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Review

Angiogenic growth factors and hypertension

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Abstract

Emerging evidence supports a novel view of hypertension as a disease of inadequate or aberrant responses to angiogenic growth factors (AGF). Patients with hypertension have reduced microvascular density, with some evidence supporting a primary role for rarefaction in causing hypertension. Two clinical models have demonstrated a link between inhibition of AGF activity and hypertension. A major side effect of bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), is hypertension. Pre-eclampsia is accompanied by high circulating levels of soluble VEGF receptor-1, which forms inactive complexes with VEGF and placental growth factor (PlGF). Paradoxically, early studies have demonstrated *high* circulating levels of AGF in hypertension. Several mechanisms may account for this finding including increased vascular stretch, tissue ischemia, compensatory responses, decreased clearance or a combination of these mechanisms. High AGF in hypertension could contribute to clinical sequelae such as peripheral and pulmonary edema, microalbuminuria, and progression of atherosclerosis. However, a role for altered angiogenesis in the pathogenesis of hypertension or its sequelae has not been established. Novel studies to understand the roles of AGF in hypertensive patients are warranted.

Abbreviations: EGFR – epidermal growth factor receptor; ELISA – enzyme linked immunosorbent assay; eNOS – endothelial type nitric oxide synthase; EPC – endothelial progenitor cells; EPO – erythropoietin; ERK1/2 – extracellular signal-related kinase 1/2; ET-1 – endothelin-1; ACE(-2) – angiotensin converting enzyme (-2); AGF – angiogenic growth factor(s); AKT – protein kinase B; AM – adrenomedullin; ASCOT – the Anglo Scandinavian Cardiac Outcomes Trial; AT – angiotensin II receptor; BK – bradykinin; CHF – congestive heart failure; FGF-1 – fibroblast growth factor-1 (acidic FGF); GLUT1 – glucose transporter 1; HGF – hepatocyte growth factor; HIF1α – hypoxia inducible factor-1α; IC – intracoronary; IGF-1 – insulin-like growth factor-1; IV – intravenous; KDR – kinase insert domain-containing receptor; LVH – left ventricular hypertrophy; NEPs – neutral endopeptidases; PDGF-AB – platelet derived growth factor-AB; PE – prolyl endopeptidases; PGI2 – prostacyclin; PKB – protein kinase B; PlGF – placental growth factor; SC – subcutaneous; SHR – spontaneously hypertensive rats; SU1498 – 4-amino-5-(4-cholorophenyl)-7-(*t*-butyl)pyrazolo; [3,4-*d*]pyrimidine; SVR – systemic vascular resistance; TGF-β – transforming growth factor-beta; VEGF – vascular endothelial growth factor; VEGFR-2 – VEGF receptor-2; VIVA – VEGF in Ischemia for Vascular Angiogenesis (clinical trial); VTI 4-[(4′-chloro-2′-fluoro)phenylamino]-6,7-dimethoxyquinazoline

Introduction

Hypertension is a common but incompletely understood disease. Hypertension-related diseases including stroke, myocardial infarction and heart failure pose an enormous burden to health care expenditures. As the United States population ages, an even higher prevalence of hypertension can be expected. Trials of anti-hypertensive agents show that more than two drugs are almost always required for optimum blood pressure control. Therefore, new strategies to lower blood pressure and identify patients at high risk for complications could have a strong beneficial impact on public health.

In this review, we will consider the vasomotor effects of angiogenic growth factors (AGF), the hypertensive effect of vascular endothelial growth factor (VEGF) inhibition, and

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the potential clinical significance of elevated AGF levels in hypertensive patients. Our paper will complement and extend another recent review [1].

Rarefaction

It would be rather difficult to propose a link between angiogenesis and hypertension without evidence for anatomical changes in the vasculature of hypertensive patients. Hypertensive patients are known to exhibit rarefaction, or a reduced density of microvessels in various tissues and organs [2]. Since the majority of the total vascular resistance occurs in vessels that are less than 150 μm in diameter [3], vascular rarefaction could contribute to increased vascular resistance. Furthermore, these same vessels also exhibit the greatest vasodilatory response to shear stress and other stimuli. The earliest description of rarefaction was by Hutchins and Darnell in 1974 [4] who found reduced arteriolar density in the cremasteric muscles of spontaneously hypertensive rats (SHR). Importantly, these rats exhibited rarefaction during the pre-hypertensive state. However, once hypertension occurs, rarefaction develops or worsens over a relatively short time interval. For example, rats made hypertensive by a surgical reduction of renal mass and administration of a high salt intake developed endothelial damage followed by rarefaction after only three days [5].

Although rarefaction could be a consequence of hypertension, there is also some evidence to support a primary role for rarefaction in the process of hypertension. In human subjects, skin capillary rarefaction has been described in normotensive young adults with a genetic propensity to develop high blood pressure [6, 7]. Vascular rarefaction can be detected in patients with only mild or borderline hypertension [8] and progresses in parallel with the severity of hypertension. Rarefaction has been described in a variety of tissues including the nail fold [9], skeletal muscle [10], and forearm skin [11] in hypertensive patients.

Hypertension is not the only stimulus for rarefaction. Animal models also have suggested that rarefaction develops during aging [12, 13]. A reduction in angiogenesis potential has been noted in the aged [14, 15], and hypertension is quite prevalent in the elderly [16]. Therefore, studies to examine links between rarefaction, impaired angiogenesis and hypertension in the geriatric population are warranted. Rarefaction can also develop in young animals with a normal blood pressure. Normotensive rats fed with a high salt diet exhibit rarefaction compared with controls on a low salt diet [5].

Vasomotor effects of angiogenic growth factors and their receptors

More than a decade ago, Ku et al. demonstrated that VEGF induces endothelium-dependent relaxation of isolated canine coronary arteries [17]. VEGF preferentially dilates arterioles and venules without an effect on medium-sized arteries and veins [18]. Subsequently, several studies in humans and animals have demonstrated a hypotensive effect of a variety of AGF (Table 1 [19–27]). In the VIVA (VEGF in Ischemia for Vascular Angiogenesis) trial, both intracoronary and intravenous infusions of recombinant human VEGF produced falls in systolic blood pressure of up to 22% at the highest doses [19]. The infusion of FGF-2 (basic fibroblast growth factor) in rabbits was shown to dilate the abdominal aorta and iliac arteries [20]. Both basic and acidic FGFs produce a dose-dependent hypotensive response in anesthetized rats [20]. Similarly, a single intracoronary injection of basic FGF has been shown to produce a hypotensive effect in patients, although the dose response has been more variable [21–23].

