Regulation of the peripheral circulation

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To cover, even superficially, this topic in 25 minutes is, of course, an impossible task, and therefore I will concentrate on a few aspects which might be of particular interest in this context, referring to some recent reviews and papers for details and for other aspects of the peripheral circulation.

Vascular dimensions

Needless to say, the different vascular circuits and their consecutive sections are designed to meet the particular demands of their tissues, both as to the range of blood supply and as to how this supply is distributed and put into efficient exchange within the tissue. Not only the dimensions of the resistance vessels but also the capillary permeability and surface area are therefore closely tailored both for local nutritional demands and in some tissues for such special functions as secretion and absorption (Folkow and Neil, 1971).

Principles of vascular control

Local control Vascular control, in terms of resistance, capacitance, perfused capillary surface area, and mean level of capillary pressure, is exercised by means of helically arranged smooth muscles. In general, these muscles are functionally well adapted to fit the specialized tasks of the series-coupled sections of the vascular circuits in which they are situated.

The muscle sheath that controls resistance and perfused capillary surface area forms the bulk of the relatively thick walls in precapillary resistance vessels and 'sphincters', their high wall/lumen ratio being well suited for such supply functions. This design has the advantage that only a little muscle shortening is needed to produce major luminal reductions, or even closure, since contractions appear to be initiated from the outermost muscle sheath so that deeper wall sections are pushed towards the lumen to reduce it in an escalating fashion. For such reasons it appears that the wide range from maximal dilatation to maxi-

mal constriction can be covered by 25-30 per cent change in smooth muscle length.

Regulation of flow by means of the precapillary resistance and sphincter section must, of course, first of all suit local tissue demands. This calls for dominant local control machinery, operating from a high level of 'basal tone'. This in no way belittles the importance of the superimposed remote control exercised mainly by the vasoconstrictor fibres which induce drastic restrictions and redistributions of flow whenever needed. The venous capacitance vessels, on the other hand, rather than serving primarily such local needs, may be said to form an adjustable 'fore-chamber' for priming the pump, a type of function which calls for central integration by means of nervous remote control at the expense of local control mechanisms.

Accordingly, while most precapillary vessels after acute denervation still display a pronounced tone, this is feeble or even absent in most postcapillary capacitance sections. This basal vascular tone is of truly myogenic origin, initiated from multiple, often shifting 'pacemakers' and dependent on a myogenic spread of excitation (Mellander and Johansson, 1968). This by no means denies that extrinsic excitatory factors, particularly neurogenic but also bloodborne ones, may considerably enhance such inherent activity. Further, the continuous stretch exerted by the blood pressure serves to facilitate the myogenic activity, thus forming a positive feedback of fairly limited power, which, moreover, is efficiently counterbalanced by negative feedback mechanisms of local chemical origin. Such an arrangement largely eliminates risks for any inherent instability of the system as a consequence of the positive feedback arrangement (Folkow, 1964). The local negative feedback is constituted by the steadily produced 'vasodilator metabolites', being of various kinds and of relative importance in different circuits (Mellander and Johansson, 1968; Folkow and Neil, 1971). In this way the local chemical factors serve to modify inherent vascular tone so as to automatically adjust blood supply to current nutritional demands. In a sense, there-

fore, precapillary smooth muscle functions like an inherently active stretch receptor which exhibits a built-in contractility and which is steadily damped by a potentially powerful negative feedback.

This arrangement constitutes the background for 'flow autoregulation', implying that regional blood supply and its capillary distribution as well as the capillary pressure level all tend to remain largely constant with changes in pressure head (Johnson, 1964). Thus the 'myogenic' and 'local chemical factors' both contribute to the establishment of flow autoregulation. They can, however, also be put into competition – for example, when flow reduction is caused by a rise of venous pressure. Then, the transmural pressure rise tends to initiate the 'myogenic' constrictor response while the flow reduction tends to cause metabolite accumulation and, consequently, dilatation (Folkow, 1962). When such competition is created between these two factors it appears that the myogenic one often displays the lower 'threshold', as there is usually a tendency towards constriction if the change is small or moderate. However, once tissue nutrition really becomes threatened, dilatation ultimately ensues if the pressure head, and hence flow, has become considerably reduced.

