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A Double-Edged Sword Effect of Angiogenesis in Hypertension: A Review

(Kesan Pedang Bermata Dua Angiogenesis dalam Hipertensi: Suatu Tinjauan)

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ABSTRACT

Hypertension, commonly known as high blood pressure, is a serious medical condition that significantly raises the risk of heart, brain, kidney, and blood vessel diseases. It remains one of the leading causes of morbidity and mortality worldwide, with its mechanisms still not fully understood. One emerging area of interest is the role of angiogenesis, the formation of new blood vessels, which is regulated by a delicate balance between pro- and anti-angiogenic modulators, including angiogenic factors, extracellular matrix proteins, adhesion receptors, and proteolytic enzymes. Disruption of this balance can lead to abnormal angiogenesis, potentially contributing to hypertension, as angiogenic growth factors are critical in maintaining vascular structure. If left untreated, high blood pressure damages capillaries and microvessels, accelerating the process of vascular rarefaction. Notably, microvascular rarefaction may occur independently of changes in blood pressure, indicating its potential role as a primary factor in hypertension progression. The 'double-edged sword effect' describes the paradoxical impact of both pro- and anti-angiogenic therapies, where either type of drug can induce hypertension, highlighting the dual nature of angiogenic regulation in vascular health. Given the rising use of angiogenesis-modulating therapies in treating various diseases, therapy-induced hypertension is expected to become more prevalent. This review was conducted to address the growing need to understand this dual effect of angiogenic therapies, the mechanisms underlying hypertension development, and the critical importance of early detection and long-term management of hypertension in patients undergoing such treatments.

Keywords: Angiogenesis; anti-angiogenic; hypertension; microvascular rarefaction; pro-angiogenic

ABSTRAK

Hipertensi, yang dikenali sebagai tekanan darah tinggi, adalah keadaan perubatan serius yang secara signifikan meningkatkan risiko penyakit jantung, otak, buah pinggang dan saluran darah. Ia kekal sebagai salah satu punca utama morbiditi dan mortaliti di seluruh dunia dengan mekanismenya yang masih belum difahami sepenuhnya. Salah satu bidang yang semakin mendapat perhatian ialah peranan angiogenesis, iaitu pembentukan saluran darah baharu yang dikawal oleh keseimbangan halus antara modulator pro-angiogenik dan anti-angiogenik, termasuk faktor angiogenik, protein matriks ekstrasel, reseptor adhesi dan enzim proteolitik. Gangguan pada keseimbangan ini boleh menyebabkan angiogenesis yang tidak normal, berpotensi menyumbang kepada hipertensi, kerana faktor pertumbuhan angiogenik adalah penting dalam mengekalkan struktur vaskular. Jika tidak dirawat, tekanan darah tinggi boleh merosakkan kapilari dan mikrovesel, mempercepatkan proses kekurangan vaskular. Kekurangan mikrovesel ini juga mungkin berlaku secara bebas daripada perubahan tekanan darah, menunjukkan peranannya sebagai faktor utama dalam perkembangan hipertensi. Kesan 'pedang bermata dua' menggambarkan impak paradoks kedua-dua terapi pro- dan anti-angiogenik dengan kedua-dua jenis ubat boleh menyebabkan hipertensi, menonjolkan sifat dwi pengawalan angiogenik dalam kesihatan vaskular. Memandangkan penggunaan terapi yang memodulasi angiogenesis semakin meningkat untuk merawat pelbagai penyakit, hipertensi yang disebabkan oleh terapi dijangka menjadi lebih kerap. Kajian semula ini dijalankan untuk menangani keperluan yang semakin meningkat dalam memahami kesan dwi terapi angiogenik, mekanisme yang mendasari perkembangan hipertensi, serta kepentingan kritikal pengesanan awal dan pengurusan jangka panjang hipertensi pada pesakit yang menjalani rawatan sedemikian.

Kata kunci: Angiogenesis; anti-angiogenik; hipertensi; kekurangan mikrovaskular; pro-angiogenik

INTRODUCTION

Hypertension, also known as high or raised blood pressure, is a condition characterized by persistently elevated pressure in the blood vessels, significantly increasing the risk of heart, brain, kidney, and other diseases (WHO 2019). It is widely recognized that endothelial dysfunction and structural changes in blood vessels are closely correlated. Specifically, hypertension is marked by the thickening and remodeling of arterial walls, alongside an increase in the wall-to-lumen ratio. This condition is frequently associated with stroke, peripheral arterial disease, arterial aneurysms, and renal disease (Tarsia & Caplan 2017). Recent studies have reported rarefaction, or a reduction in the density of arterioles and capillaries, in both hypertensive humans and animals. This rarefaction contributes to increased peripheral resistance, leading to elevated blood pressure, vascular damage, and inflammation (Humar, Zimmerli & Battegay 2009). Angiogenesis, the process of growing new blood vessels from existing ones, plays a critical role in both physiological and pathological conditions throughout life (Adair & Montani 2022). This process depends on a delicate balance of pro- and anti-angiogenic modulators, including angiogenic factors, extracellular matrix proteins, adhesion receptors, and proteolytic enzymes within the vascular microenvironment. The proper formation of capillaries through angiogenesis is essential for nutrient and metabolite exchange in all tissues. However, in hypertensive patients, abnormal angiogenesis may disrupt these processes, potentially leading to cardiovascular complications.

