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Review Articles

The Complex Role and Implications of VEGF-A on Cardiac and Renal Physiology and Pathology with Special Focus on Hypertensive Injury – a Critical Review

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Vascular endothelial growth factor (VEGF) is a signaling protein essential for angiogenesis. Despite vigorous research in the field for several decades, the exact role of VEGF in the sophisticated regulatory mechanisms of cardiac and renal homeostasis still remains to be fully elucidated. Recent studies have reported that the expression of VEGF in the heart and kidneys changes with age, which leads to modifications in the microvasculature and age-related remodeling of the myocardium and renal parenchyma. Furthermore, literature data suggest that the levels of VEGF are altered in response to hypertensive injury, which plays a crucial role in the pathogenesis and progression of multiple cardiac and renal pathologies. Therefore, this review strives to assess the accessible literature and provide clarity on the role of VEGF in the complex signaling cascades responsible for maintaining cardiac and renal homeostasis both under physiological and pathological conditions.

Key words: VEGF, heart, kidney, aging, hypertension

Introduction

Vascular endothelial growth factor (VEGF) is an endogenous peptide essential for the formation of blood vessels, i.e. angiogenesis. In humans, five subtypes of VEGF have been isolated. VEGF-A, VEGF-B, and the placental growth factor (PGF) are mainly responsible for forming new blood vessels. In contrast, VEGF-C and VEGF-D are primarily associated with the formation of lymph vessels [15]. The members of

the VEGF family accomplish their role via binding to specific receptors, known as VEGF receptors (VEGFR). There are three subtypes of the VEGFR, all members of the tyrosine kinase superfamily of receptors. VEGFR1 and VEGFR2 are the primary receptor subtypes predominantly expressed by endothelial cells (EC), macrophages, monocytes, and hematopoietic cells [18, 42]. VEGFR1 and VEGFR2 predominantly bind with high affinity VEGF-A, VEGF-B and PGF, thus regulating the formation of new blood vessels [18]. VEGFR3 is mainly expressed in the EC of lymph vessels and binds with high affinity VEGF-C and VEGF-D, thus playing a pivotal role in the angiogenesis of lymph vessels [7].

The VEGF/VEGFR system plays a crucial role in maintaining homeostasis. VEGF is mainly expressed by EC, as well as cardiomyocytes [4]. In addition there is evidence throughout the literature, linking VEGF expression and arterial hypertension [13]. Both the heart and kidneys are target organs for hypertensive injury, due to their rich vasculature. This makes them the perfect target organs for research on the role of VEGF/VEGFR in the pathophysiology of different cardiovascular diseases (CVD) and renal diseases [36].

This review strives to offer a comprehensive assessment of recent studies exploring the physiological and pathological role of VEGF. In particular, we aim at providing clarity on the role of the VEGF/VEGFR system in maintaining cardiac and renal homeostasis over the course of physiological aging and in the setting of various pathologies.

Expression of VEGF in the heart and kidney

VEGF expression in the heart has recently been mapped via immunohistochemistry by Stanchev et al. [46] and Iliev et al. [22]. VEGF immunoreactivity was predominantly registered in the cardiomyocytes' cytoplasm, the walls of capillaries of various size and the perivascular zones. VEGF expression was stronger in the left ventricle (LV) in comparison to the right ventricle (RV) [22, 46]. Such deviations in the distribution of VEGF correlate with the higher workload and oxygen demands of the LV [13]. An alternative method of detection of VEGF in the heart is the use of immunofluorescence. Through that methodology, Stanchev et al. revealed that VEGF expression was observed in the perinuclear and perivascular zones of cardiac muscle cells. The immunofluorescent reaction showed a similar pattern in both ventricles and was stronger in the LV [46]. Similar results were reported by Iliev et al. in another immunofluorescent study on normal rat hearts [22]. VEGF-A exerts its function on cardiomyocytes via the VEGFR1 and VEGFR2 receptors. Moreover, cardiomyocytes are not only target cells for the function of VEGF, but they can also produce VEGF [4].