Remote control Superimposed on this efficient local system controlling the regional homeostasis of blood supply and its capillary distribution, the centrally governed vasoconstrictor fibres exert a restricting influence that during rest is rather feeble but which in states of emergency can drastically interfere with flow in some tissues and, in addition, it accomplishes a considerable blood volume mobilization within the capacitance section. The activity of these fibres forms an important instrument of overall homeostasis, which is primarily governed by cardiovascular proprioceptors and integrated in the brain stem. These homeostatic centres can in turn be temporarily overruled by corticohypothalamic centres, serving to adjust the organism as a whole to face external challenges and threats.

It is well known that the very distribution of the vasoconstrictor fibres is so arranged as to allow considerable cardiac output redistributions even when they are uniformly activated. Flow is then restricted in skin, muscle, kidneys, and gastrointestinal tract, where the fibre supply is abundant; which favours the vitally important myocardium and central nervous system, where the supply is scant. However, the discharge of these fibres is not

always uniform but may be modified into differentiated patterns which are still only in part understood (Folkow and Neil, 1971).

The vasoconstrictor fibres excite directly only the outermost sheath of vascular smooth muscle, but deeper layers appear to be secondarily recruited in a most efficient way by means of myogenic cell-to-cell propagation (Johansson and Ljung, 1968). Accordingly, where the constrictor fibre supply to the outer sheath is rich, their activation causes a dominant 'centralization' of a normally dominant local control of flow. However, no single tissue is completely at the mercy of such remote flow restrictions. The reason is that with vasoconstriction, the vasodilator metabolites will then accumulate increasingly the more intense the neurogenic restriction becomes. This assures some though, in well-innervated vascular beds, fairly meagre nutritional supply, even in situations of intense sympathetic discharge. The final outcome of such a competitive battle between the 'central government' and the 'local administration' concerning regional supply is a matter of the distribution of the constrictor fibres and their current activity on the one hand, and the level of tissue metabolism and vasodilator power of produced metabolites on the other. Consequently it varies from one tissue to another and also with the situation. In the brain, for example, virtually only the local control mechanisms have any say, thus securing a satisfactory supply until the perfusion pressure becomes so low that even a maximal widening of the cerebral vessels does not help.

Arrangement of the reflex homeostasis

The reflex control is primarily based on the general inhibitory input from the various sets of stretch receptors, placed on both the low pressure and high pressure sides of the heart and adjacent major vessels. They accordingly sense both the filling of the system and the pressure (wall tension) levels in the pump and major vessels and tend to damp the extent of 'inherent' sympathetic discharge. They are assisted by the excitatory reflex influence of the chemoreceptors, which during resting equilibrium are nearly silent but which increase in importance in certain emergency situations (Folkow and Neil, 1971).

These various sets of receptor stations steadily modulate the heart and the vascular system so as to distribute a suitable cardiac output at a fairly constant pressure head to fit the total and regional nutritional demand, which on the local circuits expresses itself by means of the impact of the vasodilator

metabolites. Apart from their reflex control of pressure, flow, and its distribution, the receptors control also the blood volume and its distribution. This is done both by means of the vasoconstrictor fibre influence directly on the venous capacitance side and, more indirectly but perhaps even more importantly, by influencing the fluid distribution between the intravascular and extravascular spaces. This latter type of control is based on efficient reflex adjustments of the pre- to postcapillary resistance ratio, which occur primarily in the voluminous skeletal muscle and connective tissues (Öberg, 1964). This causes appropriate adjustments of mean capillary pressure, changing the Starling equilibrium across capillary walls so as to enhance absorption from these large fluid depots when needed and vice versa.

The various sets of cardiovascular stretch receptors induce reflex patterns that are not always equally designed as to their cardiovascular effects, though their general direction is usually the same (Folkow and Neil, 1971). These moderately different patterns provide one of the backgrounds of the differentiated cardiovascular control. There appears, in addition, to exist a set of stretch receptors in the left atrium which induce reflex tachycardia (Ledsome and Linden, 1967). This perhaps is the background of the classical Bainbridge reflex. The chemoreceptors, again, exert their particular reflex effect on the cardiovascular system in such a way that its impact is radically different depending on whether the concomitant reflex respiratory excitation is present or suppressed. When this is present, tachycardia, pressure rise, and increased flow are obtained; when respiration is suppressed, as during submersion, bradycardia and intense vasoconstriction ensue, which is the basic cardiovascular response to chemoreceptor activation. In expert divers this type of response, as reinforced by other influences, may virtually transform the cardiovascular system into an exclusive 'heart-brain' circuit (Folkow and Neil, 1971).

