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Диагностические и терапевтические аспекты нейрегулина-1: обзор литературы

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АННОТАЦИЯ

В последние десятилетия активно исследуется перспектива использования биомаркёрной стратегии ранней персонифицированной диагностики сердечно-сосудистой патологии. Применение новых маркёров представляется перспективным, активно продолжается поиск «идеального» маркёра, который даст возможность понять многие механизмы сердечно-сосудистых заболеваний. В последние годы внимание учёных сфокусировано на изучении роли нейрегулина-1 в качестве лабораторного биологического маркёра при сердечной патологии (нейрегулины принадлежат к суперсемейству эпидермальных факторов роста, которые синтезируются эндотелием сосудов в ответ на ишемию, адренергическую стимуляцию и окислительный стресс).

Ряд исследований показал потенциально важную диагностическую и прогностическую значимость нейрегулина-1 в качестве биологического маркёра. Ожидается, что дальнейшие научно-клинические исследования продемонстрируют возможности использования данного маркёра в роли дополнительного лабораторного инструмента диагностики, стратификации риска и прогнозирования сердечно-сосудистых катастроф у пациентов с кардиоваскулярной патологией. Предстоит более детально оценить терапевтическое влияние рекомбинантного нейрегулина-1 на снижение заболеваемости и смертности у пациентов кардиологического профиля.

Ключевые слова: сердечно-сосудистые заболевания; биологические маркёры; нейрегулин-1; рекомбинантные нейрегулины.

Как цитировать

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Diagnostic and therapeutic aspects of neuregulin-1: A review

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ABSTRACT

In recent decades, the prospect of using a biomarker strategy for early personalized diagnosis of cardiovascular pathologies has been actively explored. The use of new markers appears promising, and the search for an "ideal" marker is actively ongoing, which will make it possible to understand various mechanisms of cardiovascular diseases. In recent years, scientists have actively focused on studying the role of neuregulin-1 as a laboratory biological marker in cardiac pathology. Neuregulins belong to a superfamily of epidermal growth factors that are synthesized by the vascular endothelium in response to ischemia, adrenergic stimulation, and oxidative stress.

Several studies have shown the potentially important diagnostic and prognostic value of assessing neuregulin-1 as a biological marker. Thus, further scientific and clinical studies will demonstrate the possibility of using this marker as an additional laboratory tool for diagnosing, risk stratifying, and predicting cardiovascular events in patients with cardiovascular pathology. The therapeutic effect of recombinant neuregulin-1 on reducing morbidity and mortality in patients with cardiac disorders require more detailed assessments.

Keywords: cardiovascular diseases; biological markers; neuregulin-1; recombinant neuregulins.

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BACKGROUND

In recent decades, the possible use of biomarker strategy for early personalized diagnostics of cardiovascular pathology has been actively studied [1, 2]. Data on biological markers are reflected in modern clinical guidelines. To determine the probability of chronic heart failure (CHF), the level of brain natriuretic peptide (BNP) and its N-terminal precursor (NT-proBNP) in the blood is assessed [3]. However, a better understanding of the neurohumoral and biomechanical aspects of cardiovascular diseases (CVD) requires the evaluation of additional laboratory biomarkers [4–6]. The use of new markers seems promising, and the search for the "ideal" marker, which can be used to understand many mechanisms of CVD, continues [1, 7]. A critical aspect in cardiac patients is the assessment of prognosis, and given the lack of a "universal" laboratory biomarker of poor prognosis in CVD, a multimarker strategy is crucial owing to potentially broader risk stratification of this patient cohort [1, 7]. The multimarker approach is justified by the extraordinary complexity and versatility of the biochemical interactions underlying heart diseases [1, 7]. The combined use of several indicators can accurately indicate the crucial links in pathogenesis and therefore the disease course in each patient [1, 7]. In recent years, scientists have focused on studying the role of neuregulin-1 (NRG-1) as a laboratory biological marker in CVD.

SOURCE SEARCH METHODOLOGY

Analysis of the literature was conducted using the databases PubMed, Russian Science Citation Index, MEDLINE, Google Scholar, and Science Direct. International and Russian publications were analyzed. The search included the keywords neuregulin-1, heart, and cardiovascular disease. Analysis of various studies revealed a serious scientific interest in the role of NRG-1 in cardiovascular pathology.