Despite the established link between hypertension and endothelial dysfunction, there is a significant research gap in understanding the dual effects of angiogenic therapies on hypertension. While existing literature highlights the role of angiogenic factors and endothelial damage, the specific mechanisms by which both pro- and anti-angiogenic therapies contribute to hypertension are not well elucidated. Additionally, although microvascular rarefaction has been observed, its precise relationship with blood pressure changes and its role in hypertension progression remain unclear. This review aims to address these gaps by exploring the paradoxical impact of angiogenic therapies both pro- and anti-angiogenic on hypertension. It will also examine how abnormal angiogenesis affects key biomarkers like von Willebrand factor (vWf), vascular endothelial growth factor (VEGF), and its soluble receptor (sFlt-1), which are critical for understanding the pathophysiology of hypertension. By identifying these research gaps, this review seeks to advance knowledge in this area and highlight the need for targeted approaches in managing hypertension related to angiogenic processes.

HYPERTENSION

TYPES OF HYPERTENSION

There are mainly two forms of hypertension. When the aetiology of hypertension is unclear, which is the case for 95% of people with high blood pressure, it is known as essential or primary hypertension. In contrast, the disease is known as secondary hypertension when a cause can be identified (Medlineplus 2020).

ESSENTIAL HYPERTENSION

Essential hypertension is usually asymptomatic, although it can cause headaches, fatigue, dizziness, and nosebleeds. Obesity, smoking, alcohol, malnutrition, and heredity factors exhibit a role in essential hypertension, despite the fact that the origin is unclear (Iliades 2009). This form of hypertension is identified by three or more visits without any aetiology (Hecht 2019).

SECONDARY HYPERTENSION

According to MedlinePlus (2022), secondary hypertension is characterised as high blood pressure that is caused by another medical condition or use of certain medicines. It usually improves after treating the condition that is causing it, or by stopping the offending medication, which accounts for only around 5% to 10% of all hypertension cases. Secondary hypertension affects about 30% of people between the ages of 18 and 40 (Hinton et al. 2020). The most common cause of secondary hypertension is an abnormality in the arteries delivering blood to the kidneys. Airway blockage during sleep, illnesses and tumours of the adrenal glands, hormone imbalances, thyroid disorders, and a diet high in salt or alcohol are some of the other reasons. Over-the-counter drugs including ibuprofen (Motrin, Advil) and pseudoephedrine (Afrin, Sudafed, and others) can also cause secondary hypertension (Iliades 2009).

ANGIOGENESIS

Angiogenesis is described as the formation of new vessels from pre-existing functional vessels (Humar, Zimmerli & Battegay 2009). In addition to angiogenesis, several different types of vascularization exist, such as vessel co-option, vascular mimicry, intussusception or vessel splitting, endothelial cell differentiation, and vasculogenesis (Kim & Pangestuti 2011). Angiogenesis is based on the balance of positive and negative angiogenic modulators within the vascular milieu under physiological settings and needs the functional activities of a variety of molecules, including angiogenic factors, extracellular

matrix proteins, adhesion receptors, and proteolytic enzymes (Ribatti & Crivellato 2009). Pathological angiogenesis occurs in tumour formation and in chronic inflammation, and persists unabated for months or years. Endothelial cells continue to proliferate rapidly,while the new blood vessels are thin walled and pericyte poor, and they rarely regress spontaneously (Humar, Zimmerli & Battegay 2009; Ribatti 2013). Many of the new capillary blood vessels either regress or go on to become mature microvessels. These mature microvessels contain quiescent endothelial cells that rest on an intact basement membrane, and embedded in this basement membrane are pericytes. Therefore, established microvessels have a slightly thicker wall than growing vessels. In growing microvessels, the basement membrane is disrupted and pericytes are sparse or absent (Ribatti 2013).