Many AGF induce angiogenesis via a pathway that involves ligation with their receptors, followed by activation of a common set of intracellular signaling pathways [28, 29]. These include activation of AKT/protein kinase B (PKB) which stimulates the phosphorylation of eNOS, resulting in augmented, calcium-independent activity leading to enhanced nitric oxide production [30]. VEGF not only enhances eNOS activity, but also upregulates the message and protein levels of eNOS in human endothelial cells [31]. Thus, the generation of nitric oxide is an intrinsic component of the responses to a variety of AGF. A reduction in nitric oxide production is associated with a diminished angiogenic response, as demonstrated using inhibitors of eNOS [32, 33] and eNOS knockout mice [34]. AGF vary in their dependence on the NO synthase pathway for inducing angiogenesis. For example, NO production appears to be more essential for VEGF than for bFGF induced angiogenesis [33]. Suppression of PKC δ activity via NO synthase activity is required for VEGF – but not for bFGF – induced EC migration and proliferation [35]. Furthermore, there may be NO-independent mechanisms for AGF-induced vasodilation.

Table 1. Hemodynamic effects of AGF.

AGF	Animal/human	Route	Effect	Reference
VEGF	Patients with CAD	IC, IV	Hypotensive	[19]
FGF-2	Patients with CAD	IC	Hypotensive	[21–23]
EGF	CD rats	IV	Initial pressor then hypotensive	[24]
EGF	Cynomolgus monkeys	IV	Hypotensive	[24]
HGF	SD rats with MI/CHF	IV	↓ SVR	[25]
IGF-1	Postmenopausal women	SC	Hypotensive	[26]
Adrenomedullin	Healthy volunteers	IV	Hypotensive	[27]

The hemodynamic effects of a variety of AGF when administered to animals or humans are tabulated.

VEGF-induced vasodilation, for example, may be partially attributable to PGI_2 synthesis [36].

Recently, very interesting data have emerged suggesting that VEGFR-2 is sensitive to shear stress and can be activated in the absence of ligand to enhance nitric oxide production [37]. It is possible that integrin receptors, which have known roles in angiogenesis [38], arteriolar dilation [39] and mechanotransduction of shear stress [40] form functional receptor complexes with VEGFR-2. Indeed, some evidence suggests that a complex of the vitronectin receptor ($\alpha_v\beta_3$) and VEGFR-2, is necessary for mechanotransduction [41]. Stimulation of VEGFR-2 at 12 dynes/cm^2 (simulating arterial level laminar shear stress), produced more intense and more sustained phosphorylation of the receptor itself, AKT, eNOS, and ERK1/2 than did ligand-mediated activation [37]. Furthermore, the VEGFR-2 tyrosine kinase inhibitors SU1498 and VTI were able to inhibit flow-mediated dilation [37]. Together, these *in vitro*, animal and human studies point to a significant role for AGF and their receptors in regulating vasomotor tone at the level of the microvasculature.

Hypertensive effect of inhibition of VEGF

Studies with bevacizumab, a recombinant human monoclonal antibody to VEGF, have demonstrated that inhibition of VEGF induces or exacerbates hypertension in some patients. Bevacizumab has been used as anti-angiogenic therapy for a variety of tumors including renal cell carcinoma, colorectal carcinoma, and breast carcinoma [42–44]. In a study by Yang et al., patients with clear cell renal carcinoma were randomly assigned to placebo, low dose bevacizumab or high dose bevacizumab [42]. The primary endpoints included time to disease progression and response rates. Patients treated with high dose bevacizumab had a clear reduction in tumor progression. However, the high dose group also experienced hypertension in more than one-third of the treated patients. There was also a significant increase in the prevalence of proteinuria in the high dose group. Hypertension has also been reported as a side effect of the VEGF receptor tyrosine kinase inhibitor PTK787/ZK222584 [45]. These studies support the concept that VEGF is necessary for maintenance of a healthy endothelium and further suggest that VEGF exerts a hypotensive effect *in vivo*.

Angiogenic growth factor levels in hypertension

An analysis of 248 patients with hypertension and other cardiovascular risk factors from the ASCOT trial demonstrated a positive correlation between more severe hypertension and higher VEGF levels [46]. This is somewhat a paradoxical finding given in our previous discussion that *lower* VEGF levels might pre-dispose to a hypertensive state. The first concern would be that total VEGF (VEGF plus soluble VEGFR-1) rather than exclusively free, active VEGF was measured in this study. However, soluble VEGFR-1 was independently measured and was also found to be *lower* in the most hypertensive patients [46]. Furthermore, von Willebrand's factor (vWF) was found to be significantly elevated with hypertension [46]. The authors suggested that VEGF was increased secondary to endothelial cell injury, since vWF was known to be released by this mechanism. Of further interest from this study was the finding that VEGF levels were significantly reduced after six months of intensive cardiovascular risk factor management. Soluble VEGFR-1 levels increased slightly while vWF levels decreased [46]. These findings are consistent with the hypothesis that higher levels of VEGF are produced in response to endothelial trauma and that improved blood pressure control leads to reduced VEGF levels.

Several other AGF have been studied in hypertensive patients. Hepatocyte growth factor (HGF) is also elevated in hypertensive patients, with a significant correlation between both systolic and diastolic blood pressures and circulating HGF concentration [47]. Furthermore, HGF concentration is reduced when the blood pressure is lowered, and a similar reduction is achieved with calcium antagonist, ACE inhibitor or a combination of these therapies [47]. Insulin growth factor-1 (IGF-1) has AGF activity, and induces NO production [48–50]. Levels of insulin growth factor binding protein-1 (IGBP-1) are elevated in hypertension [51]. FGF-2 levels are elevated in mild-moderate hypertension compared with normotensive controls [52]. PDGF-AB levels are not elevated in hypertensive patients compared to controls, except in the subset of hypertensive patients with microalbuminuria [52]. Endothelin-1 (ET-1), which stimulates angiogenesis directly, as well as indirectly by inducing VEGF [53] is elevated in hypertensive patients [52]. Transforming growth factor-β_1 has a complex role in angiogenesis with deficits in its signaling pathway causing impairments of vascular development and physiology [54]. The plasma concentration of active and total TGF-β_1 levels are significantly higher in patients with essential hypertension compared with normotensive controls [55]. Serum TGF-β_1 levels are higher in hypertensive blacks than whites [56] and in obese hypertensives compared with nonobese hypertensives [57]. TGF-β_1 may contribute to hypertension by stimulating ET-1 production by the endothelium, while suppressing nitric oxide production, and promoting renin release from juxtaglomerular cells [58]. TGF-β_1 promotes extracellular matrix deposition and is involved in the development of LVH, arterial stiffness and renal fibrosis in hypertensive patients [58]. Adrenomedullin, a potent vasodilator [59] that also stimulates angiogenesis [60], is elevated in hypertensive patients compared with controls and declines after anti-hypertensive therapy [61].

