Hypothesis

Is inactivity the origin of essential hypertension: should we all be runners?

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Introduction

Irvine Page [1] thought that essential hypertension arose from ‘a constellation of facets, one or even none being more or less dominant’. On the other hand, Guyton and his colleagues [2] posited a single patho-genetic mechanism. In their view, long-term arterial blood pressure control is a function of the fluid-balance system and depends upon the capacity of the kidney to excrete sodium and water. However, they clearly demonstrated that the relationship between blood pressure and fluid excretion is itself subject to feedback from a dozen or more variables which may modify the constituents, volume, pressure or rate of flow of blood, and glomerular filtrate within the vessels and tubules of the kidney. De Wardener [3] rejected Page’s mosaic hypothesis in favour of a single triggering factor for essential hypertension, namely an abnormal kidney with diminished ability to excrete sodium. However, we are left with the problem of identifying the mechanism by which the excretion of sodium is inhibited. Furthermore, de Wardener’s key evidence comes from animals selectively bred for genetic impairment of renal function, while virtually all of the data on which Guyton’s analysis is based were derived from an animal model in which two-thirds of the renal tissue mass had been removed and the cardiovascular system overloaded by continuous saline infusion. In effect these are models of renal hypertension and are not, by definition, essential hypertension.

How is essential hypertensive initiated?

The question that must be answered with regard to the fundamental origin of essential hypertension is how does a crucial shift take place in one part of the control system, that causes the resting arterial pressure to rise, without instantly provoking reflex activity in another part, directed toward pressure reduction. Guyton et al. [2] state that a primary increase in total peripheral resistance does not cause hypertension, because in the overall control system the peripheral resistance is dependent on the cardiac output. Nevertheless, one of the few constant findings in essential hypertension is the increase in the wall-to-lumen ratio of the resistance arterioles occasioned by a reduction in internal diameter and an apparent increase in the medial smooth muscle. At the same time, neither the total exchangeable sodium [4] nor the blood volume [5] is increased and there is no evidence of a raised cardiac output or of renal dysfunction. Thus, in a search for the initiating causes of true essential hypertension, there is a strong case for focusing on the determinants of the peripheral resistance. Since genetic factors contribute only about 30% to blood pressure variance when blood pressure is measured under screening conditions [6], it may be useful to consider whether the known environmental risk factors for essential hypertension have any impact on the peripheral resistance in healthy human subjects.

Blood flow in trained muscle

The peripheral resistance is determined predominantly by the need of the skeletal muscle for oxygen. Not only does skeletal muscle comprise almost half of the lean body mass but it has a 25-fold range of blood flow requirement, between rest and peak activity. Autoregulation of blood flow in muscle is a response to local hypoxia and is controlled by the endothelial cells of nutritive capillaries that synthesize and release nitric oxide. Before the recognition of the regulatory role of the endothelium, it was proposed [7] that the pressure-induced myogenic response of the arterioles described by Folkow [8], provides an autoregulatory control, stabilizing blood flow in the tissues in the face of variations in arterial pressure.

Thus regulation of peripheral blood flow was seen as a function of the vessels, rather than of the tissues they supply. It is, however, important to recognize the unique features of blood flow in skeletal muscle, since not only is there a very wide variation in flow between vigorous exercise and rest, but also there are between trained and untrained muscle important structural and metabolic differences that modify blood flow.

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Electron microscopy studies of muscle biopsies in trained and untrained men [9] and women [10] show that regular endurance exercise markedly increases the capillary density of skeletal muscle. The number of capillaries serving each muscle fibre rises during endurance training by the same order of magnitude as the increase in maximal oxygen uptake. This training-induced enhancement of oxidative capacity and endothelial cell mass within skeletal muscle is accompanied by increases in the activity of two endothelial enzymes, nitric oxide synthase and lipoprotein lipase [11]. Skeletal muscle insulin receptor sensitivity also is up-regulated, leading to a rise within the myocyte of the glucose-6-phosphate concentration and increased glycogen synthesis. At the same time there is an increase in both the number and the size of mitochondria in each myocyte. Thus, not only are blood flow and oxygen uptake augmented by training, but the capacity to take up and metabolize glucose and fatty acid fuels is also up-rated.

There is evidence also that endothelial nitric oxide synthase activity in the main conduit arteries supplying skeletal muscle increases in response to the enhanced blood flow and increased shear stress during endurance training, and that this underlies the up-regulation of the flow-dependent vasodilator response in these large vessels [12]. Training also increases blood volume and cardiac stroke volume, resulting in a lower heart rate [13] while baroreflex sensitivity is heightened and resting blood pressure reduced [14]. Jennings et al. [15] have shown that the noradrenaline spill-over rate (an index of sympathetic activity) is reduced to a third of its sedentary level by daily vigorous exercise.