THE ASSOCIATION OF ANGIOGENESIS AND HYPERTENSION

Changes in microcirculation have a significant role in the pathophysiology of hypertension. Microvascular rarefaction is characterised by the loss of precapillary arterioles and capillaries (Humar, Zimmerli & Battegay 2009; Levy et al. 2001). Figure 1 shows the three conditions of microcirculation. Furthermore, it has been discovered that angiogenesis changes during foetal development contribute to microvascular underdevelopment and therefore predispose to hypertension later in life (Humar, Zimmerli & Battegay 2009). Studies in established hypertension have identified the patients as having either high or low blood pressure in early adulthood, and they are further classified on the basis of their parents' blood pressures (Humar, Zimmerli & Battegay 2009). Factors which are associated with higher blood pressure in offspring, irrespective of parental blood pressure, are more likely to be secondary to high blood pressure, or to be influenced by environmental determinants of blood pressure that occur in all offspring. Oncological investigations have also highlighted the importance of efficient angiogenesis in maintaining normal blood pressure (Wasserstum et al. 2015). According to the National Cancer Institute, anti-angiogenic medicines aimed at preventing tumour vascular sprouting have been discovered to cause hypertension as a frequent adverse effect. Nonetheless, although some studies demonstrated that hypertension is linked to a reduction in angiogenesis, others illustrate that hypertensive individuals have higher blood levels of specific angiogenic agents.

A decrease in microvascular density has been implicated in the onset of hypertension (Adair & Montani 2022) in which lower skin capillary density serves a pathogenic role in increased peripheral resistance and hypertension (Humar, Zimmerli & Battegay 2009). Rarefaction can be functional or structural. Functional rarefaction of microvessels results from vasoconstriction, and in the setting of hypertension, the loss of perfusion that precedes structural rarefaction of the microvasculature is considered reversible and can result from decreased availability of nitric oxide, increased presence of endogenous vasoconstrictors, such as endothelin and prostaglandins, or sympathetic tone, as well as reduced availability of growth factors. In contrast, structural rarefaction of the resistance vessels, arterioles and capillaries, entails a loss of vessels in a vascular network. This effect can occur in response to vasoconstriction and loss of perfusion, or to a decrease in the availability of endogenous vascular growth factors that are responsible for cellular functions, including survival, migration and differentiation of neuronal and glial cells (D'Souza et al. 2011).

Figure 2 shows that if the cardiac output is permanently increased by any mechanism, an increase of vascular tone and inward remodeling will be observed (Takeshita 2001; Vermissen et al. 2019; Vilar et al. 2008), as well as pruning, evident from vascular rarefaction (D'Souza et al. 2011). This causes a decrease in blood supply and, more importantly for chronic hypertension, an increase of peripheral flow resistance, which raises blood pressure via positive feedback. Furthermore, it will cause a vicious cycle of the rises of blood pressure and peripheral resistance, amplifying the hypertension above the level caused by the initial increase in cardiac output. The increased peripheral resistance and its constituents such as the increased tone of vascular smooth muscle cells, inward remodeling, and rarefaction, likely lead to deficits in supply of oxygen and nutrients and consequently to end-organ damage (Pries 2015).

FIGURE 1. Three conditions of microcirculation. 1) Normal arteriole, 2) Functional rarefaction, and 3) Anatomic rarefaction (de Jesus-Gonzalez et al. 2012)

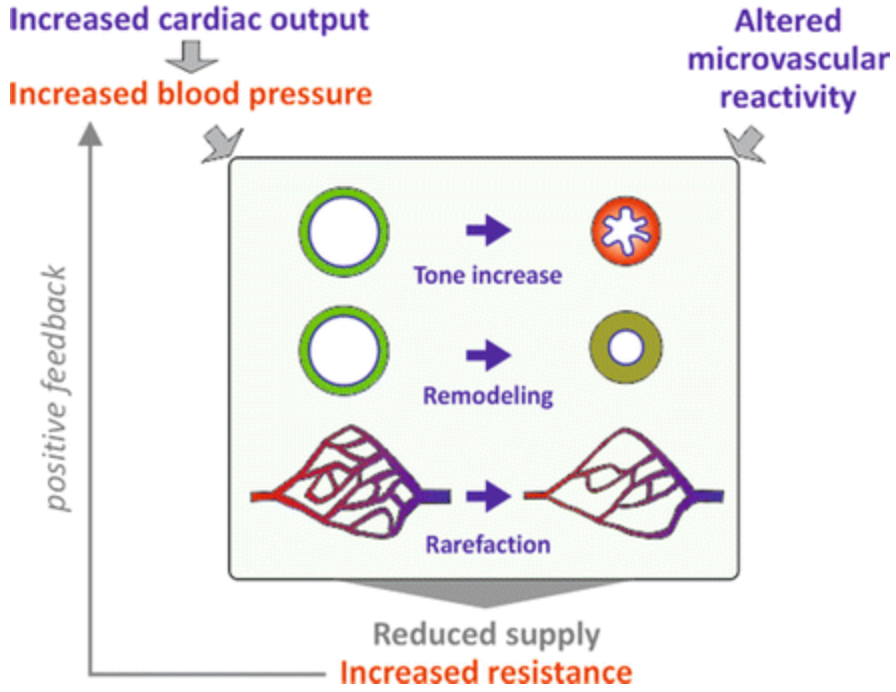

FIGURE 2. Relationship between the angioadaptive processes of tone, remodelling, and rarefaction and the development of hypertension. All changes may lead to a further increase in peripheral vascular resistance (Pries 2015)

After the development of hypertension, microvascular rarefaction emerges or worsens over a short time interval (Humar, Zimmerli & Battegay 2009). The fundamental structural changes in these microvessels appear to be a loss of vessel integrity caused by the separation of the arteriolar wall's endothelial and smooth muscle components. Microvascular rarefaction can be a primary event because remodelling resistance arteries and microvessels can be totally or partially independent of blood pressure (Humar, Zimmerli & Battegay 2009).

