Review Article

Predictive Role of Circulating Vascular Endothelial Growth Factor-1 in Patients with Cardiovascular Diseases

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Abstract

Vascular endothelial growth factor-1 (VEGF-1) is a glycoprotein that belongs super family of vascular endothelial factors with sufficient capacity to stimulation of angiogenesis in vivo. VEGF-1 is widely expressed in various tissues and over expressed due to hypoxia and inflammation by different spectrum of the cells. A regulation of the VEGF-1 synthesis is mediated by paracrine mechanisms with involvement of specific solubilized receptor VEGFR that plays a pivotal role in a reduction of ischemic tissue injury through modulation of target organ protection, neurogenesis, and angiogenesis. The clinical correlations of circulating levels of VEGF-1 in subjects with cardiovascular diseases are still unclear. It has been suggested exaggerated concentration of VEGF-1 might refer a better prognosis in CAD patients, while a negative effect of neovascularization in plaque region supporting by VEGF-1 is defined. The negative effect of VEGF-1 on progression in age-related diseases, such as early diabetic retinopathy, has been reported. This review is dedicated the discussion of controversial role of the VEGF-1 among cardiovascular disease patients and assay to predictive value of VEGF-1 as biomarker at risk stratification.

Keywords: Vascular endothelial growth factor; Angiogenesis; Neovascularization; Cardiovascular diseases; Age-related diseases; Metabolic comorbidities

Introduction

Angiogenesis and neovascularization might have a controversial role in pathogenesis of several cardiovascular diseases [1]. On the one hand, generating new blood vessels mediated is considered a powerful mechanism that leads to attenuation of ischemic damage and restore of tissue perfusion [2]. On the other hand, new vessel formation plays a critical role in the progression of atherosclerotic lesions and appearance of vulnerability [3-5]. It is known that neovascularization may distribute to the plaque throughout vessel wall resulting induce of instability, mechanical plaque' cap disorders and rupture [4]. Vascular endothelial growth factor-1 (VEGF-1) appears to be a glycoprotein that belongs super family of vascular endothelial factors that are synthesized by a wide spectrum of cells and possessed a sufficient angiopoetic activity [6]. VEGF-1 is a main player in processing of revascularization, neoangiogenesis, reperfusion, as well as neuro protection and cardio protection. This review is dedicated the consideration of controversial role of the VEGF-1 among cardiovascular disease patients and assay to predictive value of VEGF-1 as biomarker at risk stratification.

Biological Role of VEGF-1

Vascular endothelial growth factor-1 (VEGF-1) is synthesized by a cells different origin and produces sufficient angiopoetic activity in vivo [6]. Recent investigations have shown VEGF-1 appears to be stimulated angiogenesis in several settings by an association with the tyrosine kinas receptors VEGF receptor-2 (VEGFR-2) located on the endothelial cells surface [7, 8]. Binding of VEGF-1 with VEGFR-2 causes cell growth, proliferation, and migration, neovascularization and angiogenesis [9, 10]. Therefore, VEGF-1 as a ligand for

alpha-5 / beta-1 integrin may activate the migration of progenitor cells, endothelial cells and mononuclear's that leads to potentiate vasodilatation and to increase an inflammation [11, 12]. Figure presents a key mechanisms that are involved VEGF-1 in pathogenesis of cardiovascular disease.

A regulation of the VEGF-1 synthesis is mediated by paracrine mechanisms with involvement of VEGFR that plays a pivotal role in a reduction of ischemic tissue injury through modulation of target organ protection, neurogenesis, and angiogenesis [13]. It is well known that the initial stimuli for over expression of VEGF-1 are active forms of oxygen in the tissue that may modulate the expression of hypoxia inducible factor-1α (HIF-1α) [1]. Both growth factors are controlled by prolyl hydroxylase domain proteins (PHD), which is
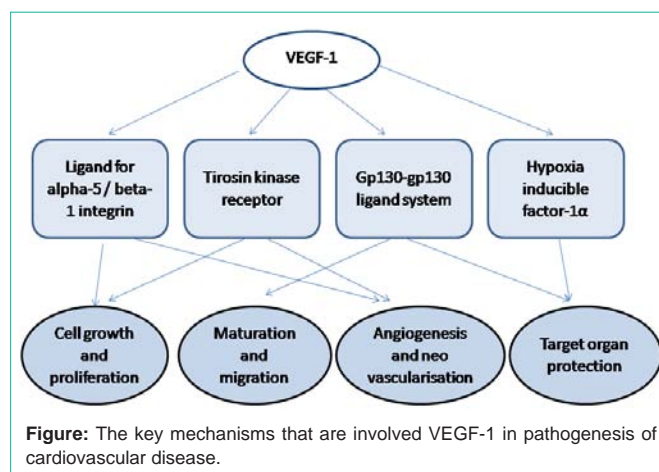