Corticohypothalamic influences

Superimposed on these most efficient homeostatic control systems, the local and central ones, the corticohypothalamic autonomic centres can temporarily so adjust the cardiovascular system as to fit particular needs of the organism as a whole – for example, in situations of danger. Responses like the dramatic defence reaction; the peculiar response seen in emotional fainting or 'playing dead' reactions; the circulatory adjustments in connexion with temperature regulation,

feeding, copulation, sleep, etc., are all examples of patterns that are governed by such higher centres (see Folkow and Neil, 1971). These centres exert their influence partly by modifying the homeostatic reflex machinery and partly by affecting directly the 'final common path' of the sympathetic nervous system, the spinal preganglionic neurons.

Thus the important defence reaction, being proportionally engaged in states of mere alertness up to fulminating attack or flight responses, forms a neurohormonal response pattern that is provoked in certain types of stressful situations in virtually all species, including man. In essence, a powerful neurogenic drive on the heart and the veins is established within seconds, coupled to flow restrictions in, for example, kidneys, gastrointestinal tract, and skin. In the skeletal muscles, on the other hand, the constrictor fibre activity is inhibited and the ensuing flow increase is here strongly reinforced by the activation of sympathetic cholinergic dilator fibres (at least in some species) and by the dilator influence of secreted adrenaline. Meanwhile the damping effect of the baroreceptor reflexes seems to be centrally suppressed with respect to the heart (Hilton, 1963), but not with respect to the vessels (Kylstra and Lisander, 1970). As a net result of this differentiated interaction between a central excitatory pattern and an inhibitory reflex one a considerable further increase in cardiac output can be gained that particularly favours muscles, myocardium, and perhaps the brain, but at a less pronounced pressure increase than if the baroreceptors had been totally excluded. The excellent studies by Brod *et al.* (1959) have in man revealed largely the same cardiovascular pattern as that traced throughout the animal kingdom.

Pathophysiological considerations

It appears, as mentioned, that the defence reaction is repeatedly and more or less strongly evoked in the normal strain of daily life of man, and it has been discussed whether such intermittent corticohypothalamic discharges might be involved in the gradual transfer from normotension to hypertension, particularly in the early labile phases of this disturbance (Folkow and Neil, 1971). Thus a cardiovascular pattern of this general type seems to be often met with in early cases of essential hypertension (Pickering, 1968). It has further been shown in rats that often repeated intermittent excitations of the hypothalamic defence area can gradually lead to a state of hypertension that persists when no hypothalamic stimulation is going on (Fol-

kow and Rubinstein, 1966). Continuous pressure measurements in human subjects reveal that intermittently the pressure load on the cardiovascular system can be remarkably enhanced during normal daily life (Hinman, Engel, and Bickford, 1962; Bevan, Honour, and Stott, 1969).

It may in addition be of interest that the 'anticipatory' enhancement of muscle blood supply that occurs in the defence reaction often tends to be counteracted by the earlier mentioned mechanisms for flow autoregulation. As most human beings usually feel forced to suppress their tendencies to attack or flight, a centrally induced flow increase is thus enforced upon largely resting skeletal muscles at an increased pressure. Consequently, the autoregulatory mechanisms try to re-establish flow resistance within the muscles, which would tend to enhance the pressure, compared with the situation where the natural somatomotor response is allowed to occur. In other words, civilized man is forced by common decency to dissociate his anticipatory visceromotor-hormonal discharge from what this is designed to serve—namely, to make the heart and muscles better fitted for flight and attack. As a consequence it is possible that an intrinsically normal and appropriate cardiovascular response, designed to increase cardiac output and muscle blood supply at a moderately raised pressure, might become transformed into one of a more profound pressure load but with less of cardiac output rise. (Whether the frustration of not being allowed to kick the antagonist in the pants also helps to *prolong* the visceromotor discharge is difficult to say, but one no doubt sometimes feels that this must be so: it might help to substitute some type of less aggressive physical exertion such as running up the stairs.)

