VASOPRESSORS¹

P. R. BROMAGE, M.B., B.S., D.A., F.F.A.R.C.S.²

WHEN a man travels in dangerous country, he carries a gun and if he is wise he knows what his gun will do in terms of range, stopping power, and speed of action. We often turn to vasopressors as a weapon to get our patients and ourselves out of difficult situations, but unfortunately we do not always have a very clear idea of what these drugs can do, and we sometimes find ourselves in the embarrassing situation of trying to stop an elephant with a shotgun, or worse still we may be overanxious and trigger-happy, and our foolishness may stir up trouble amongst the natives who might otherwise have been peaceably disposed towards us.

But before we turn to violent methods of self-protection against the dangers of hypotension we must make sure that gentler ways may not be better. Perhaps we should feed the prowling enemy, and win him over by replete contentment. If the circulation is half empty, we will continue to deal with a dangerous situation until it is filled and appeased. One often sees anaesthetists using vasopressor drugs to treat hypovolaemic hypotension when their time would be better spent restoring a depleted blood volume.

Let us consider the blood pressure in terms of blood volume and distension of the vascular bed, without the complicating factor of cardiac output. Imagine that the heart is momentarily arrested, and the pressure throughout the circulatory system can be measured simultaneously. This has been done experimentally in dogs by Guyton and his colleagues (1). The pressure obtained under these circumstances is called "the static blood pressure," or "mean circulatory filling pressure." This pressure is the basic background pressure on which the pumping action of the heart is superimposed. Figure 1 is constructed from Guyton's data, and shows the relationship between the blood volume, and the static blood pressure, and the tone of the blood vessel walls.

Normally the static blood pressure is about 6–8 cm. H₂O. If the blood volume is reduced by haemorrhage or dehydration, the static filling pressure also falls until it reaches zero. This point is reached after losing about 40 per cent of the blood volume, and at this point the animal dies, for no matter how hard the heart pumps there is just not enough fluid to fill the whole vascular system. Beyond this point vasodilatation and vasoconstriction have no meaning, for their pressure-volume (or compliance) curves have all reached zero.

However, at points between the normal blood volume and the "bled-out volume" vasoconstriction may be very important, and at extremes of low blood volume it may make all the difference between life and death. For example,

¹Paper read at a meeting of the Quebec Division of the Canadian Anaesthetists' Society, February 6, 1960.

²Department of Anaesthesia, Royal Victoria Hospital, Montreal, P.Q.

**PRESSURE - VOLUME CHARACTERISTICS OF VASCULAR BED
IN DOGS WITH ARRESTED HEART** (After Guyton et al., 1954)

FIGURE 1

prolonged bed-rest in itself reduces the blood volume (2) and many bed-ridden patients live happily with only about two-thirds of the normal amount of blood in their bodies, but they have constricted large areas of their vascular bed to make up for the loss of volume. Now, if we take such a patient and suddenly remove his vasoconstriction by means of a high spinal blockade or by deep general anaesthesia, we will precipitate his "static blood pressure" from a fairly useful level to one which is almost lethally low, and death may occur from acute hypotension and coronary ischaemia. On the other hand, a patient with a large blood volume and vasodilatation (as in pregnancy) may be living on the bottom line, labelled "Vasodilatation" in Figure 1. If we exhibit a vasoconstrictor here the "static blood pressure" may rise to alarming heights with signs of left ventricular failure and encephalopathy.

Therefore when we think of vasopressors, we should think of them applied to the broad background of blood volume and "static filling pressure," and in this way we shall be spared many disappointments and embarrassing moments.

Let me give an actual example. A 200 lb. woman with hypertension and chronic bronchitis was to have a pelvic repair under spinal analgesia. In the hospital concerned it was the practice to give a vasopressor drug before spinal blocks, and the patient was given 50 mg. ephedrine subcutaneously. The spinal was administered and a few minutes later she was placed in the lithotomy position. The block only extended to T₁₀ and everyone was amazed when the patient suddenly convulsed and showed all the signs of a cerebrovascular accident.