Clinical significance of angiogenic growth factors, including the example of pre-eclampsia

Pre-eclampsia has emerged as an example of the hypertensive effect of withdrawing AGF stimulus to the endothelium. Pre-eclampsia affects about 5% of pregnant women and is characterized by the onset of hypertension and proteinuria during the second trimester. In the most severe

forms, renal failure, thrombocytopenia, liver and brain edema, and seizures may occur [62]. Several recent studies have demonstrated that pre-eclamptic patients have elevated levels of a soluble form of VEGF receptor-1 (sVEGFR-1) also known as soluble Flt-1(sFlt-1) [63–67]. Soluble VEGF receptor-1 forms complexes with VEGF and placental growth factor (PlGF), reducing the levels of free active AGF. PlGF is an AGF with homology to VEGF [68]. In an animal model, intravenous infusions of soluble VEGFR-1 induced hypertension and proteinuria in both pregnant and non-pregnant rats [63], providing direct support for this receptor in the pathogenesis of pre-eclampsia.

This revolutionary understanding of the pathogenesis of pre-eclampsia and the example of bevacizumab both highlight the importance of PlGF and VEGF in maintaining normal endothelial function. With the withdrawal of free PlGF and VEGF, hypertension and glomerular dysfunction occur over a relatively short time period. VEGF and PLGF have been shown to induce the mobilization of endothelial progenitor cells (EPCs) that are involved in endothelial cell repair at sites of vascular injury [69]. Thus, there is emerging evidence that VEGF (and other AGF) are necessary to maintain normal endothelial health. In this capacity, AGF protect against endothelial dysfunction, a role that extends beyond the classical domain of angiogenesis.

In order to assess the clinical significance (Table 2) of AGF we should first reconsider the origin of VEGF, HGF, and other growth factors (Figure 1). As discussed, in one model, these factors could be produced in response to endothelial damage caused by hypertension. However, there is little direct evidence for VEGF release by this mechanism. Instead, the effect of hypertension may be produced through an exaggerated cyclical mechanical stretch, which has been shown to induce VEGF [70, 71], as well as HIF1α [72] expression. If AGF are released by increased mechanical stretch, then growth factors would simply be markers of the severity of hypertension and would perhaps be no more useful than von Willebrand's factor or, for that matter, the blood pressure value itself.

It is also possible that AGF are elaborated in response to tissue ischemia. In a rat model of hypertension, HIF1α and VEGF are induced in medial SMC during arterial remodeling, probably reflecting medial hypoxia [73]. If this hypothesis is correct, then VEGF and HGF could be useful to monitor the extent of tissue ischemia and should be elevated in concert with other hypoxia inducible genes. HIFα in combination with HIFβ, which is constitutively expressed, produces the active hypoxia inducible factor. HIF, in turn, induces a variety of gene products including VEGF, PDGF, TGFα, TGFβ, EGFR, EPO, GLUT1, IGF-1 and eNOS [74].

Another intriguing possibility is that AGF are induced, as a compensatory mechanism, by other factors that contribute directly to the elevated blood pressure. Examples would include the induction of VEGF by ET-1 [53] and angiotensin II [75, 76]. A final possibility is that AGF are released to maintain endothelial health in the setting of hypertension-induced endothelial dysfunction.

Table 2. Potential clinical significance of elevated VEGF levels in hypertension.

Potential clinical significance of elevated VEGF levels in hypertension	
Possible marker for	Increased mechanical stretch [70–72] Tissue ischemia/hypoxia [73] Endothelial dysfunction/resistance [77] Platelet activation/thrombosis [86, 87]
Possible contributor to	Pulmonary and peripheral edema [78] Encephalopathy [80–82] Plaque angiogenesis/ progression [83] Pro-thrombotic state [87] Inflammatory state [84, 85] Nephropathy/albuminuria [88–92]

Other AGF would have similar effects. HGF, IGF-1 and TGF-β_1 might additionally contribute to the development of left ventricular hypertrophy [47, 50, 51, 55–58].

If AGF are released in hypertension in response to ischemia, then an accompanying question must be answered: Why do these factors not promote angiogenesis, thereby restoring adequate blood flow to ischemic tissues? It is possible that the endothelium in hypertensive patients is resistant, at a cellular or post-receptor level, to AGF. Animal models support this concept. For example, both basal NO (before VEGF) and VEGF-induced NO production is blunted in SHR rats compared to WKY controls [77]. Finally, AGF may be cleared at a slower rate in hypertensive patients as documented for VEGF in SHR [77].

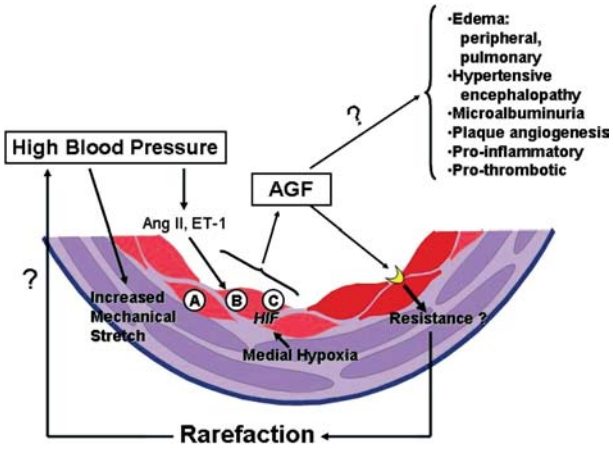

Figure 1. Possible origins and actions of AGF in hypertension. AGF may be released in response to increased mechanical stretch (mechanism A; [70–72]). Several mediators of hypertension including angiotensin II and ET-1 have been reported to induce VEGF production by endothelial cells (B [53, 75, 76]). This effect could serve to counter the hypertensive effect of these agents or be viewed as a compensatory response to hypertension-induced endothelial dysfunction. With hypertension-induced vascular hyperplasia, medial SMC may become hypoxic, elaborating HIF1α, (C [73]) which induces the expression of several AGF. Misdirected AGF activity, acting on capillaries at remote sites, may contribute to edema, hypertensive encephalopathy, nephropathy, and plaque angiogenesis. Some AGF may also exert pro-inflammatory and pro-thrombotic effects [84–87]. Endothelial cell resistance to AGF activity may lead to lack of adequate angiogenesis, thereby promoting rarefaction, which could be a factor contributing to the development or severity of hypertension.