What happens with a cardiovascular system that is often exposed to such bouts of an intrinsically perfectly appropriate central response pattern, as provoked by various situations in the individual's daily life? It should in this context be stressed that, for example, a pressure load on the cardiovascular system does of course not need to be continuous to initiate secondary, potentially harmful effects: the important thing is probably the *mean* increase of pressure over weeks and months. Is it possible that particularly often repeated neurogenic excitatory influences of such a nature may act as 'trigger' mechanisms which in predisposed individuals invite secondary vascular changes that gradually lead to established hypertension? It should again be stressed that normal rats can indeed show

such a development when a neurogenic drive of this very nature is intermittently enforced upon them during long periods.

It has further been shown that within a few weeks resistance vessels structurally adapt themselves to changes in pressure load by appropriate changes of their wall/lumen ratio and consequently of their 'reactivity' (Folkow and Sivertsson, 1968). While autoregulatory shifts in tone of the resistance vessels may be looked upon as the *immediate* local vascular response to an arterial pressure rise (Folkow, Grimby, and Thulesius, 1958), such structural changes may be considered as the *long-range* local response, but even this type of response thus occurs as rapidly as within a few weeks. These structural changes of the resistance vessels still allow for a perfectly normal range of adjustments but at a higher pressure equilibrium. Flow resistance is thus raised even at complete smooth muscle relaxation, presumably mainly by the increased bulk of contractile tissue in the vascular walls, and appears to result in exaggerated resistance responses for given degrees of muscle shortening (that is, increased vascular reactivity but not necessarily increased smooth muscle reactivity). It also expresses itself as an enhanced maximal contractile strength of the resistance vessels, to judge from experiments on spontaneously hypertensive rats of the Okamoto strain (Folkow *et al.*, 1970a, b). The same seems to be true in man (Sivertsson, 1970).

Possibly such structural changes of the resistance vessels are precipitated by trigger mechanisms like those discussed above, if these are pronounced and repeated often enough. The experiments mentioned above show, however, that the structural vascular changes are usually severe enough to *alone* largely explain the entire increase of flow resistance in the resting state and at a perfectly normal level of smooth muscle activity. In a sense, therefore, the entire vascular bed is structurally 'reset' to a higher pressure equilibrium, where evidently also the baroreceptors become reset by a similar rebuilding of the arterial walls in which they are situated (Aars, 1968). However, the serious consequence of the vascular adaptation, which from the local point of view may be as appropriate as the increase in bulk seen in the tissues of a hand exposed to an increased work load, is that it invites a vicious circle for the cardiovascular system as a whole. The reason is that excitatory influences of an intrinsically normal extent will now produce exaggerated resistance and pressure responses, in turn inviting further structural changes and so on. Ultimately this may deteriorate into true

vascular lesions which, when occurring in the renal vascular bed – which appears to be one of the more vulnerable – may precipitate an enhanced renin-angiotensin release. Such a potential combination of factors (neuro-hormonal, adaptive-structural, lesional, renal, etc., with mutual reinforcement) deserves to be considered seriously in discussions of the background of essential hypertension.

Perfectly normal types of functional loads might invite such structural adaptations and therefore gradually shift the cardiovascular equilibrium towards established hypertension, if strong and frequent enough or if affecting especially predisposed individuals, or both. Such a gradual transfer, being perhaps in part due to intermittent neurohormonal influences, is necessarily very difficult to pin down in studies on man, especially in the early but important phases. It may therefore be more profitably studied in, for example, the spontaneously hypertensive rat, which appears to be the closest 'animal model' so far of primary hypertension in man. We are at present involved in such types of investigations, trying to reveal what might be the genetical element – for example, enhanced neurohormonal activity or an increased tendency of the vessels to respond with structural rebuilding, and what are the relationships between 'trigger' and 'maintenance' mechanisms. If a development of this general nature forms the background of primary hypertension – and evidence is beginning to accumulate – this type of high blood pressure certainly deserves to be called a 'disease of regulation'.

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