In effect, it would have been surprising if she had not had one, for she was already hypertensive and yet she was given a powerful pressor drug when it was not needed, and in addition she had an autotransfusion of blood from her own elevated legs.

Now, supposing we decide we are likely to need a pressor drug, what are we going to use and why? Most of us would answer: "Well, I use so-and-so, because I'm used to it, and it works pretty well." We may even advance scientific reasons for our choice, arguing that it either is, or is not, a drug which affects the force and pace of the heart, depending on whether or not we favour such a property. In the genealogical tree of vasopressors, we find that the families are divided mostly according to their effects on the heart—the inotropic and non-inotropic drugs. The body has been diplomatic in its patronage, and has chosen for its natural vasopressor one which has a foot in both camps: that is, noradrenaline, which is both vasoconstrictive and positively inotropic. When we try to correct a faulty pressure system, perhaps we might be wise to plan our vasopressor campaign in terms of what the body would choose if it could, keeping noradrenaline prominently in our minds. I do not mean that we should use noradrenaline infusions every time we need a vasopressor, but that it should not be too far from our thoughts.

Professor Burn and his colleagues in the Department of Pharmacology at Oxford have done much to place vasopressor medication on more rational grounds (3-6). Figure 2 is a synopsis of Burn's hypothesis. He postulates that all nerves (post-ganglionic as well as pre-ganglionic) are cholinergic. The post-ganglionic nerves secrete acetylcholine, which in turn releases noradrenaline from depots close to the effector organ (that is, the smooth muscle of the vessel walls).

VASOCONSTRICTIVE RESPONSE TO SYMPATHETIC STIMULATION (after Burn)

FIGURE 2

Under normal circumstances the noradrenaline depots are responsive to all sorts of pressor agents, both noradrenaline itself and that group of pressor agents which are indirect vasopressors, that is, which act by releasing noradrenaline. Now, if the noradrenaline depots are empty (as in the reserpine-treated patient), then the indirect stimulators no longer work since there is no noradrenaline for them to release. Under these circumstances methedrine and ephedrine are useless, but, oddly enough, the effector organ is extremely responsive to very small doses of circulating noradrenaline.

On the other hand, when the noradrenaline stores are overfilled (as after prolonged noradrenaline infusion), they show signs of constipation, and cannot evacuate themselves without aid. Under these circumstances a noradrenaline liberator, such as methedrine, is the drug of choice and members of this group should be considered when a noradrenaline drip fails to raise the blood pressure.

Two cases serve to illustrate this point.

Figure 3 shows the blood pressure chart of a patient undergoing an operation for splenorenal shunt under continuous epidural blockade. Notice the very small amounts of noradrenaline required to raise the blood pressure. 1-2 $\mu\text{g.}/\text{min.}$ is all that is required (that is 10-20 drops per minute of a solution containing 0.5 mg. noradrenaline in 500 ml.). This is the right strength of noradrenaline to use, but it is one-quarter of that recommended by the makers.

FIGURE 3

Figure 4 shows the blood pressure chart of a patient having a phaeochromocytoma removed. After excision of the tumour he was unresponsive to enormous amounts of infused noradrenaline. At point M, 10 mg. methedrine were injected intravenously. This enabled him to release his own noradrenaline stores, and he maintained a good blood pressure thereafter.

FIGURE 4. Blood pressure chart of 8-year-old boy undergoing excision of phaeochromocytoma. Epidural using 1.5 per cent Xylocaine. 10 mg. methedrine injected intravenously at M. Blood samples (for catecholamines) taken at S₁-S₅.

In this brief outline I want to confine most of my remarks to the effects of vasopressors on the peripheral resistance, but in passing I will just touch on a few points concerning the cardiac output.

Pulse rate has an important effect on the cardiac output; so in hypotensive states associated with bradycardia we should turn to drugs which increase the heart rate rather than those which slow it. Atropine by itself is a useful vasopressor under these circumstances; 1/300-1/150 gr. will raise the pulse rate and elevate the blood pressure by about 15-20 mm. Hg. Consciousness may do the same thing, as we can see in Figure 5 (7). Here is a patient with an epidural block to T₇. Under light nitrous oxide sleep the blood pressure fell 35 mm. Hg, but returned to the previous level immediately the patient awoke.