Figure: The key mechanisms that are involved VEGF-1 in pathogenesis of cardiovascular disease.

considered a potential cardio protective and neuro protective factor, as well as certain angiopoetic modulator [14]. As known, VEGF-1 increases the permeability of the layer of endothelial cells, leads to plasma proteins to extravasate and lay down a provisional extracellular matrix scaffold and, thereby, promote sufficient pro-angiogenic effect [1]. Therefore, it is suggested that the glycoprotein 130- glycoprotein 130 ligand systems may involve in VEGF-related regulation in human cardiac myocytes [15]. Indeed, increased VEGF-1 expression was found in myocardial tissue obtained from a patient with acute myocarditis and a selective stimulation of VEGF by gp130 ligand was reflected by a specific receptor expression on cardiac myocytes [15]. Because glycoprotein 130 is a common receptor subunit for several inflammatory cytokines, such as interleukins (IL) -6, IL-11, cardiotrophin-1 etc, the ability of glycoprotein 130-glycoprotein 130 ligand system to up-regulate VEGF expression in the myocardium is crucial for maintenance of cardiac function in myocarditis and ischemic cardiomyopathies [1, 15].

In fact, several pathological processes, such as hypoxia and inflammation via induction of VEGF through auto- and paracrine mechanisms may play a pivotal role in myocardial revascularization. Exaggerated production of VEGF-1 may depend on over expression micro RNAs (miRNAs) that involved in the modulation of various angiopoetic factors. It has been found that miR-181a, miR-106a and miR-20b may regulate various biological processes independently associated with angiogenesis, such as cell migration, cell growth and proliferation through modulation of VEGF-1 over-expression [16]. VEGF-1 may improve survival of endothelial cells through an activation of intracellular regulating enzymes, such as PI3-kinase, Akt and Src [17]. Overall, VEGF-1 promotes proliferative changes by two ways: a classical promotion of endothelial cell layer and a non canonical ability to engage platelet-derived growth factor receptor α and gp130-gp130 ligand system [18]. We do not know whether one of these mechanisms is key player in cardiovascular remodeling in patients with various settings and what is the predictive role of circulating VEGF-1 in different clinical settings.

VEGF-1 in Atherosclerosis and Coronary Artery Disease

The clinical correlations of circulating levels of VEGF-1 in asymptomatic atherosclerosis and symptomatic coronary artery disease (CAD), including unstable CAD subjects who are required PCI are largely unclear. For acute and stable CAD, asymptomatic atherosclerosis and planned or post pounded revascularization procedures (CABG, PCI) VEGF-1 may produce multi-directed effects [19].

It is well known that formation of new vessels from vasa origin characterized severely stenotic lesions and correlated well with the extent of inflammatory cell infiltration of lipid core and lipid core size [20]. VEGF-1 produced by peripheral blood mononuclear cells, which are accumulated in the rupture plaque. Interestingly, new vessels from lumen origin were found in plaques with 40% and 50% artery stenosis and were associated frequently with hemorrhage in the plaque [21]. On the one hand, there is closely interrelationship between neovascularization and plaque instability that is considered a potentially unfavorable condition for survival of the patients [22]. On the other hand, the extent of ischemic myocardial damage