The relationship between obesity and essential hypertension

Visceral obesity correlates strongly with blood pressure [16]. Intervention trials show that there is a reduction in blood pressure in association with a reduction in body weight. Fatty acids released from omental fat stores via the portal circulation may inhibit insulin extraction by the liver. Elevated levels of insulin in the plasma, insulin resistance, and glucose intolerance are frequently associated with visceral obesity and may be important in the genesis of essential hypertension [17]. Recently, Stenvinkel [18] has proposed that leptin, the ob gene product synthesized by the adipocyte in obesity, may have important regulatory functions beyond the control of appetite and energy metabolism, since this protein appears to stimulate both the renin–angiotensin system and the sympathetic nervous system, which together regulate blood pressure. However, in none of these associations are the causal pathways established, and despite the fact that there are epidemiological and metabolic links between obesity and hypertension, there is no real understanding of the aetiology of obesity itself or whether prevention of obesity will prevent the emergence of hypertension.

Endurance training of single muscle groups, using the contralateral muscle group as control [11], shows that even at rest there is a doubling of the arteriovenous difference in concentration of very-low-density lipoprotein triglyceride across the trained muscle when compared with the untrained control, indicating increased fatty acid uptake by trained muscle. The training-induced increase in capillary density in muscle enhances the activity of two particular endothelial enzymes, nitric oxide synthase and lipoprotein lipase [11]. The former, by synthesizing nitric oxide in response to local tissue hypoxia, is the key determinant of blood flow in muscle and hence of the peripheral resistance. The latter is deployed within the capillary lumen, attached to the glycocalyx of the endothelial basement membrane, where it is responsible for capturing circulating chylomicrons and very-low-density lipoprotein particles and releasing their triglyceride fatty acids for uptake (by simple diffusion) and β-oxidation by the myocytes of skeletal muscle. Lipoprotein lipase activity is also present in capillaries in adipose tissue where the fatty acids are taken up by the adipocyte for re-esterification and storage. Endurance-trained individuals show enhanced lipoprotein lipase activity in muscle capillaries, which can be further increased acutely by up to 25-fold following heavy exercise [19]. Thus, in active subjects, fat absorbed from the digestive tract is mostly oxidized in muscle with release of energy, while in sedentary subjects, adipose tissue takes the great preponderance of absorbed fat for storage.

It can be seen that there is a close parallelism between the mechanisms responsible for control of the peripheral resistance, and the partitioning of absorbed fatty acids between oxidation and storage. This may explain the association of hypertension with obesity, since the activities of both nitric oxide synthase and lipoprotein lipase in skeletal muscle are similarly reduced by loss of functioning capillary endothelium during prolonged inactivity.

Autoregulation in untrained muscle

As its state of training wanes or fails to be established, the oxygen demand of unused voluntary muscle declines below its normal physiological minimum. At that juncture, it is likely that the basal myogenic tone of the arterioles and pre-capillary sphincters in the much reduced capillary network is insufficient, by itself, to down-regulate blood flow in line with the abnormally low oxygen demand. In his medical degree thesis on the myogenic response of resistance vessels to changes in arterial pressure, Folkow [8] focused on the vasodilatation which follows brief occlusion of the arterial supply and identified the reflex development of tension in smooth muscle in response to stretch, as a better explanation for the observed reactive hyperaemia than the activities either of locally produced metabolites or of local nervous structures. It is now clear, however, in the light of recent discoveries, that dilatation of the resistance vessels in skeletal muscle
occurs in response to local tissue hypoxia and is mediated by the endothelium, which, among several other regulatory activities, synthesizes and releases nitric oxide. It is thus entirely possible that in pathologically inactive individuals, despite complete cessation of nitric oxide synthesis, persistent overperfusion will stimulate the autoregulatory release by the endothelium of active vasoconstrictors. Components of the renin–angiotensin system have been identified in the peripheral vasculature, raising the possibility that the local constrictor is angiotensin II [20].