ANGIOGENESIS-RELATED THERAPY IN HYPERTENSION

Hypertension is associated with low levels of physiologically pro-angiogenic factors in the blood, as well as high levels of angiogenesis inhibitors (Marek-Trzonkowska et al. 2015). Pro-angiogenesis has the potential to interrupt the vicious cycle of hypertension and vascular rarefaction. Increased blood pressure, if left untreated, damages microvessels, destroys capillaries, and expedites the pathogenic consequences of vascular rarefaction (Humar, Zimmerli & Battegay 2009). This vascular rarefaction raises peripheral resistance, which leads to the development of hypertension (Joyner, Schrage & Eisenach 2007). The stabilisation of vascular homeostasis and the creation of new microvessels with pro-angiogenic or long-term anti-hypertensive treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers might interrupt this vicious cycle (Humar, Zimmerli & Battegay 2009).

Microvascular rarefaction occurs or worsens in a short period of time. Microvascular density during the development of hypertension has been extensively reported in various studies on animal models and tissues in earlier research (Humar, Zimmerli & Battegay 2009). In a previous study by Humar, Zimmerli and Battegay (2009), rats that were made hypertensive by surgically reducing renal mass and by the administration of a high salt diet experienced endothelial damage, which was followed by rarefaction within three days. The fundamental structural changes in these microvessels appear to be a loss of vessel integrity caused by the separation of the arteriolar wall's endothelial and smooth muscle components (Humar, Zimmerli & Battegay 2009).

In individuals with minor increment of blood pressure, functional capillary rarefaction was found rather than structural (Cheng, Diamond & Falkner 2008). Microvascular rarefaction can be a primary event because remodeling of resistance arteries and microvessels can be totally or partially independent of blood pressure (Gohlke et al. 1997; Humar, Zimmerli & Battegay 2009; Levy et al. 2001; Takeshita 2001). Furthermore, a family propensity to essential hypertension is linked to poor microvascular vasodilation and capillary rarefaction (Boegehold 2007). In addition, the establishment of microvascular networks

is characterised by poor embryonic vascular development, low birth weight, and decreased postembryonic vascular expansion. Capillary rarefaction therefore usually precedes, but can sometimes occur after, persistent hypertension as shown in Figure 3 (Humar, Zimmerli & Battegay 2009).

PRO ANGIOGENIC AGENT

The growth and function of the vascular, lymphatic system, and glomerular filtration barrier are all influenced by vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs). Their pro-angiogenic activities are essential not just during normal physiological processes that include embryogenesis, menstruation, and wound healing, but also during cancer development and metastasis (Lange et al. 2016). There are four VEGF isoforms (A, B, C, and D) as well as the placental growth factor in the VEGF family (PlGF). The major pro-angiogenic isoform among the four VEGF members is VEGF A (De Falco 2012). It is a soluble protein released by tumours that binds to and activates the VEGF receptor 2 (VEGFR2), which is expressed in endothelial cell membranes, and its downstream pathways to recruit and promote endothelial cell proliferation, migration, and survival (Cébe-Suarez, Zehnder-Fjällman & Ballmer-Hofer 2006). VEGFR1 and VEGFR2 are primarily expressed by endothelial cells in the vascular wall (Shibuya 2011). The most significant receptor for VEGF-induced angiogenesis and vascular permeability is VEGFR2. Figure 4 shows the VEGF family of growth factors.

