope, while it is well known that the faint is preceded by pallor. It may be, however, that the local action of the epinephrine on the skin vessels more than compensates for loss of vasmotor activity. Overventilation, which likewise reduces vasmotor activity, also causes skin pallor and therefore may not produce a fall of arterial blood pressure (see McDowall).

REFERENCES

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