Although we cannot pinpoint the exact mechanism by which AGF are elevated in hypertensive patients, we can speculate that, regardless of their origin, these factors might contribute to clinical features in certain patients (Table 2). In support of this concept is the finding that patients with hypertension-related complications have significantly higher levels of HGF than patients with hypertension who have an uncomplicated course [47]. AGF enhance endothelial cell permeability. The strongest agent is VEGF which was co-discovered as 'vascular permeability factor' (VPF) [78]. Elevated VEGF levels could contribute to peripheral and pulmonary edema by enhancing endothelial cell permeability. From the Framingham study, approximately 15% of patients with hypertension developed congestive heart failure after 15 years [79]. It is unclear what biochemical features place these patients at risk of CHF, while 85% remain free of this complication. Studies are warranted to examine the levels of VEGF in patients with hypertension who present with congestive heart failure symptoms vs. those who are asymptomatic. Similarly, the pathophysiology of hypertensive encephalopathy involves cerebral vasodilatation and disruption of the blood brain barrier, both potentially initiated by elevated levels of AGF [80–82]. Finally, elevated AGF could promote atherogenesis. Increased endothelial permeability is recognized as an early event in atherogenesis [83]. Misdirected angiogenesis could enhance the growth of the microvasculature in atherosclerotic plaques. VEGF can stimulate T cell activation [84] and endothelial adhesion molecule expression [85], potentially contributing to the inflammatory states that stimulate the progression of atherosclerosis. Furthermore, VEGF is released during platelet activation [86] and can trigger tissue factor expression [87], indicating that this AGF can potentially be both a marker for and a contributor to a prothrombotic state. These links could help explain the accelerated progression of atherosclerosis observed in hypertensive patients.

A basal level of VEGF appears essential for maintaining the health of the kidney. Mice with podocyte specific heterozygosity for VEGF develop renal disease manifest as proteinuria and endotheliosis, the same renal lesion observed in pre-eclampsia [88]. In diabetic patients, glomerular VEGF mRNA levels were found to be inversely correlated with albumin excretion rates [89]. On the other hand, mice with renal-specific overexpression of VEGF develop a 'collapsing glomerulopathy' [90]. Furthermore, increased levels of VEGF have been associated with the development of microalbuminuria in an ambulatory population [91] and elevated levels of VEGF is a risk factor for the development of microalbuminuria in Type I diabetics [92]. VEGF may induce microalbuminuria by afferent glomerular arteriolar vasodilation and enhanced EC permeability. ET-1, FGF-2 and PDGF-AB levels are elevated in hypertensive patients with microalbuminuria compared to hypertensive patients without microalbuminuria and to normotensive controls [93]. Early clinical trials with FGF-2 have also reported proteinuria as a significant side effect [21, 94]. Thus, it appears that both deficient and excessive AGF could contribute to hypertensive nephropathy.

Possible contributions of decreased angiogenesis to hypertension in the elderly

The prevalence of hypertension, especially systolic hypertension, increases in the elderly. Vasan et al. have shown that a normotensive person of 65 years has a 90% risk of developing hypertension if he/she lives to be 85 years old [95]. VEGF [96], IGF-1 [97, 98] and perhaps other AGF decrease with aging. Thus, there may be a more direct correlation between withdrawal of AGF and hypertension in the elderly, but further studies to clarify the relationship are needed. Circulating EPCs were also found to decrease as a function of aging [96]. Recent work has demonstrated that circulating EPCs can contribute to angiogenesis in the adult, constituting an amalgam of the concepts of angiogenesis and vasculogenesis. Therefore, both the age-related decline in VEGF and EPCs could contribute to the decline in angiogenesis potential [99].

The interactions between the renin-angiotensin and kallikrein systems and angiogenesis

The components of the renin-angiotensin system have been shown to function as growth factors as well as to regulate blood pressure and homeostasis. Two of the components, the octapeptide Ang II and the heptapeptide Ang-(1-7), act in opposition as tissue growth regulators (Figure 2). Ang II induces angiogenesis in several *in vivo* models [100–103], including the chroioallantoic membrane assay [102] and the corneal pocket model of the rabbit [103]. Angiotensin II infusion increases capillary density in several animal models [101–103]. Angiotensin II has several stimulatory effects on angiogenesis including the induction of VEGF [75, 76], HIF1α [104], and VEGFR-2 [105] expression. The pro-angiogenic effects of angiotensin II appear to be mediated by the AT1 receptor [101, 106, 107]. In mice lacking the AT1 receptor, angiogenesis induced by hind-limb ischemia [108] or myocardial infarction [109] is reduced compared with wild type mice. As predicted from these observations, AT1 receptor antagonists, losartan and candesartan, and ACE inhibitors, captopril and perindopril, have been reported to inhibit angiogenesis in animal models and in the cornea [108–110].

Ang II can also act at the AT2 receptor and activation of the AT2 receptor has been reported to have an *inhibitory* effect on angiogenesis. In further support of this concept, vascular density and perfusion were augmented in AT2 knock out mice compared with wild type controls in a hind-limb ischemia model [111]. Angiotensin II has been reported to inhibit VEGF mediated tube formation by endothelial cells through AT2 activation [112]. However, the role of the AT2 receptor is not without controversy [113, 114], and further studies are required to understand the effects of Ang II on angiogenesis via the AT2 receptor. Part of the controversy may depend on the preponderance of AT1 vs. AT2 receptors in the tissue and animal model studied [115], and the uncovering of the actions of the AT2 receptor when the AT1 receptor is blocked.

Angiotensin-(1-7), a recently discovered peptide of the RAS [116–121], inhibits angiogenesis and smooth muscle proliferation. Freeman et al. [117] and Zeng et al. [118] showed that nanamolar concentrations of Ang-(1-7) inhibited mitogen-stimulated growth of cultured rat thoracic aortic vascular smooth muscle cells through activation of a specific receptor antagonist of Ang-(1-7), [D-Ala7] Ang-(1-7). Ang-(1-7) has anti-proliferative properties *in vivo*, reducing neointimal formation following balloon catheter injury to the rat carotid artery [119]. Using a mouse sponge model of angiogenesis, Machado et al. [120] demonstrated opposing actions of Ang II (stimulatory) and Ang-(1-7) (inhibitory) on angiogenesis and fibrovascular tissue growth. In addition, AT1 (Losartan) and AT2 (PD-123319) antagonists and ACE inhibitors did not reverse this anti-angiogenic effect [121], whereas D-Ala-Ang-(1-7) (A779) inhibited the anti-angiogenic effects. In addition, the mechanism of Ang-(1-7) induced inhibition of angiogenesis involved the release of NO since NOS inhibitors abolished the response.

In some studies, therapy with angiotensin converting enzyme inhibitors has been associated with *increased* angiogenesis [122–124]. For example, quinaprilat is nearly as effective as VEGF in a hind-limb ischemic model [124]. Recent studies have implicated bradykinin (BK), which induces endothelial nitric oxide and prostacyclin synthesis, as the mediator of ACE inhibitor-induced angiogenesis. In addition to catalyzing the conversion of angiotensin I to angiotensin II, ACE also degrades BK [125]. Thus, ACE inhibitors would augment levels of BK. The angiogenic effect of BK is primarily mediated by B2 receptors since B2 receptor null mice do not exhibit increased capillary density in response to ACE inhibitors [126].