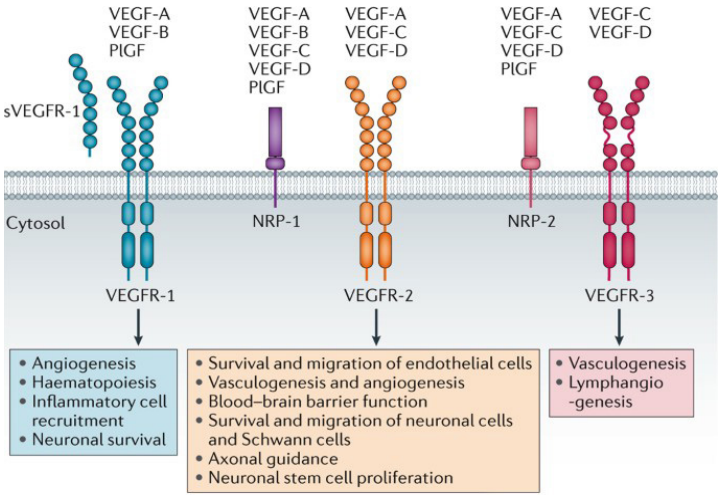

FIGURE 3. Hypertension and microvascular rarefaction. Increased and untreated blood pressure harms microvessels, leads to the destruction of capillaries and accelerates the pathogenic effects of vascular rarefaction. This vascular rarefaction increases peripheral resistance and eventually contributes to the development of hypertension (Humar, Zimmerli & Battegay 2009)

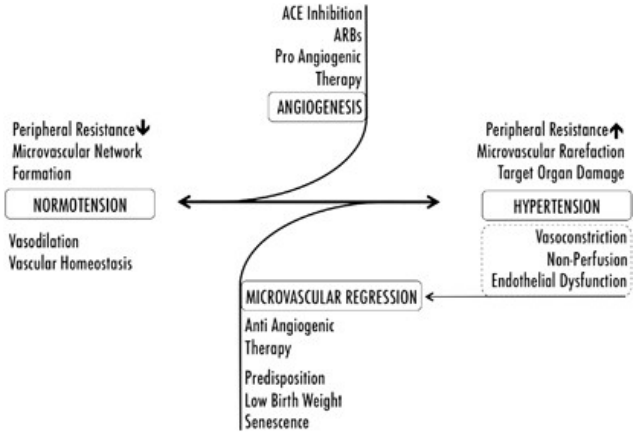

FIGURE 4. VEGF family of growth factors (Lange et al. 2016)

TABLE 1. Pro-angiogenic agents, its function and molecular target

Pro-angiogenic agents	Function	Target	References
VEGF	Recruit and promote endothelial proliferation, migration, and survival.	VEGFR-2	(Cébe-Suarez, Zehnder-Fjällman & Ballmer-Hofer 2006; De Falco 2012)
Transcription Factor Hypoxia-Inducible Factor 1-Alpha	Activate all genes needed for microvessel growth	Hypoxia-Inducible Factors (HIFs)	(Krock, Skuli & Simon 2011 & Rajagopalan et al. 2007)
Bone Marrow-Derived Mononuclear Cells	Induced coordinated microvessel growth	Microphages and pericytes	(Ding, Song & Luo 2012; Humar, Zimmerli & Battegay 2009)
Endothelial Progenitor Cells	Contribute directly to neovascularization	Monocytic cells	(Kalka et al. 2000; Kawamoto et al. 2001; Marçola & Rodrigues 2015; Ott et al. 2005)
COMP-Ang-1 of Angiopoietin-1	Enhance protection and microvessel density and reduced microvascular rarefaction and tissue damage	Steroid Hormone Receptors (SHR)	(Cho et al. 2004 & Humar, Zimmerli & Battegay 2009)

The administration of many angiogenic agents induces a more secure and stable vasculature than single growth factors. This concept has been tested in a clinical phase-I trial by introducing the pro-angiogenic transcription factor, hypoxia-inducible factor 1-alpha (HIF-1ɑ), which is expected to activate all genes needed for proper microvessel growth by upregulating multiple pro-angiogenic pathways that mediate key aspects of endothelial, stromal, and vascular support cell biology (Krock, Skuli & Simon 2011; Rajagopalan et al. 2007). Most transcriptional responses to low oxygen are mediated by hypoxia-inducible factors (HIFs), which are highly conserved transcription factors that control the expression of numerous angiogenic, metabolic, and cell cycle genes (Krock, Skuli & Simon 2011). Infusion of bone marrow-derived mononuclear cells is a promising possibility for inducing coordinated microvessel growth (Humar, Zimmerli & Battegay 2009). It is evident that tumour infiltrating macrophages and pericytes originated from bone-marrow derived cells contribute to tumour angiogenesis. These infiltrating cells can release paracrine angiogenic factors, or provide permissive conditions, thus inducing the growth and maturation of the newly formed vasculatures (Ding, Song & Luo 2012).

Other than that, endothelial progenitor cells (EPCs) from this source can assist the angiogenic process indirectly by secreting a variety of factors that induce angiogenesis, vasculogenesis or vasodilation, and progenitor cell mobilisation and recruitment, or reduce apoptosis (Humar, Zimmerli & Battegay 2009). EPCs contribute directly to neovascularization by forming the structural components of capillaries, arterioles, and the heart by differentiation into endothelial cells or transdifferentiation into vascular smooth-muscle cells and cardiomyocytes. These cells can promote angiogenesis by two different mechanisms serving as the substrate for new vessel formation and exerting a paracrine effect. In fact, there are two main cell types within the EPC designation, which are early EPCs (angiogenic cells) and late EPCs. Early EPCs have features of hematopoietic cells, can generate monocytic cells, and play a role in vasculogenesis by secreting large quantities of angiogenic factors that act via paracrine mechanisms, whereas late EPCs (endothelial outgrowth cells) are able to differentiate into endothelial cells and promote vascular tube formation (Marçola & Rodrigues 2015).