and appearance of acute myocardial infarction (MI) contributes to the elevation of serum VEGF-1 levels that allows VEGF-1 to improve left ventricular function by promoting angiogenesis and re endothelialization after MI [23]. Indeed, there are evidences that the patients with acute MI have elevated circulating VEGF-1 levels when compared with healthy subjects [24]. After reperfusion, the serum VEGF-1 levels rapidly returned almost completely to the normal control range. These data allowed authors to strongly suggest that the serum level of VEGF-1 is one of the most sensitive indicators of myocardial ischemia. Kranz et al [25] have been measured the levels of VEGF-1 in the serum and in the coronary sinus of the patients after acute MI. Surprisingly, accordingly data obtained the main source for VEGF-1 in the blood stream is not the infarcted myocardium, while concentration of VEGF-1 in coronary sinus was higher compared with peripheral blood stream. Authors concluded that the most likely source of the elevated VEGF-1 in acute MI patients is circulating platelets, rather than the infracted myocardium. However, obtained data of the investigation have suggested that VEGF-1 is key player in endogenous activation of coronary collateral formation in the human heart. This suggesting is confirmed the results obtained by Ramos et al [26]. Authors examined the longitudinal changes of VEGF-1 concentrations after PCI for predicting major adverse cardiac events (MACE) in CAD patients. The VEGF-1 concentration showed a positive evolution through one year in 84% of patients enrolled in the study. The longitudinal changes of circulating VEGF-1 levels in the patients significantly increased to one month and remained relatively steady to one year approaching the VEGF-1 levels of healthy volunteers. Low baseline VEGF concentration (<40.8 pg/mL) conveyed increased risk for recurrent hospitalization and MACE in a 5-year follow-up after PCI with drug eluting stent placement. According opinion of investigators the results reflect a positive role of elevated VEGF-1 in serum in recovery and support its importance in CAD prognosis. It is needed to take into consideration that VEGF-1 levels were below detection limit in almost 50% of the acute MI or acute coronary syndrome (ACS) and non-ACS patients at the baseline in majority investigations dedicated this issue. Noted the data obtained from the patients with acute MI, who were not candidates for PCI, indicated a sufficient predictive role of circulating VEGF-1 too [27, 28]. However, exaggerated VEGF-1 level would confer a better prognosis in CAD patients undergoing PCI or without it as its actions may contribute to ameliorate the damaged endothelium and promote rapid recovery after stinting and reperfusion due to thrombolysis.

Nevertheless, this issue seems to be not obviously, because there are evidences for negative effects of VEGF-1 toward atherothrombosis. There are at least two facts that are confirmed a negative effect of neovascularization in plaque region [4]. The recent human researches have been shown reducing micro vessel formation in fibrocalcific plaques when compared with vulnerable ruptured and lipid-rich plaques that are considered a life-threatening finding [2]. Therefore, second fact relating neo vessels to plaque regression is the impressive 85% and 70% reduction of atherosclerosis in apo-E knockout mice treated with the angiogenic inhibitors endostatin and TNP-470 respectively [29]. Moreover, over expression of VEGF-1 in endothelial cells and circulating mononuclear's may contribute in thrombosis and thrombus remodeling [2]. Because VEGF-1 is considered a key pro-angiogenic factor in atherosclerotic plaques,

which is expressed in the necrotic nucleus of the atheroma, the final result of the expression will define plaque evolution and small vessel growth around ischemic or necrotic zone [3]. Probably, VEGF-1 may involve in the cardiovascular remodeling through ST2/IL33 pathway that is activated by biomechanical stress or as result in ischemia injury [30]. However, it is reported that tumor necrosis factor alpha may enhance transcription of ST2 on surface of the endothelial cells and thereby modulate revascularization [30]. On the other hand, interleukin-33 as a functional ligand of ST2 ligand activates mitogen-activated protein kinase (MAPK)-kinases on surface of circulating inflammatory cells that leads to inhibition of the nuclear factor-κB (NF-κB) kinase complex and suppression of the production cytokines and activation of inflammatory cells. In fact, over expression of VEGF-1 and ST2/IL33 pathway in endothelial cells may be two faces of one process aimed neovascularization that is enhanced by inflammatory stimuli. Overall, a dual role of VEGF-1 in cardiovascular disease is presented in Table.

Thus, the role of the VEGF-1 in CAD patients may depend on clinical settings, requirement of reperfusion procedures, and, probably, type and generation of the stent. This issue is required more detail investigations with higher statistical power, while preliminary reports regarding predictive role of exaggerated VEGF-1 levels, seems to be optimistic.

The Role of VEGF-1 in Age-related Diseases

The role of VEGF-1 in age-related diseases is still under discussion and appears to be very controversial. The negative effect of VEGF-1 on disease progression in age-related diseases, such as early diabetic retinopathy, has been defined very well in animal model and in the clinical studies [31, 32]. Overall, for diabetic patients with retinopathy, nephropathy, and neuropathy, the final result of stimulation of angiogenesis is certainly negative, on the other hand, for subjects with obesity, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease [7, 33, 34]. Probably the role of VEGF-1 over expression is defined uncertain or harm [34, 35]. In fact, suppression of angiogenesis might be favorable in diabetic population [36, 37]. Indeed, using anti-VEGF drugs has been shown that there is a positive responses affected metabolic faces of age-related diseases [38]. However, these suggestions are not obviously [40]. Surprisingly, anti-VEGF treatment increased insulin sensitivity in young and old mice but had no effects in the mid-aged group. Therefore, anti-VEGF remedies significantly improved insulin sensitivity in mid-aged obese mice fed a high-fat diet [40].