Although the main site of synthesis of angiotensin-converting enzyme is believed to be the endothelial cells of the capillary circulation in the lung, the surface area of skeletal muscle capillary endothelium is at least as great. Furthermore, there is clear evidence of a functionally active renin–angiotensin system in the skeletal muscle vasculature in normal healthy subjects [21]. The activity of angiotensin-converting enzyme is regulated in response to local stimuli in the heart [22] and it seems a strong possibility that this occurs in the peripheral circulation also. However, the nature of the stimulus is unknown and a mechanism by which angiotensin II activity may be increased in response to overperfusion has yet to be identified.

**Effects of local activation of angiotensin II**

If the constrictor element of the autoregulatory control of blood flow in skeletal muscle is, indeed, angiotensin II, its local participation in blood-flow control will be greatest in individuals who are habitually the least active and whose skeletal musculature is untrained. Angiotensin II has a plasma half-life of 1–2 min; much longer than the few seconds half-life of nitric oxide. Thus, following activation in the skeletal muscle capillaries, angiotensin spills over into the venous circulation and increases vasomotor tone in the post-capillary capacitance vessels. The effect is to maintain a higher venous return to the heart and an elevated cardiac output, despite a reduction in blood volume due to increased capillary filtration pressure. In these circumstances, the consequent rise in blood pressure normally invokes a pressure diuresis, increasing sodium and water excretion by the kidney and reducing blood volume. However, the increased concentration of angiotensin II in the systemic circulation may well be sufficient to trigger the release of aldosterone. This activity of angiotensin is manifest at concentrations well below those leading to vasoconstriction, and by inhibiting sodium excretion will maintain blood volume at or near normal despite the increased blood pressure. Furthermore, unlike the rise in renal vascular resistance associated with sympathetic nervous system activity, which fades in a few days, the release of aldosterone in response to angiotensin tends to increase with time owing to hypertrophy of the cells of the zona glomerulosa. In this way, a sustained primary rise in peripheral resistance leads to hypertension despite perfectly healthy kidneys with no evidence of functional abnormality. In addition, the characteristic change in the wall-to-lumen ratio of the resistance vessels is explained by the well-recognized trophic effect on vascular smooth muscle of angiotensin II.

**Testing the hypothesis**

There is no experimental animal model of human essential hypertension because, apart from those in which renal function has been mechanically impaired, animals are selectively bred to exhibit a genetic form of renal hypertension. Of interest is the environmentally induced rise in pressure associated with habitual inactivity. Although the study of dietary salt and blood pressure in captive chimpanzees by Denton et al. [23] is interesting because this primate is closely related to man, it is in the wild a largely vegetarian browser, living in the rain forest with no access to salt. The chimpanzee has no unusual endurance capacity and none of the thermoregulatory problems of early man hunting the large herbivores for meat on the open equatorial savannah, which clearly required a massive capacity to sweat plus a high salt intake (from the salt lakes of the Great Rift Valley).

Ingle [24] demonstrated that obesity can be produced in the normal laboratory rat by restricting activity and providing *ad libitum* access to a palatable diet. Normally active rats on a stock diet seldom reach a weight of more than 500 g but the confined animals continued with linear weight gain to about double that figure. Ingle’s study reproduces rather well the human condition, but regrettably he did not measure the blood pressures of his animals. It would be an interesting test of this hypothesis to repeat the experiment in randomly allocated, confined or active animals while monitoring blood pressure. A third group, confined but fed on the stock diet, would show whether any change in blood pressure observed in obese animals occurred also in animals which were confined but not obese.

**Population-wide decline in activity**

It is quite clear that the level of physical activity of individuals in urban populations has declined to a significant degree during the latter half of the twentieth century. In British adults, average energy intake has fallen by a third since 1950 [25]. At the same time, there is an epidemic of obesity in children and adults, with prevalence rising progressively throughout childhood and into late middle-age. *Homo sapiens* evolved as a hunter with an univalued capacity for endurance running that is in evidence, even today, in the mass marathons put on annually in London, New York, and elsewhere. It is not difficult to envisage how a progressive, population-wide decline in habitual activity may be reflected in reduced capillary density and metabolic capacity of skeletal muscle in virtually all adults and children not engaged in specific programmes of physical training.
If it becomes evident from trials that endurance training can prevent the emergence of essential hypertension and obesity, then its therapeutic application becomes a major challenge, since individuals who are obese are loath to take any form of exercise. However, the critical window may well be at puberty when, in males at least, the instinct for physical competition may be at its height and demands on time less acute. Furthermore, as with so many other aspects of development, it may be that if exercise is restricted during maturation of the skeletal musculature it will be unable later to reach full functional capacity. In any case, charging schools with the responsibility for persuading youngsters to develop the activity habit should be an appropriate extension to the use of resources already in place.

References