Meanwhile, an engineered variant (COMP-Ang-1) of angiopoietin-1, a potent angiogenic growth factor, was shown to enhance endothelial protection and microvessel density in steroid hormone receptors (SHR). COMP-Ang-1 reduced microvascular rarefaction and tissue damage in the heart and the kidney and, intriguingly, also prevented the development of hypertension (Cho et al. 2004; Humar, Zimmerli & Battegay 2009). Thus, therapeutic angiogenesis might potentially be used as an anti-hypertensive treatment.

PRO-ANGIOGENESIS AGENTS AS HYPERTENSION THERAPY

Rarefaction in hypertension is counterbalanced by pro-angiogenesis as shown in Table 1. In response to angiogenic chemicals and hypoxia caused by tissue damage, pre-existing cells multiply and move to create a new vessel during angiogenesis (Carmeliet & Jain 2011). Therapeutic angiogenesis, or the promotion of new vessel growth to treat ischemic diseases, is critical for nearly all attempts to

re-grow or re-create new tissue and is a fascinating area to be ventured in cardiovascular medicine (Deveza, Choi & Yang 2012). Nevertheless, pro-angiogenic treatment, is still in its infancy (Humar, Zimmerli & Battegay 2009). So far, none of the major placebo-controlled trials that have been done to investigate single angiogenic growth factors in patients with myocardial or limb ischaemia have produced any compelling positive outcomes (Cooke & Losordo 2015). Overall, these unsatisfactory outcomes may have been caused by inefficient delivery and inappropriate targeting.

Single-growth-factor therapy that results in the production of mature, permanent, and functioning vasculature *in vivo* only works when the release of the growth factor is properly timed (Ehrbar et al. 2004). This can be accomplished by incorporating angiogenic chemicals into carrier devices such as natural or synthetic polymers, or by implanted minipumps that release the triggers at certain times (Zisch, Lutolf & Hubbell 2003). The administration of many angiogenic agents results in a more secure and stable vasculature than single growth factor (Cao et al. 2003). The pro-angiogenic transcription factor HIF-1ɑ, which is predicted to activate all genes required for optimal microvessel formation, have been examined for this purpose (Rajagopalan et al. 2007). In a recent study, hypoxia was found to be the primary cause of angiogenesis (Humar, Zimmerli & Battegay 2009; Vilar et al. 2008). When compared to normoxia, chronic normobaric hypoxia (10% O2) is characterised by reduced vascular resistance and, as a result, systolic blood pressure by 26% within three weeks (21% O2) (Vilar et al. 2008). Hypoxia-induced angiogenesis was blocked by neutralising VEGF-A antibody treatment, which aggravated arterial hypertension. Chronic hypoxia thereby stimulates VEGF-A-induced angiogenesis, which then prevents or normalises microvascular rarefaction and hypertension (Vilar et al. 2008).

As mentioned earlier, the use of bone marrow-derived mononuclear cells as a source of coordinated microvessel development is also one of the potential options being explored (Humar, Zimmerli & Battegay 2009). Endothelial progenitor cells indirectly aid the angiogenic process by secreting a number of substances that promote angiogenesis, vasculogenesis or vasodilation, stem or progenitor cell mobility and recruitment, and minimise apoptosis (Lachmann & Nikol 2007). Endothelial progenitor cells contribute directly to neovascularization by forming the structural components of capillaries, arterioles, and the heart by differentiation into endothelial cells or transdifferentiation into vascular smooth-muscle cells and cardiomyocytes (Kalka et al. 2000; Kawamoto et al. 2001; Ott et al. 2005). Endothelial progenitor cells for regenerative medicine are now being studied in clinical trials (Jujo, Ii & Losordo 2008).

