The structural basis of hypertension: vascular remodelling, rarefaction and angiogenesis/arteriogenesis

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The established phase of human essential hypertension is characterized by a normal cardiac output and an elevation in peripheral resistance. A considerable part of this increase in vascular resistance is determined by the structure of the microvasculature, in particular the small arteries and precapillary arterioles, where increases in the wall thickness : lumen ratios are frequently observed [1]. In addition, other abnormalities in the microvasculature are also known to occur, such as a reduction in microvessels. Rarefaction of capillaries and arterioles has been reported in many animal models of hypertension [2,3], and may also be involved in increasing peripheral resistance in essential hypertension [4]. Rarefaction of capillaries is caused by an absence of capillaries or a functional rarefaction, in which the capillaries are present but not perfused. Capillary rarefaction has not only been reported in established essential hypertension [4], but also in borderline essential hypertension [5] and young adults with a predisposition to high blood pressure [6]. This latter observation suggests that defective angiogenesis/arteriogenesis may be an etiological component in the inheritance of high blood pressure, and raises the possibility that genetic factors may be responsible for at least a component of microvascular rarefaction.

It is also possible that angiogenesis/arteriogenesis is depressed during the development of hypertension, regulated by autoregulatory mechanisms as well as genetic factors [7,8]. Angiogenesis generally describes the growth and remodelling processes associated with endotherium forming new capillaries and can be considered as the first step in developing microvessels, which subsequently involves recruitment of vascular smooth muscle cells via the process of arteriogenesis. Angiogenic sprouting is a major mechanism for blood vessel formation and involves nitric oxide and various endothelial growth factors, particularly vascular endothelial growth factor (VEGF), which stimulates endothelial cell proliferation and the development of networks of endothelial cell tubes [9]. Angiopoietin-1 subsequently stabilizes these networks by stimulating the interaction between endothelial cells and periendothelial cells, inducing vessel maturation and stabilization. In addition, overexpression of angiopoietin-1 can increase vascularization [10]. A balance between activators and inhibitors controls angiogenic sprouting. VEGF is a major activator but other factors can also initiate angiogenesis, including members of the fibroblast growth factor family, platelet-derived growth factor, hepatocyte growth factor and various other molecules, such as erythropoietin [9,11]; inhibitors include angiostatin, a fragment of plasminogen, endostatin, a fragment of collagen XVIII and leukemia inhibitory factor. Once endothelial cells are assembled in vessels, they become quiescent and can survive for years. Any reduction in endothelial cell survival may lead to vascular regression. Endothelial cell apoptosis is a natural mechanism of vessel regression and has been reported in animal models of hypertension [3,12]. Endothelial cell apoptosis is induced through deprivation of nutrients or attenuation of survival signals such as reductions in VEGF, particularly in the presence of angiopoietin-2 [13–15]; reductions in delta-like 4 ligand, which binds to Notch receptors has also been associated with vascular regression [16]. Few factors have been identified that actively promote regression, although bone morphogenetic protein 4 has been shown to mediate apoptosis of endothelial cells and promote capillary regression [17]. Vascular inflammation can also influence remodelling and has been implicated in angiotensin-induced hypertension [18]. Macrophages, which are best known for their ability to promote angiogenesis, are also capable of promoting vascular regression by killing capillary cells [19].