Along with Ang II and Ang-(1-7), another protein of the renin-angiotensin system, angiotensinogen (AGT), has been shown to have an effect on angiogenesis. AGT is cleaved by renin to form Ang I, leaving a large fragment intact called des(angiotensin I)angiotensinogen (des[Ang I]AGT). Celerier et al. have found that both AGT and des[Ang I]AGT have the ability to inhibit angiogenesis as measured by *in vitro* capillary tube formation and chorioallantoic membrane assay [127]. The opposing effect of Ang II (predominantly pro-angiogenic) vs. its precursor, AGT, (anti-angiogenic) emphasizes the complexity of the role of the rennin-angiotensin system on angiogenesis. It is believed that local conditions, such as clearance rates of the proteins or presence of renin, may determine whether the effect of Ang II or AGT is the predominant one observed on angiogenesis [128]. The inhibition of angiogenesis by des[Ang 1]AGT is analogous to the effect of domain 5 of high molecular weight kininogen [129]. Both are precursors of products that stimulate angiogenesis (BK and angiotensin II).

In conclusion, the RAS system, a major force in regulating blood pressure has both stimulatory and inhibitory effects on angiogenesis. The direction and magnitude of the effects may depend on the activity of activating enzymes and the distribution of receptor subtypes within specific tissues. It is clear that more research needs to be done in this field.

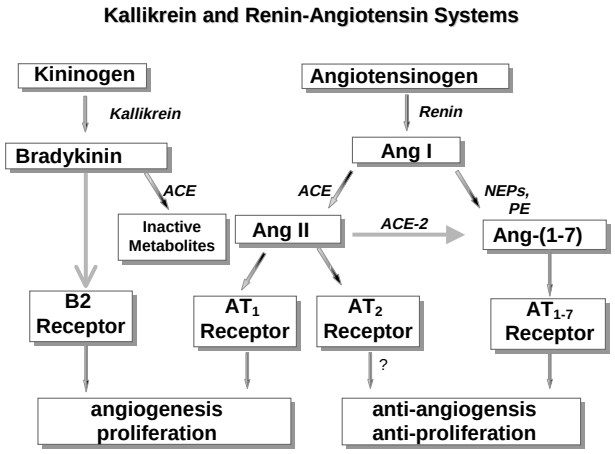

Figure 2. An overview of the kallikrein and renin-angiotensin systems. Pathways of formation of angiotensin and BK and proposed effects of BK, Ang II, Ang-(1-7) and their receptors on angiogenesis.

Summary and implications

Rarefaction is documented in the capillaries and the arterioles of hypertensive and elderly patients. However, it is currently unclear whether rarefaction is a cause of or simply a response to hypertension, and whether rarefaction represents an impairment of angiogenesis. Even though early studies have documented elevated levels of VEGF and HGF in hypertensive patients, the hypotensive properties of these and other AGF could be diminished by endothelial dysfunction and resistance. It is conceivable that VEGF or other AGF could be used therapeutically to lower blood pressure, although caution must be exerted since hypotension has been reported in hypertensive animals treated with VEGF [77]. However, it is more likely that therapies to improve endothelial health by cigarette cessation, reduction in cholesterol and triglyceride levels, weight loss, or novel strategies could be exploited to enhance the responses to endogenous levels of VEGF and other AGF. Further studies are warranted to determine whether VEGF, HGF and other AGF contribute to manifestations of hypertension including edema, congestive heart failure, hypertensive encephalopathy, and renal insufficiency. Refinements in the assays for VEGFs and HGFs are needed to distinguish between free and total levels of these growth factors. Potential inhibitors of AGF including soluble receptors, should be measured simultaneously to assess the global angiogenic potential.

References

1. Kiefer FN, Neysari S, Humar R et al. Hypertension and angiogenesis. Curr Pharm Des 2003; 9: 1733–44.
2. Greene, AS. Microvascular regulation and dysregulation. In Izzo JL, Black HR (eds) Hypertension Primer, 3rd edition. Philadelphia: Lippincott Williams & Wilkins 2003; 183–5.
3. Koller A. Signaling pathways of mechanotransduction in arteriolar endothelium and smooth muscle cells in hypertension. Microcirculation 2002; 9: 277–94.