ANTI-ANGIOGENIC AGENTS

Anti-angiogenic drugs are currently under development which target the VEGF signalling pathway, as well as other tyrosine-kinase-based signalling pathways (Niu & Chen 2010). Inhibitors of the VEGF signalling pathway target the molecule, its receptor, or downstream pathways (Shibuya 2011). Anti-angiogenic agents approved by the FDA include bevacizumab, a recombinant, humanised of a mouse anti VEGF-A monoclonal antibody that binds and sequesters the VEGF molecule, and multi-targeted tyrosine kinase inhibitors (TKI), such as sunitinib, sorafenib, and pazopanib, which are small molecules with competitive or allosteric inhibitory activity at the catalytic binding (de Jesus-Gonzalez et al. 2012). The latter class of medicines, however, is less selective and targets additional tyrosine kinase receptors, such as platelet derived growth factor receptor (PDGFR) and c-kit (Broekman 2011). Other than that, peptides have emerged as important therapeutics that are being rigorously tested in angiogenesis-dependent diseases due to their low toxicity and high specificity since the discovery of endogenous proteins and protein fragments that inhibit microvessel formation such as thrombospondin and endostatin (Rosca et al. 2011). Peptides have been synthesised from thrombospondin, collagens, chemokines, coagulation cascade proteins, growth factors, and other protein classes, and they target a variety of receptors (Rosca et al. 2011). Table 2 lists all anti-angiogenesis agents that are used to treat hypertension.

ANTI-ANGIOGENESIS AGENTS AS HYPERTENSION THERAPY

GROWTH FACTOR INHIBITORS

Bevacizumab-induced hypertension

Angiogenesis does not cause cancer, but it will worsen the consequences, as seen in tumour growth and metastasis. The only authorised anti-angiogenic medicine for cancer therapy is bevacizumab which as mentioned earlier, is a humanised form of a mouse anti VEGF-A monoclonal antibody (Vilar et al. 2008). The VEGF receptor-2 pathway that is required for both embryonic and pathological angiogenesis, and its function in the formation and maintenance of blood vessels, as well as tumour growth and metastasis, has been widely researched (Shibuya 2011). Endothelial cells generate endogenous VEGF, which is important for vascular homeostasis (E.G et al. 2012). As a result, treatments that target VEGF may disrupt existing microvessels, resulting in vascular rarefaction, hence causing hypertension in those who are not predisposed to it (Robinson et al. 2010). Angiogenesis inhibitors have now been related to the development of hypertension in a series of studies (de Jesus-Gonzalez et al. 2012; Humar,

Zimmerli & Battegay 2009; Robinson et al. 2010). A large meta-analysis of individuals treated with bevacizumab in randomised controlled trials found a substantial dose-dependent increase in the incidence of hypertension (Zhu et al. 2007). Hypertension was detected in 22% of patients in early studies using bevacizumab, compared to 8% in control groups. In the bevacizumab-treated group, 11% experienced stage 3 hypertension (Hurwitz et al. 2004). According to the Journal of Human Hypertension, bevacizumab treatment-induced hypertension was associated with endothelial dysfunction and capillary rarefaction involving 20 participants. Both changes are related to and may be responsible for the elevation in blood pressure seen in the majority of individuals. In patients from that trial, bevacizumab targeted not just the disease and 'switched' arteries supplying the tumour region, but also the 'normal' arterioles and capillaries further from the tumour zone (Mourad et al. 2008). The authors conclude that anti-angiogenic treatment promotes or aggravates hypertension by causing microvascular rarefaction.

Telatinib induced hypertension

In a previous clinical phase-I study, the multi-growth factor kinase inhibitor telatinib produced hypertension, microvascular rarefaction, and modified microvascular features in patients with advanced solid tumours (Steeghs et al. 2008). However, it is uncertain if the rarefaction seen was structural or functional. It is still unclear if changes in microvessel architecture in response to anti-angiogenic treatment are reversible (Humar, Zimmerli & Battegay 2009). The effects of telatinib, a tyrosine kinase inhibitor and effective angiogenesis inhibitor, on the vasculature were studied in order to determine how small molecule angiogenesis inhibitors cause blood pressure to rise (Robinson et al. 2010; Steeghs et al. 2008). The findings by Olufsen et al. (2012) on rarefaction and changes in microvascular features give a credible explanation for the rise in systolic and diastolic blood pressure. Telatinib reduced endothelium-dependent and endothelium-independent vasodilation by a substantial amount (Sun et al. 2020). By itself, VEGF suppression reduces nitric oxide (NO) production, which promotes vasoconstriction, raises peripheral resistance, hence raises blood pressure (de Jesus-Gonzalez et al. 2012; Robinson et al. 2010). It is unclear if the major issue is decreased NO production, a change in capillary shape that leads to reduced NO vascular smooth muscle cell responsiveness, or a combination of both.

Rarefaction is a common finding in hypertensive patients, and it has also been found in young individuals with a hereditary susceptibility to high blood pressure (Wang & Snieder 2017). Blocking the formation of capillaries with VEGFR inhibitors and other angiogenesis inhibitors may provide similar benefits in those who are not prone to hypertension. Although rapid normalisation of blood pressure and reversal of proteinuria in certain individuals following telatinib withdrawal may imply improvement in functional rarefaction, this is more probable in functional rarefaction than structural rarefaction (Steeghs et al. 2008).