The innate exact mechanisms affected VEGF and their role in

metabolism is not still understood. Because levels of VEGF expression in various white adipose tissues may change uninterruptedly in various age populations, it has been suggested adipose vasculature sufficiently modulates fat mass, adipocyte functions, blood lipid composition, as wells as insulin sensitivity [41]. By now it is known that the pro angiogenic mononuclear phagocytes are able selectively recruited to sites of pathological neovascularization in response to locally produced semaphoring 3A as well as VEGF-1 that is essential for disease progression [32]. Therefore, hyperglycemia may increase VEGF-1 and VEGFR mRNA without changing their intracellular protein levels in neurons different origin, such as dorsal root ganglion that may leads to early affected neurite outgrowth through the impairment of VEGF/VEGFR signaling [41-43].

Thus, VEGF-1-related pathological neovascularization is defined a pivotal mechanism of negative evolution of age-related diseases, such as diabetes, obesity and insulin resistance [40]. More evidences for predictive role of VEGF-1 in the diabetes and other metabolic comorbidities in patients with cardiovascular diseases are required. Recent clinical studies have shown that serum VEGF increases in diabetic poly neuropathy [39], particularly in the neurologically active symptomatic stage [42, 45].

The Role of VEGF-1 in Systemic Hypertension

By now it is known that hypertension is common complication of the anti-VEGF signaling pathway therapy. Therefore, the incidence and severity of hypertension are dependent mainly on the type and the dose of the anti-VEGF drugs. But exact mechanisms that are lead to hypertension in subjects treated with anti-VEGF are still unclear. Results of recent studies have been allowed to suggest that the therapeutic use of the VEGF antagonist sunitinib is able to induced hypertension through Rho kinase (ROCK) inhibition in nephron that leads to increasing of renal vascular resistance (RVR) and renal sodium re-absorption [46]. Overall, VEGFR may regulate renal sodium absorption and attenuate vasomotion. In this context, anti-VEGF- drug induced hypertension is considered a model of primary sodium retention deterioration associated with increased RVR. Therefore, anti-VEGF drugs may suppress metabolism of podocites and thereby lead to their dysregulation, proteinuria and hypertension [47]. Thus, blocking of VEGF signaling pathway is key mechanism of hypertension in patients with advanced or recurrent malignancy underwent chemotherapy.

There are attempts to use circulating VEGF-1 level as biomarker of clinical evolution of hypertension in small patient cohorts. Although circulating level of VEGF-1 in hypertensive patients is low,

Table: The dual role of VEGF-1 in cardiovascular diseases.

Positive effects	Negative effects
Target organ protection followed by a potentially pathogenic induction of vascular remodeling.	Neovascularization of plaque region with increased vulnerability of patients
Attenuation of endothelial lesion	Stimulation of instability of plaque
Supporting of cardiac pump and diastolic function	Increased tissue and vascular remodeling
Stimulation of collateral blood flow	Pro-apoptotic effect in nitric oxide dependent manner
Increasing vasa permeability	
Regulation of systemic blood pressure	
Stimulation of natriuresis	
Low-intensive anti-inflammatory effect	

there are evidences that increased VEGF levels in pregnant women with severe hypertension may be discussed a risk of preeclampsia and predictor of impaired fetal growth [48, 49]. Some pregnancy-related antihypertensive drugs (methyldopa) may affect placental vascularization and prevent gestosis by increased VEGF concentration [50]. Lacchini et al. [51] reported that VEGF-1 polymorphisms is associated well with cardiac remodeling and left ventricular hypertrophy in hypertensive patients. Moreover, genotypes for VEGF-1 polymorphisms can be useful to help to identify hypertensive patients at greater intrinsic risk for heart failure. Probably we need novel investigations to be understanding of the predictive role of the VEGF-1 in pre hypertension and hypertensive state.

VEGF-1 and Cardiac Dysfunction in Myocarditis

The exact innate molecular mechanisms of cardiac dysfunction in myocarditis have not been understood. Given data obtained in recent clinical studies it remains controversial whether angiogenesis is beneficial or harmful in inflammatory disease, because there are evidences that sufficient vascular lesions is able possibly to impair global cardiac pump function in myocarditis [52, 53]. It has been suggested that neovascularization supporting by over expression of VEGF-1 is able to improve contractility function in myocarditis through suppression of oxidative stress [54]. These are data indicated that over expression of VEGF-1 appears not only the ability to regulate cardiac remodeling, as well as contribute to prevent the development of post myocarditis dilated cardio myopathy [55]. Although recent studies have shown that the increased level of VEGF-1 mRNA has been detected after transient inflammatory and ischemic injury [23, 56], the predictive role of circulating VEGF-1 mRNA in myocardities and dilated cardiomyopathies is still not clear.