Expression of VEGF in the kidney has been described in the visceral epithelial cells of Bowman's capsule (podocytes), distal tubules and collecting ducts and less often in proximal tubules [1, 35]. VEGFR-2 is the receptor most often found in the kidney, on the membrane of preglomerular and glomerular endothelial cells, as well as on endothelial cells in blood vessels surrounding the proximal and distal tubules and collecting ducts. VEGFR-2 has also been observed on the membrane of cortical fibroblasts, interstitial cells in the medulla and mesangial cells [1, 35, 55]. According to Stanchev et al., in the renal cortex (RC), VEGF immunoreactivity is observed

in the visceral layer of Bowman's capsule and the epithelial cells of proximal and distal tubular segments. On the other hand, scarce to no staining was observed in the glomerular capillary tufts. The staining in the renal medulla (RM) was most prominent in Henle's collecting ducts and loop [46].

Role of VEGF in the heart and kidney

The exact physiological role of VEGF in the heart after embryological development is yet unclear. Giordano et al. performed a heart-specific VEGF knockout – using genetic engineering techniques, they developed mice with cardiomyocyte-specific deletion of the third exon of the VEGF coding gene. The results were mice with lower body weight, the density of the wall of their hearts was significantly lower, and their hearts were dilated, hypovascularized and with contractile dysfunction. Moreover, the number of coronary microvessels in the hearts of these gene-altered mice was lower [17]. Several studies suggest that cardiomyocytes secrete VEGF in response to different stimuli as per se: hypoxia [30], IL-1β [38], stretching [56, 31], gp130 [16], etc. Karpanen et al. performed a study on the effects of VEGF-B on the heart. They used genetically altered mice with overexpression of VEGF-B via alpha myosin heavy chain promoter. The study revealed a scarce angiogenetic effect of VEGF-B, but surprisingly the gene-modified mice developed cardiac hypertrophy with lower blood pressure and heart rate. These results were explained by altered lipid metabolism leading to mitochondrial morphology changes, enlargement of the cardiomyocytes and development of cardiomyopathy. Thus was concluded that VEGF-B played a crucial role in lipid metabolism in cardiomyocytes [27].

VEGF-A plays an important role in several aspects of the normal renal anatomy and physiology, particularly in glomerular capillary formation and repair and in the maintenance of the fenestrated endothelium of glomerular capillaries [55]. In addition, VEGF-A takes part in the proliferation and apoptosis of tubular epithelial cells [39]. Although the role of VEGF in renal pathology and physiology has been the focus of many studies, results are controversial. Some studies have shown that inhibition of VEGF does not lead to significant alterations in the glomerular filtration barrier [25]. Baderca et al. reported a negative expression of VEGF in the renal corpuscles of the normal renal parenchyma, suggesting that it is not normally present under physiological conditions [2]. Others have reported on potential renoprotective effects under pathological conditions [32]. VEGF is responsible for glomerular and tubular proliferation and hypertrophy in response to nephron reduction and thus, any subsequent decrease in VEGF levels may lead to the development of glomerulosclerosis and tubulointerstitial fibrosis in the remnant kidney. Furthermore, VEGF has been suggested as a major modulator of glomerular recovery in proliferative glomerulonephritis. Last but not least, glomerular and tubulointerstitial repair in pathological conditions such as thrombotic microangiopathy and cyclosporin nephrotoxicity may also be VEGF-dependent [43].

VEGF expression in the heart and kidney during physiological aging

Aging is a physiological process driven by a plethora of factors, such as genetics, environment, gender, nutrition, etc. As a result, old age is considered a significant risk factor for the development and deterioration of CVD [8]. Age-related remodeling of the myocardium is characterized by cardiac hypertrophy, due to an increase in the volume of the cardiomyocytes mainly in the LV, in contrast to the RV, where hypertrophy is not as significant [34]. Moreover, older age exacerbates the energy supply and depletion of angiogenesis in the heart [14]. Despite older age being a significant risk factor, the main emphasis of research has been on the role of VEGF in the pathogenesis and progression of CVD, and only a few studies have focused on the expression of VEGF during physiological aging. Several studies have shown decreased angiogenesis activity with age, which leads to impaired revascularization of ischemic tissues, thus hindering the recovery ability of the myocardium [40]. Capillary density (CD) is a histomorphometric marker of myocardial perfusion, which was found to decrease with age in both ventricles [21]. Iliev et al. reported a statistically significant elevation in VEGF expression with age progression in both ventricles, predominantly in the LV. Furthermore, a statistically significant positive correlation was reported between VEGF expression and CD in both ventricles with age progression [22].