4. Hutchins PM, Darnell AE. Observation of a decreased number of small arterioles in spontaneously hypertensive rats. Circ Res 1974; 34: I161–5.
5. Hansen-Smith FM, Morris LW, Greene AS et al. Rapid microvessel rarefaction with elevated salt intake and reduced renal mass hypertension in rats. Circ Res 1996; 79: 324–30.
6. Noon JP, Walker BR, Webb DJ et al. Impaired microvascular dilatation and capillary rarefaction in young adults with a predisposition to high blood pressure. J Clin Invest 1997; 99: 1873–9.
7. Antonios TFT, Rattray FM, Singer DRJ et al. Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension. Heart 2003; 89: 175–8.
8. Sullivan JM, Prewitt RL, Josephs JA. Attenuation of the microcirculation in young patients with high-output borderline hypertension. Hypertension 1983; 5: 844–51.
9. Gasser P, Buhler FR. Nailfold microcirculation in normotensive and essential hypertensive subjects, as assessed by video-microscopy. J Hypertens 1992; 10: 83–6.
10. Henrich HA, Romen W, Heimgartner W et al. Capillary rarefaction characteristic of the skeletal muscle of hypertensive patients. Klin Wochenshrift 1998; 66: 54–60.
11. Prasad A, Dunnill GS, Mortimer PS et al. Capillary rarefaction in the forearm skin in essential hypertension. J Hypertension 1995; 13: 265–8.
12. Sonntag WE, Lynch CD, Cooney PT et al. Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. Endocrinology 1997; 138: 3515–20.
13. Khan AS, Lynch CD, Sane DC et al. Growth hormone increases regional coronary blood flow and capillary density in aged rats. J Gerontol Ser A, Biol Sci Med Sci 2001; 56: B364–71.
14. Edelberg TM, Reed MJ. Aging and angiogenesis. Front Biosci 2003; 8: s1199–209.
15. Hutchins PM, Lynch CD, Cooney PT et al. The microcirculation in experimental hypertension and aging. Cardiovasc Res 1996; 32: 772–80.
16. Vasan RS, Beiser A, Seshadri S et al. Residual lifetime risk for developing hypertension in middle-aged women and men. JAMA 2002; 287: 1003–10.
17. Ku DD, Zaleski JE, Liu S, Brock TA. Vascular endothelial growth factor induces EDRF-dependent relaxation in coronary arteries. Am J Physiol 1993; 265: H586–92.
18. Laham RJ, Li J, Tofukuji M et al. Spatial heterogeneity in VEGF-induced vasodilation: VEGF dilates microvessels but not epicardial and systemic arteries and veins. Ann Vasc Surg 2003; 17: 245–52.
19. Henry TD, Annex BH, McKendall GR et al. The VIVA trial: Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. Circulation 2003; 107: 1359–65.
20. Cuevas P, Carceller F, Ortega S et al. Hypotensive activity of fibroblast growth factor. Science 1991; 254: 1208–10.
21. Unger EF, Goncalves L, Epstein SE et al. Effects of a single intracoronary injection of basic fibroblast growth factor in stable angina pectoris. Am J Cardiol 2000; 85: 1414–9.
22. Laham RJ, Chronos NA, Pike M et al. Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart disease: Results of a phase I open-label dose escalation study. J Am Coll Cardiol 2000; 36: 2132–9.
23. Simons M, Annex BH, Laham RJ et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: Double-blind, randomized, controlled clinical trial. Circulation 2002; 105: 788–93.
24. Keiser JA, Ryan MJ. Hemodynamic effects of epidermal growth factor in conscious rats and monkeys. Proc Natl Acad Sci USA 1996; 93: 4957–61.
25. Jin H, Yang R, Li W et al. Early treatment with hepatocyte growth factor improves cardiac function in experimental heart failure induced by myocardial infarction. J Pharmacol Exp Ther 2003; 304: 654–60.
26. Ebeling PR, Jones JD, O'Fallon WM et al. Short-term effects of recombinant human insulin-like growth factor I on bone turnover in normal women. J Clin Endocrin Metab 1993; 77: 1384–7.
27. Lainchbury JG, Troughton RW, Lewis LK et al. Hemodynamic, hormonal, and renal effects of short-term adrenomedullin infusion in healthy volunteers. J Clin Endocrinol Metab 2000; 85: 1016–20.
28. Zachary I, Gliki G. Signaling transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. Cardiovas Res 2001; 49: 568–81.
29. Chavakis E, Dimmeler S. Regulation of endothelilal cell survival and apoptosis during angiogenesis. Arterioscler Thromb Vasc Biol 2002; 22: 887–93.
30. Dimmeler S, Fisslthaler B, Fleming I et al. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. Nature 1999; 399: 601–5.
31. Hood JD, Meininger CJ, Ziche M et al. VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. Am J Physiol 1998; 274: H1054–8.
32. Cooke JP. NO and angiogenesis. Atherosclerosis Supplements 2003; 4: 53–60.
33. Ziche M, Morbidelli L, Choudhuri R et al. Nitric oxide synthase lies downstream from vascular endothelial growth factor-induced buy not basic fibroblast growth factor-induced angiogenesis. J Clin Invest 1997; 99: 2625–34.
34. Murohara T, Asahara T, Silver M et al. Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. J Clin Invest 1998; 101: 2567–78.
35. Shizukuda Y, Tang S, Yokota R et al. Vascular endothelial growth factor-induced endothelial cell migration and proliferation depend on a nitric oxide-mediated decrease in protein kinase Cδ activity. Circ Res 1999; 85: 247–56.
36. He H, Venema VJ, Gu X et al. Vascular endothelial growth factor signals endothelial cell production of nitric oxide and prostacyclin through Flk-1/KDR activation of c-Src. J Biol Chem 1999; 274: 25130–5.
37. Jin Z-G, Ueba H, Tanimoto T et al. Ligand-independent activation of vascular endothelial growth factor receptor 2 by fluid shear stress regulates activation of endothelial nitric oxide synthase. Circ Res 2003; 93: 354–63.
38. Friedlander M, Brooks PC, Shaffer RW et al. Definition of two angiogenic pathways by distinct α_v integrins. Science 1995; 270: 1500–10.
39. Mogford JE, David GE, Platts SH et al. Vascular smooth muscle $\alpha_v\beta_3$ integrin mediates arteriolar vasodilation in response to RGD peptides. Circ Res 1996; 79: 821–6.
40. Shyy JYJ, Chien S. Role of integrins in endothelial mechanosensing of shear stress. Circ Res 2002; 91: 769–75.
41. Wang Y, Miao H, Li S et al. Interplay between integrins and FLK-1 in shear stress-induced signaling. Am J Physiol Cell Physiol 2002; 283: C1540–7.
42. Yang JC, Haworth L, Sherry RM et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. NEJM 2003; 349: 427–34.
43. Cobleigh MA, Langmuir VK, Sledge GW et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Seminars in Oncology 2003; 30(Suppl 16): 117–24.
44. Willett CG, Boucher Y, di Tomaso E et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004; 10: 145–7.
45. Thomas AL, Morgan B, Drevs J et al. Vascular endothelial growth factor receptor tyrosine kinase inhibitors: PTK787/ZK 222584. Semin Oncol 2003; 30(suppl 6): 32–8.
46. Felmeden DC, Spencer CG, Belgore FM et al. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. Am J Hypertens 2003; 16: 11–20.
47. Nakamura S, Moriguchi A, Morishita R et al. A novel vascular modulator, hepatocyte growth factor (HGF), as a potential index of the severity of hypertension. Biochem Biophys Res Commun 1998; 242: 238–43
48. Nakao-Hayashi J, Ito H, Kanayasu T et al. Stimulatory effects of insulin and insulin-like growth factor I on migration and tube formation by vascular endothelial cells. Atherosclerosis 1992; 92: 141–9.