Predictive Role of VEGF-1 in Acute Stroke

Inflammation appears to be a key mechanism in the pathogenesis of acute stroke [57, 58]. Given data of recent clinical studies, which demonstrated an indirect interrelation between level of pro-inflammatory cytokines in serum and a cardiovascular risk in acute ischemic stroke subjects [59-61], the effect of low intensity pro-inflammatory activation on modulation of recurrent cardiovascular events is still understood and remains controversial [62, 63]. Pro-inflammatory cytokines were postulated to be able to modulate the activity of endothelial cells via induction of synthesis of VEGF [6].

It has been known that VEGF-1 improved blood-brain barrier integrity [9]. While an induction of VEGF-1 on endogenous neurogenesis and angiogenesis is known, the innate mechanisms of atherothrombosis-related evolution of brain injury and activated endogenous repair mechanisms are not fully understood. The production of VEGF-1 due to focal brain ischemia was found to be able to create a neuro protection, to improve neoangiogenesis and neurogenesis [5, 64]. Therefore, VEGF-1 is able to induce post-ischemic neurovascular remodeling and apoptosis [65]. Probably, these mechanisms underlie the derangement of progressive three-dimensional per vascular cytoarchitectonics, expanding the penumbra zone and worsening cerebral ischemia [66]. Since the angiopoetic VEGF-1 effect is systemic, it might be assumed that neovascularization in the vulnerable atheroma site should promote progressive worsening of the mechanical capacity of the atheroma cap,

the formation of the phenomenon of "fatigue" cap, the appearance of endothelial dysfunction and deregulation of vascular tone, which ultimately leads to a corresponding atherothrombosis events in any vascular territories [22, 67]. It has been supposed that immediate VEGF-1 effects are probably adaptive in nature in hypertensive patients after ischemic stroke, while delayed VEGF-1 effects may be associated with recurrent clinical events, in particular, mediated by atherothrombosis [62, 63].

In this context, clinical studies are required, probably, using comparison various biologic markers, including VEGF-1. Really, recent investigations have revealed that some biological markers of endothelial dysfunction, such as VEGF-1, and some indicators of pro-inflammatory activation had a predictive value for clinical outcomes in patients at high cardiovascular risk only [68-72]. It has been hypothesized that the predictive value of the repeatedly measured circulating VEGF-1 level will be better than single peak VEGF-1 level for predicting of recurrent cardiovascular events in patients with acute ischemic stroke [62]. There are the preliminary results of the small studies that appear to be optimistic for use of VEGF-1 monitoring in acute stroke patient with further risk stratification [63]. Thus, VEGF-1 level in acute ischemic stroke patients might be have a value for at risk stratification. On the other hand, data regarding VEGF-1 in patients with other types of stroke, including intracranial hemorrhage, is very limited.

Conclusions

Although there are not sufficient evidences that the clinical correlations of circulating levels of VEGF-1 in subjects with cardiovascular diseases might have predictive value, it has been suggested exaggerated VEGF-1 level would confer a better prognosis in CAD patients, especially those who are underwent revascularization procedures or have acute / acutely decompensate heart failure due to ischemic and inflammatory reasons. By now it has data for potentially negative effect of VEGF-1–related neovascularization in plaque region that might be considered a mechanism of vulnerability of patient. Therefore, the negative effect of VEGF-1 on progression in age-related diseases, such as early diabetic retinopathy, has been reported. Although currently the continued monitoring for changes in VEGF-1 level is not recommended, but vulnerable patient populations at high cardiovascular risk, probably, may have some benefit in prediction of clinical outcomes based on circulating VEGF-1 measurement.

List of all Abbreviation

ACS - acute coronary syndrome

CABG - coronary artery bypass grafting

HIF-1α - hypoxia inducible factor-1α

MACE - major adverse cardiac events

MAPK - mitogen-activated protein kinase

MI - myocardial infarction

NF-κB - nuclear factor-κB

PHD - prolyl hydroxylase domain-containing protein

PCI - percutaneous transluminal coronary intervention

ROCK - Rho kinase

RVR - renal vascular resistance

VEGF – vascular endothelial growth factor

VEGFR - receptor-2 for vascular endothelial growth factor

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