According to literature data, renal aging has been associated with the development of glomerulosclerosis, loss of tubules and development of interstitial fibrosis [10, 57]. Normally, kidneys are organs rich in vasculature due to their physiological demands. Decrease in CD is pivotal for the physiological and morphological changes which occur with age and might be paramount for the development of chronic kidney disease [6]. Undoubtedly, VEGF plays a central role in the maintenance of the sophisticated regulation of renal homeostasis, since both podocytes and tubular EC produce VEGF. Furthermore, both EC and podocytes express VEGFR1 and VEGF2, which further highlights the complexity of renal vascular maintenance and underlines the possible role of VEGF in renal aging [6]. In addition compared VEGF expression in hypoxia in old and young rat kidney and reported a statistically significant decrease of VEGF-A, VEGF-B and VEGFR-2 in the old rat kidney [41]. Because of the vital role which VEGF has in the renal vascular repair after acute kidney injury, it is likely that reduced VEGF expression in the aging rat kidney contributes to repair defects. The decrease in VEGF expression results in an increased expression of thrombospondin-1 (TSP-1). TSP-1 is an antagonist of the VEGF. The imbalance between pro- and antiangiogenic factors could be an explanation of the age-dependent progressive rarefaction of peritubular capillaries and the deficiency of adequate oxygen supply and vascular remodeling during renal repair [26]. The recent study of Iliev et al. demonstrated a decrease in the expression of VEGF in older versus younger Wistar rats in both the RC and RM. Comparing the two age groups, a statistically significant decrease in capillary density was also reported. It has been demonstrated that tubulointerstitial fibrosis, one of the hallmarks of renal aging, is accelerated by the loss of peritubular capillary density [51, 54]. The data of Iliev et al. [22] showed a positive correlation between the decreased expression of VEGF and the lower capillary density which confirmed earlier literature data of Kang et al. [26]. Podocytes and tubular epithelial cells are also subject to age-related alterations, but a possible link between them and the parallel decrease of VEGF and capillary density has not been fully explored [5, 47]. It is likely that podocytes and

tubular epithelial cells, as primary sources of renal VEGF, fail to produce sufficient levels, which leads to an impaired vasculogenesis and reduced capillary density and in turn – to tubulointerstitial fibrosis.

Role of VEGF in cardiac and renal pathology

The role of VEGF in different cardiac pathologies has been the subject of intense research over the last few decades, although it is yet unclear and debatable. Multiple studies have suggested that VEGF plays a key role in the pathogenesis of several CVD, such as arterial hypertension (AH) and heart failure (HF) [13, 46, 53].

AH is among the leading health problems and poses a major risk factor for stroke, myocardial infarction, and HF [36, 37, 48]. AH initially leads to compensatory myocardial hypertrophy as an adaptive response to the higher workload demands. Another compensatory mechanism during the adaptive phase is the elevated angiogenesis manifested with higher CD. An intriguing detail is that the deterioration of AH is accompanied by a significant decrease in CD [21]. Furthermore, the progression of AH leads to the depletion of the compensatory mechanisms, and they can no longer reduce the discrepancy between the enlarged cardiac volume and the decreased CD [13, 52]. Moreover, with time this adaptive hypertrophy advances to HF, which can be explained by structural damage to the membranes of the cardiomyocytes due to physical overstretching on the one hand and in response to reactive oxygen radicals, pathological cytokines and endothelial damage [3, 44]. Despite vigorous research in the last few decades, the etiology of hypertension is not yet completely known. VEGF, in particular, is of utmost significance for the compensatory mechanisms during the progression of AH [53]. Jesmin et al. performed a comparison study on the age-related level of expression of VEGF in the hearts of spontaneously hypertensive rats (SHR), stroke-prone spontaneously hypertensive rats (SHRSP), and a control group of Wistar-Kyoto rats (WKY). Their study found no age-related changes in VEGF expression in the LV of WHY; in the SHR group, VEGF expression in the LV was increased in 6-week-old animals and then decreased with age; contrariwise, VEGF expression in the LV of the SHRSP group was significantly higher in the 6 and 20-week-olds, thus confirming the age-related increase in the expression of VEGF in the LV of SHRSP. Furthermore, Jesmin et al. reported that VEGF expression in the LV was significantly decreased in 40-week-old SHR and SHRSP [23]. The exact role of VEGF in the pathogenesis, development, and advancement of hypertension is not yet completely identified. However, several studies indicate that pressure overload increases VEGF expression during compensatory hypertrophy. VEGF is paramount for angiogenesis in the hypertrophied myocardium, and its levels increase in correlation with the hypertension stage [13, 23]. Stanchev et al., in their recent study, demonstrated a statistically significant depletion of VEGF expression in both ventricles, predominantly in the LV. Furthermore, they reported a statistically significant positive correlation between VEGF expression and CD in both ventricles with the progression of AH. Depleting these critical vascular compensatory mechanisms is key in the deterioration of AH to HF. [46].