Hydrocortisone and calcium are two other important drugs which should not be forgotten in our concern for the blood pressure. Since they are not vasopressors in the strict sense of the word, we will not dwell on them, but we may find them indispensable under certain circumstances: hydrocortisone, where corticoids have been administered before operation; calcium in states where the circulating ionisable calcium is low, as after massive blood transfusion.

Finally, we turn to what I call the Therapy of Desperation--the use of vasopressors when we cannot think of anything else to do, as in such conditions as

FIGURE 5. Effect of consciousness on blood pressure.

coronary thrombosis and other forms of intractable hypotension. Figure 6 shows the blood pressure chart of a girl who had some infected blood given to her during a spinal fusion. Toxaemia followed, accompanied by severe hypotension which was resistant to methedrine, hydrocortisone, noradrenaline, and phenylephrine. However, she had the resilience of youth, and she felt better with her hypotension than she did with the enormous doses of vasopressors which were poured into her; so her blood pressure was suffered to remain low. In the fulness of time the fever left her, and then, and then only, did she become normally responsive to reasonable doses of vasopressors, but by this time, of course, there was no point in using them.

When faced with this type of case we are sorely tempted to use poisonous doses of pressor drugs. We are tempted because we are ignorant and know no better, and it seems the only thing left in our power to do—apart from leaving things to Nature. But we are not always very good at doing that.

My view on vasopressors can be summed up quite briefly. Employ them as you would a lawyer—that is, do not use one unless you have to, and if one *does* have to, choose the best you can get. If you decide to follow Nature's example and use noradrenaline, use it with the same moderation that the body does. Recent work has shown this to be about 2–3 $\mu\text{g./min.}$ (8). This is 20–30 drops per minute of a solution containing $\frac{1}{2}$ ml. noradrenaline solution in a 500 ml. bottle, and this is more than you need to keep the blood pressure at normal levels after a total spinal blockade.

If the noradrenaline stores have become overfilled and constipated after prolonged noradrenaline overdosage, we must use a cathartic or noradrenaline releaser, such as methedrine.

FIGURE 6. Toxaemic hypotension refractory to vasoconstrictor drugs.

Under normal circumstances we can be lazy and use other and longer-lasting pressor drugs if we wish, but when the noradrenaline stores are depleted, or when we want quick and certain action, we should turn to noradrenaline as the bulwark of our defence.

In toxaemia and central cardiac failure our knowledge is still incomplete, but at present it seems that vasoconstrictors are not likely to do much good.

REFERENCES

1. GUYTON, A. C., POLIZO, D., & ARMSTRONG, G. G. Mean Circulatory Filling Pressure Measured Immediately after Cessation of Heart Pumping. *Am. J. Physiol.* 179: 261 (1954).
2. TAYLOR, H. L.; ERICKSON, L.; HENSCH, H.; & KEYS, A. The Effect of Bed Rest on the Blood Volume of Normal Young Men. *Am. J. Physiol.* 144: 227 (1945).
3. BURN, J. H., & RAND, M. J. Sympathetic Postganglionic Mechanism. *Nature* 184: 163 (1959).
4. BURN, J. H.
5. BURN, J. H., & RAND, M. J. Noradrenaline in Artery Walls and Its Dispersal by Reserpine. *Brit. Med. J.* i: 903 (1958).
6. BURN, J. H., & WALKER, J. M. The Action of Sympathomimetic Amines on the Heart Rate. *J. Physiol.* 145: 10 (Proc.) (1959).
7. BROMAGE, P. R. Spinal Epidural Analgesia, p. 23. Edinburgh: E. & S. Livingstone Ltd. (1954).
8. COHEN, G.; HOLLAND, B.; SHA, J.; & GOLDENBERG, M. Plasma Concentrations of Epinephrine and Norepinephrine during Intravenous Infusions in Man. *J. Clin. Invest.* 38: 1935 (1959).