Which, if any, of these mechanisms contributes to the rarefaction of microvessels and capillaries in experimental and essential hypertension is still unclear. Microvascular rarefaction in the cremaster muscle of spontaneously hypertensive rats (SHR) occurs during the early stages of hypertension (by 5–6 weeks of age) with reductions in the number of terminal third- and fourth order arterioles, as well as capillaries [20], and persists in adulthood [21]. Both pressure-dependent and pressure-independent mechanisms have been proposed to induce rarefaction, but the cellular and molecular mechanisms have not been investigated [22,23]. In this issue of the journal, Hudlett et al. [24] compare the ability of prehypertensive SHR and age-matched Wistar–Kyoto (WKY) rats to vascularize fibrin gel chambers implanted in the dorsal subcutaneous space, to determine if early reductions in microvessel numbers.
in SHR are a consequence of reduced angiogenesis/arteriogenesis and whether the effects were related to expression of angiogenic factors. Fibrin is a temporary matrix, which not only covers a wound, but also provides a structure for invading cells during healing. After 14 days, they examined the extent of vascularization quantifying microvessels, including capillaries. Somewhat unexpectedly, they found greater numbers of microvessels developing in fibrin gels implanted into SHR than WKY rats. This increase appeared to be due to both the formation of capillaries and microvessels with at least two layers of smooth muscle cells. Vessels in the fibrin gel were confirmed by staining for both von Willebrand factor and alpha smooth muscle actin. The authors conclude that angiogenesis and arteriogenesis are both higher in pre-hypertensive SHR than WKY rats and that rarefaction reported in SHR is most likely the consequence of hypertension. They also indicate that collagen formation is greater in gels implanted into SHR. However, the authors did not investigate whether this was associated with greater numbers of fibroblasts and macrophages invading the fibrin gel. Higher FGF-2, but not VEGF expression, was also associated with the greater vascularization of gels implanted into SHR, suggesting that this may be the angiogenic factor responsible for the increased angiogenesis/arteriogenesis. The use of fibrin gels raises the question as to whether the increased angiogenesis/arteriogenesis reflects a greater capacity of SHR to respond to tissue injury or whether it truly reflects a greater capacity to vascularize tissue under normal circumstances. Further characterization and quantification of the cells that invade the fibrin gels, including macrophages and fibroblasts, and a comparison with the cells present in healing wounds would address this issue. It would also be of interest to compare vascularization of another matrix gel such as collagen to investigate whether the greater vascularization is independent of the matrix used. The experiments performed by Hudlett et al. [24] also raise the question of why young (5–6-week old) SHR, who are only developing hypertension, already appear to exhibit reductions in pre-capillary arterioles [20] when their capacity to form new vessels is greater than in WKY; Hudlett et al. [24] studied 4-week-old animals. It is possible that rarefaction is rapidly induced with only modest elevations in blood pressure in these animals, but other possibilities also need to be considered. As already mentioned, the vascularization studied by Hudlett et al. [24] very likely reflects that associated with the initial stages of wound healing in granulation tissue. Assessment of vascularization at later stages of wound healing after cessation of angiogenesis/arteriogenesis and vessel regression may be more reflective of vascularization in normal tissue [25]. It has been suggested that endothelial and vascular smooth muscle cells of SHR may be more prone to apoptosis [26]. It is possible that vascularization from tissue in their experiments does not entirely reflect vascularization of other tissues, such as the cremaster muscle, where rarefaction has been reported. Microvascular rarefaction in SHR has also been reported in the retinal vasculature [27] but not in the cerebral vasculature [28]. It is also possible that the factors regulating vascularization are different during development/maturation of the rats compared to those stimulating vascularization of fibrin gels. Hudlett et al. [24] found that FGF-2 rather than VEGF was elevated, suggesting that FGF-2 may contribute to the increased angiogenesis/arteriogenesis in fibrin gels implanted into SHR. Unfortunately, the authors did not examine the extent to which FGF-2 contributes to these processes or the expression or roles of other systems capable of regulating vascularization, such as angiopoietin-1 [10], angiotatin [29] or corticotrophin-releasing factor receptor 2 which is expressed by endothelial and vascular smooth muscle cells and is a tonic suppressor of vascularization [30].

Although the results of Hudlett et al. [24] are preliminary, they do provide: (i) the first significant insight as to how microvascular density might be regulated in hypertension, possibly via elevations in blood pressure and (ii) a novel experimental model that appears to be particularly useful for studying the factors regulating vascular density in vivo. Further elaborations of their model focusing on gels composed of different matrix proteins, studies of longer duration, as well as gene expression and interventional studies on factors known to regulate microvessel density, should provide new insights into mechanisms regulating angiogenesis/arteriogenesis in genetic hypertension. In addition, interventional studies that prevent hypertension development in SHR could also help elucidate whether rarefaction is a consequence of hypertension or dependent on genetic factors related to their maturation.

References