Due to the fact that the kidneys are highly vascularized organs, they are also target for hypertensive injury [36]. The balance of proangiogenic and antiangiogenic

factors is essential for the maintenance of renal vasculature [50]. Despite various previous studies the exact role of VEGF in renal pathology is yet unclear. One study implied that a higher expression of VEGF in SHR compared to normotensive animals might participate in a renoprotective mechanism under hypertensive conditions. Moreover, the inhibition of VEGF leads to glomerular sclerosis and alterations in the podocytes, which are also seen in the hypertensive kidney [1]. The renoprotective effect of VEGF in SHR was recently studied in detail by Liu et al. [33]. The authors reported a reduction in the infiltration of inflammatory cells in the tubulointerstitium and preservation of the structural morphology of the glomerular filtration barrier, the endothelial fenestrations and podocyte foot processes in particular. An earlier study by Kelly et al. [28] established a link between nephron injury, VEGF expression and renal microvasculature changes. The study found that nephron reduction was initially compensated through proliferation of peritubular and glomerular endothelial cells, which was then followed by a loss of peritubular and glomerular capillaries along with a decrease in the expression of VEGF. Dimke et al. [11] highlighted the key significance of VEGF for the maintenance of renal microvasculature. The authors discovered that a specific deletion of VEGF in the renal tubules is associated with disruption of the peritubular capillaries and decreased capillary density. VEGF apparently mediates the hypertrophy of the remaining functional glomeruli in kidney injury which takes place in the early stage of glomerular sclerosis. As kidney damage progresses, the glomerular capillary tufts are subjected to glomerular shrinkage, which first reduces their size back to the initial one, before a progressive decrease in the size of the glomeruli is observed in the late stage of glomerular sclerosis. In addition, more data have supported the role of peritubular capillary rarefaction in the development of hypertensive nephrosclerosis and shown that a correlation exists with the severity of tubulointerstitial injury [29]. Recently, Stanchev et al. [46] demonstrated a decrease in VEGF immunohistochemical expression in the renal cortex and medulla in SHR with the progression of hypertension-induced kidney injury, which was also accompanied by a statistically significant decrease in capillary density. In their previous work, the authors reported a significant increase in two parameters of kidney injury – glomerular sclerosis index and tubulointestinal damage index – in 12-month-old SHR compared to 6-month-old [46]. As suggested earlier, this altered expression of VEGF could be among the triggers for the development of hypertension-induced renal damage.

Conclusion

In conclusion, multiple literature data suggest that the VEGF/VEGFR system plays an essential role in the maintenance of cardiac and renal homeostasis. The results discussed in this review highlight the pivotal role of the changes in the expression of VEGF which take place in conjunction with the decrease in CD during physiological aging. The elevated VEGF expression in the myocardium strives to compensate for the continuously decreasing CD. On the other hand, in the kidney VEGF depletion mirrors the imminent decline in CD. Under pathological conditions, the alterations in VEGF expression are more straightforward, manifesting with perpetual drastic depletion of VEGF along with the diminishment of CD. Such findings further underscore the critical role of the VEGF/VEGFR system in the pathogenesis and deterioration of AH to HF.

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