Telatinib causes rarefaction and hypertension through an unknown mechanism. Telatinib is a small chemical tyrosine kinase inhibitor that inhibits the VEGFR-2, VEGFR-3, platelet-derived growth factor receptor, and c-Kit receptors by inhibiting the ATP-binding site (Robinson et al. 2010; Steeghs et al. 2008). The activation of platelet-derived growth factor and the c-Kit receptor leads to the

TABLE 2 Anti-angiogenic agents, its function and molecular target

Anti-angiogenic agents		Function	Target	References
Growth Factor Inhibitor	Bevacizumab	VEGF inhibitor	VEGF by disrupt the existing microvessel which lead to microvascular rarefaction	(de Jesus-Gonzalez et al. 2012; Humar, Zimmerli & Battegay 2009; Kong et al. 2017; Robinson et al. 2010
	Telatinib	Multi-Growth Factor Kinase Inhibitor Suppress VEGFR signaling pathway	Inhibit VEGFR-2 and VEGFR-3, Platelet-Derived Growth Factor, and c-Kit receptor	(Chi & Wen 2012; de Jesus-Gonzalez et al. 2012; Robinson et al. 2010 & Steeghs et al. 2008)
RTKs Inhibitor	Tyrosine Kinase Inhibitor (TKI)	Inhibit VEGF signaling pathway Prevent formation of vasodilator prostacyclin	VEGF by binding to VEGFR-2 and stimulate Tyrosine Kinase activity	(Bazzazi, Isenberg & Popel 2017, Niu & Chen 2010, Ptinopoulou & Sprangers 2020)

activation of pathways which are, for the most part, also activated by VEGFR-2 (Chi & Wen 2012). Hypertension is uncommon in patients on platelet-derived growth factor and c-Kit inhibitors such as imatinib and nilotinib (Montani et al. 2012). The suppression of VEGFR signalling is thus most likely to blame for the rise in blood pressure. However, we cannot rule out the possibility that c-KIT or platelet-derived growth factor inhibition is involved in mediating changes in blood pressure or any of the other variables which it will lead to (de Jesus-Gonzalez et al. 2012; Robinson et al. 2010; Wasserstrum et al. 2015).

RTKS INHIBITORS: TYROSINE KINASE INHIBITOR-INDUCED HYPERTENSION

Tyrosine kinase inhibitors (TKIs) are inhibitors of VEGF signalling pathway that are utilised to treat solid organ malignancies (Ptinopoulou & Spranger 2020). On the basis of the assumption that tumour development and metastasis are angiogenesis-dependent processes, inhibiting angiogenesis is an effective cancer treatment (Ptinopoulou & Sprangers 2020). As a result, disrupting pro-angiogenic signalling pathways, including VEGF as a key target, is a fundamental objective of emerging anti-tumour medicines (Niu & Chen 2010). Binding to VEGFR2 stimulates its intrinsic tyrosine kinase activity, which in turn activates a slew of downstream signalling pathways involved in capillary permeability, nitric oxide (NO) generation, endothelial cell proliferation, migration, and stress survival (Bazzazi, Isenberg & Popel 2017; Ptinopoulou & Sprangers 2020). NO production causes vascular smooth muscle relaxation, while NO depletion causes increased vascular tone, increased peripheral resistance, and systemic blood pressure elevation, as well as sodium retention and extracellular fluid volume increase (Brozovich et al. 2016). Inhibition of VEGFR also prevents the formation of the vasodilator prostacyclin. Chronic VEGF deficiency reduces the lifespan of capillary endothelial cells, which can result in apoptosis and microvascular rarefaction. It is also possible that it will raise the peripheral resistance (Robinson et al. 2010). Regarding the mechanism of action, the most prevalent side effect of TKI therapy is an increase in blood pressure (Ptinopoulou & Sprangers 2020). As a result, virtually all TKI-exposed individuals have a dose-dependent rise in blood pressure, showing that TKI causes hypertension.

CONCLUSIONS

Angiogenesis plays a crucial role in the development of hypertension, as impaired angiogenesis can lead to an inadequate microcirculatory system, predisposing individuals to high blood pressure. This dual role underscores the 'double-edged sword effect' of both pro- and anti-angiogenic therapies, which can induce hypertension and complicate treatment strategies. Additionally, angiogenesis is vital for tumor growth and metastasis, making it challenging to quantify its rates and influencing treatment guidelines. The increasing use of angiogenic agents whether pro- or anti-angiogenic is expected to lead to more cases of treatment-induced hypertension, highlighting the need for earlier diagnosis and extended therapy. The impact of angioadaptation on hypertension involves evaluating the efficacy of various therapies in improving endothelial function and normalizing the microcirculatory system. Unresolved questions remain about the mechanisms linking angiogenesis to hypertension, particularly in relation to microvascular rarefaction. A deeper understanding of these mechanisms is essential for developing effective, hypertension-specific therapeutic strategies in the future.

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