49. Nicosia RF, Nicosia SV, Smith M. Vascular endothelial growth factor, platelet-derived growth factor, and insulin-like growth factor-1 promote rat aortic angiogenesis *in vitro*. Am J Pathol 1994; 145: 1023–9.
50. Delafontaine P, Song Y-H, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arterioscler Thromb Vasc Biol 2004; 24: 1–10.
51. Díez J. Insulin-like growth factor I in essential hypertension. Kidney Int 1999; 55: 744–59.
52. Cottone S, Vadalá A, Mangano MT et al. Endothelium-derived factors in microalbuminuric and nonmicroalbuminuric essential hypertensives. Am J Hypertens 2000; 13: 172–6.
53. Bagnato A, Spinella F. Emerging role of endothelin-1 in tumor angiogenesis. Trends Endocrinol Metab 2003; 14: 44–50.
54. Goumans M-J, Lebrin F, Valdimarsdotti G. Controlling the angiogenic switch. A balance between two distinct TGF-β receptor signaling pathways. Trends Cardiovasc Med 2003; 13: 301–7.
55. Derhaschnig U, Shehata M, Herkner H et al. Increased levels of transforming growth factor-β_1 in essential hypertension. Am J Hypertens 2002; 15: 207–11.
56. Suthanthiran M, Li B, Song JO et al. Transforming growth factor-β_1 hyperexpression in African–American hypertensives: A novel mediator of hypertension and/or target organ damage. Proc Natl Acad Sci USA 2000; 97: 3479–84.
57. Porreca E, Febbo CD, Vitacolonna E et al. Transforming growth factor-β_1 levels in hypertensive patients: association with body mass index and leptin. Am J Hypertens 2002; 15: 759–65.
58. Lijnen PJ, Petrov VV, Fagard RH. Association between transforming growth factor-β and hypertension. Am J Hypertens 2003; 16: 604–11.
59. De Matteo R, May CN. Direct coronary vasodilator action of adrenomedullin is mediated by nitric oxide. Br J Pharmacol 2003; 140: 1414–20.
60. Zhao Y, Hague S, Manek S et al. PCR display identifies tamoxifen induction of the novel angiogenic factor adrenomedullin by a non estrogenic mechanism in the human endometrium. Oncogene 1998; 16: 409–15.
61. Kato J, Kitamura K, Matsui E et al. Plasma adrenomedullin and natriuretic peptides in patients with essential or malignant hypertension. Hypertens Res 1999; 22: 61–5.
62. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001; 357: 53–6.
63. Maynard SE, Min JY, Merchan J et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. JCI 2003; 111: 649–58.
64. Tsatsaris V, Goffin F, Munaut C et al. Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: Pathophysiological consequences. J Clin Endocrine Metab 2003; 88: 5555–63.
65. Levine RJ, Maynard SE, Qian C et al. Circulating angiogenic factors and the risk of preeclampsia. New Engl J Med 2004; 350: 672–83.
66. Luttun A, Carmeliet P. Soluble VEGF receptor Flt1: The elusive preeclampsia factor discovered? JCI 2003; 111: 600–2.
67. Solomon CG, Seely EW. Preeclampsia – searching for the cause. New Engl J Med 2004; 350: 641–2.
68. Cross MJ, Dixelius J, Matsumoto T et al. VEGF-receptor signal transduction. Trends Biochem Sci 2003; 28: 488–94.
69. Robelink TJ, de Boer HC, de Koning EJP, van Zonneveld A-J. Endothelial progenitor cells: More than an inflammatory response? Arterioscler Thromb Vasc Biol 2004; 24: 834–8.
70. Zheng W, Sefton EA, Meininger CJ et al. Mechanisms of coronary angiogenesis in response to stretch: Role of VEGF and TGF-β. Am J Physiol 2001; 280: H909–17.
71. Feng Y, Yang JH, Huang H et al. Transcriptional profile of mechanically induced genes in human vascular smooth muscle cells. Circ Res 1999; 85: 1118–23.
72. Chang H, Shyu K-G, Wang B-W et al. Regulation of hypoxia-inducible factor-1α by cyclical mechanical stretch in rat vascular smooth muscle cells. Clin Sci 2003; 105: 447–56.
73. Kuwahara F, Kai H, Tokuda K et al. Hypoxia-inducible factor-1α/vascular endothelial growth factor pathway for adventitial vasa vasorum formation in hypertensive rat aorta. Hypertension 2002; 39 46–50.
74. Safran M, Kaelin, Jr. WG. HIF hydroxylation and the mammalian oxygen-sensing pathway. J Clin Invest 2003; 111: 779–83.
75. Chua CC, Hamdy RC, Chua BH. Upregulation of vascular endothelial growth factor by anigiotensin II in rat heart endothelial cells. Biochim Biophys Acta 1998; 1401: 187–194.
76. Williams B, Baker AQ, Gallacher B et al. Angiotensin II increases vascular permeability factor gene expression by human vascular smooth muscle cells. Hypertension 1995; 25: 913–7.
77. Yang R, Ogasawara AK, Zioncheck TF et al. Exaggerated hypotensive effect of vascular endothelial growth factor in spontaneously hypertensive rats. Hypertension 2002; 39: 815–20.
78. Senger Dr, Perruzzi CA, Feder J et al. A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. Cancer Res 1986; 46: 5629–32.
79. Lenfant C, Roccella EJ. A call to action for more aggressive treatment of hypertension. J Hypertens 1999; 17(Suppl 1): S3–7.
80. Heistad DD, Lawton WJ, Talman WT. Pathogenesis of acute hypertension encephalopathy. In Izzo JL, Black HR (eds) Hypertension Primer, 3rd edition. Philadelphia: Lippincott Williams & Wilkins 2003; 201–3.
81. Schoch HJ, Fischer S, Marti HH. Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain. Brain 2002; 125: 2549–57.
82. Josko J, Knefel K. The role of vascular endothelial growth factor in cerebral oedema formation. Folia Neuropathol 2003; 41: 161–6.
83. Jensen JS, Borch-Johnsen K, Jensen G et al. Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. Clin Sci (Colch) 1995; 88: 629–33.
84. Mor F, Quintana FJ, Cohen IR. Angiogenesis-inflammation cross-talk: Vascular endothelial growth factor is secreted by activated T cells and induces Th1 polarization. J Immunol 2004; 172: 4618–23.
85. Kim I, Moon S-O, Kim SH et al. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-κB activation in endothelial cells. J Biol Chem 2001; 276: 7614-20.
86. Arisato T, Hashiguchi T, Sarker KP et al. Highly accumulated platelet vascular endothelial growth factor in coagulant thrombotic region. J Thromb Haemost 2003; 1: 2589–93.
87. Shen BQ, Lee DY, Cortopassi KM et al. Vascular endothelial growth factor KDR receptor signaling potentiates tumor necrosis factor-induced tissue factor expression in endothelial cells. J Biol Chem 2001; 276: 5281–6.
88. Eremina V, Sood M, Haigh J, et al Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal disease. J Clin Invest 2003; 111: 707–16.
89. Bortoloso E, Prete D, Vestra M et al. Quantitate and qualitative changes in vascular endothelial growth factor gene expression in glomeruli of patients with type 2 diabetes. Eur J Endocrinol 2004; 150: 799–807.
90. Eremina V, Sood M, Haigh J et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal disease. J Clin Invest 2003; 111: 707–16.
91. Asselbergs FW, deBoer RA, Diercks GFH et al. Vascular endothelial growth factor: the link between cardiovascular risk factors and microalbuminuria? Int J Cardiol 2004; 93: 211–5.
92. Santilli F, Spagnoli A, Mohn A et al. Increased vascular endothelial growth factor serum concentrations may help identify patients with onset of Type I diabetes during childhood at risk for developing persistent microalbuminuria. J Clin Endocrinol Metab 2001; 86: 3871–6.
93. Cottone S, Vadalá A, Mangano MT et al. Endothelium-derived factors in microalbuminuric and nonmicroalbuminuric essential hypertensives. Am J Hypertens 2000; 13: 172–6.
94. Cooper LT, Hiatt WR, Creager MA et al. Proteinuria in a placebo-controlled study of basic fibroblast growth factor for intermittent claudication. Vasc Med 2001; 6: 235–9.
95. Vasan RS, Beiser A, Seshadri S et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA 2002; 287: 1003–10.

96. Scheubel RJ, Zorn H, Silber RE et al. Age-dependent depression in circulating endothelial progenitor cells in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2003; 42: 2073–80.
97. Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women. The Rancho Bernardo Study Am J Epidemiol 1997; 145: 970–6.
98. Harris TB, Kiel D, Roubenoff R et al. Association of insulin-like growth factor-I with body composition weight history, and past health behaviors in the very old: the Framingham Heart Study. J Am Ger Soc 1997; 45: 133–9.
99. Dimmeler S, Vasa-Nicotera M. Aging of progenitor cells: Limitation for regenerative capacity? J Am Coll Cardiol 2003; 42: 2081–2.
100. Emanueli C, Salis MB, Stacca T et al. Angiotensin AT1 receptor signaling modulates reparative angiogenesis induced by limb ischemia. Br J Pharmacol 2002; 135: 87–92.
101. Munzemaier DH, Greene AS. Opposing actions of antgiotensin II on microvascular growth and arterial blood pressure. Hypertension 1996; 27: 760–5.
102. Le Noble FA, schreurs NH, van Straaten HW et al. Evidence for a novel angiotensin II receptor involved in angiogenesis in chick embryo chorioallantoic membrane. Am J Physiol 1993; 264: R460–5.
103. Fernandez LA, Twickler J, Mead A. Neovascularization produced by angiotensin II. J Lab Invest Clin 1985; 105: R141–5.
104. Page EL, Robitaille GA, Poussegur J et al. Induction of hypoxia-inducible factor-1α by transcriptional and translational mechanisms. J Biol Chem 2002; 277: 48403–9.
105. Otani A, Takagi H, Suzuma K, Honda Y. Angiotensin II potentiates vascular endothelial growth factor-induced angiogenic activity in retinal microcapillary endothelial cells. Circ Res 1998; 82: 619–28.
106. Amaral SL, Linderman JR, Morse MM et al. Angiogenesis induced by electrical stimulation is mediated by angiotensin II and VEGF. Microcirculation 2001; 8: 57–67.
107. Stoll M, Steckelings UM, Paul M et al. The angiotensin AT2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. J Clin Invest 1995; 95: 651–7.
108. Sasaki K, Murohara T, Ikeda H et al. Evidence for the importance of angiotensin II type 1 receptor in ischemia-induced angiogenesis. J Clin Invest 2002; 109: 603–11.
109. Toko H, Zou Y, Minamino T et al. Angiotensin II type 1a receptor is involved in cell infiltration, cytokine production, and neovascularization in infarcted myocardium. Arterioscler Thromb Vasc Biol 2004; 24: 664–70.
110. Volpert OV, Ward WF, Lingen MW et al. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. J Clin Invest 1996; 98: 671–9.
111. Silvestre JS, Tamarat R, Senbonmatsu T et al. Antiangiogenic effect of angiotensin II type 2 receptor in ischemia-induced angiogenesis in mice hindlimb. Circ Res 2002; 90: 1072–9.
112. Benndorf R, Böger RH, Ergün S et al. Angiotensin II type 2 receptor inhibits vascular endothelial growth factor-induced migration and *in vitro* tube formation of human endothelial cells. Circ Res 2003; 93: 438–47.
113. Levy BI. Can angiotensin II type 2 receptors have deleterious effects in cardiovascular disease? Implications for therapeutic blockade of the renin-angiotensin system. Circulation 2004; 109: 8–13.
114. Walther T, Menrad A, Orzechowski H et al. Differential regulation of *in vivo* angiogenesis by angiotensin II receptors. FASEB J 2003; 17: 2061–7.
115. De Gaspara M, Catt KJ, Inagami T et al. International union of pharmacology. XXXII. The angiotensin II receptors. Pharmacol Rev 2000; 52: 415–72.
116. Ferrario CM, Brosnihan KB, Diz DI et al. Angiotensin-(1-7): A new hormone of the angiotensin system. Hypertension. 1991; 18(Suppl 5): 126–33.
117. Freeman EJ, Chisolm GM, Ferrario CM et al. Angiotensin-(1-7) inhibits vascular smooth muscle cell growth. Hypertension 1996; 28: 104–8.
118. Zeng W, Hong MA, Wang L et al. The role of angiontensin-(1-7) in the proliferative response of vascular smooth cells induced by endothelin-1. Chin J Geriatr Cardiovasc Cerebrovasc Dis 2001; 3: 107–9.
119. Strawn WB, Ferrario CM, Tallant EA. Angiotensin-(1-7) reduces smooth muscle growth after vascular injury. Hypertension 1999; 33: 207–11.
120. Machado RD, Santos RA, Andrade SP. Opposing actions of angiotensins on angiogenesis. Life Sci 2000; 66: 67–76.
121. Machado RD, Santos RA, Andrade SP. Mechanisms of angiotensin-(1-7)-induced inhibition of angiogenesis. Am J Physiol Regul Integr Comp Physiol. 2001; 280: R994–1000.
122. Cameron NE, Cotter MA, Robertson S. Angiotensin converting enzyme inhibition prevents development of muscle and nerve dysfunction and stimulates angiogenesis in streptozotocin-diabetic rats. Diabetologia 1992; 35: 12–18.
123. Gohlke P, Kuwer I, Schnell A et al. Blockade of bradykinin B_2 receptors prevents the increase in capillary density induced by chronic angiotensin-converting enzyme inhibitor treatment in stroke-prone spontaneously hypertensive rats. Hypertension. 1997; 29: 478–82.
124. Fabre JE, Rivard A, Magner M et al. Tissue inhibition of angiotensin-converting enzyme activity stimulates angiogenesis *in vivo*. Circulation 1999; 99: 3043–49.
125. Kokkonen JO, Lindstedt KA, Kuoppala A et al. Kinin-degrading pathways in the human heart. Trends Cardiovasc Med 2000; 10: 42–5.
126. Silvestre JS, Bergaya S, Tamarat R et al. Proangiogenic effect of angiotensin-converting enzyme inhibition is mediated by the bradykinin B_2 receptor pathway. Circ Res 2001; 89: 678–83.
127. Celerier J, Cruz A, Lamande N et al. Angiotensinogen and its cleaved derivatives inhibit angiogenesis. Hypertension 2002; 39: 224–28.
128. Tewksbury D. Angiotensinogen: Biochemistry and molecular biology. In Laragh JH, Brenner GM (eds) Hypertension. New York: Raven Press 1990; 1197–216.
129. Colman RW, Jameson BA, Lin Y et al. Domain 5 of high molecular weight kininogen (kinostatin) down-regulates endothelial cell proliferation and migration and inhibits angiogenesis. Blood 2000; 95: 543–50.