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF NEUREGULIN-1

Neuregulins belong to the epidermal growth factor (EGF) superfamily and are synthesized by the vascular endothelium in response to ischemia, adrenergic stimulation, and oxidative stress [8]. NRG-1, NRG-2, NRG-3, and NRG-4 have been identified and are encoded by four genes of the same name [8]. NRG-1 consists of NH_2-terminal extracellular structural (NH_2 is an amino group), transmembrane structural, and highly conserved COOH-terminal intracellular structural domains (COOH is a carboxyl group) [9]. NRG-1 is secreted or activated in a juxtacrine or paracrine manner through proteolytic cleavage by membrane-associated proteinases [10]. The β isoform of NRG-1 is required for heart development and is the most studied among the NRGs [10]. NRGs act on the ErbB family of transmembrane receptors, which includes the EGFR, ErbB2, ErbB3, and ErbB4 receptors [10]. The role of NRG-1β in cardiac development is well established, and the importance of the NRG-1/ErbB signaling system in the adult heart should be recognized.

Several studies [10, 11] have shown NRG-1/ErbB signal involvement in maintaining the normal physiology of the cardiovascular system in adults. NRG-1 involvement in the regulation of cardiac adaptation to physiological and pathological stress has been proven (Fig. 1). NRG-1 is involved in cellular and systemic effects that support the adaptive role of NRG-1/ErbB signaling in various conditions. NRG-1β increases the survival of cardiomyocytes, differentiation of embryonic stem cells, cell migration, angiogenesis, cytoskeletal assembly, and formation of neuromuscular junction [12, 13]. Moreover, NRG-1 activates mitogen-activated protein kinase (MAPK), PI3K/AKT (an intracellular signaling pathway in which the central components are the enzymes phosphoinositide 3-kinase PI3K, AKT kinase), ribosomal protein S6 kinase beta 1 (p70/S6K), and Src (protein kinase from the Src-kinase/FAK family of the same name) [10, 14, 15].

Endothelial cells isolated from rodent hearts express multiple isoforms of NRG-1, most of which are inactive transmembrane proteins [16]. In response to stress, NRG-1β is proteolytically released by cardiac endothelial cells, and ErbB receptors are activated [17]. The expression of NRG and its receptors fluctuates in response to injury and physiological and pathological stress and is dependent on metabolic status. NRG-1/ErbB signaling is activated in tissues under various stress conditions. Inhibition of ErbB2 activity or NRG-1 expression significantly impairs cardiac contractile function recovery after injury [18]. Preconditioning of NRG-1

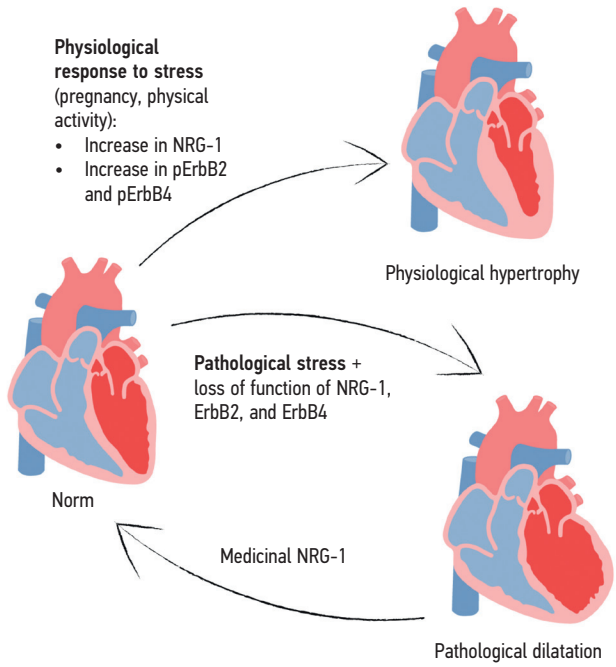

Fig. 1. Role of NRG-1 in physiological and pathological stress.

has cardioprotective effects in ischemia–reperfusion injury through a PI3K/AKT-dependent mechanism *in vivo* [19]. ErbB2 messenger ribonucleic acid (mRNA) and ErbB4 mRNA levels in mice increase in response to ventricular pressure overload during compensatory cardiac hypertrophy but decrease when cardiac dilatation develops [20]. NRG-1 and ErbB2/ErbB4 expression is reduced in rats with diabetic cardiomyopathy [21]. NRG-1 levels are increased in patients with advanced heart failure, whereas the expression and activity of ErbB2 and ErbB4 are decreased [22].

Xu et al. [23] revealed that the anti-inflammatory effect of NRG-1 is associated with its ability to reduce interleukin (IL)-1 synthesis and regulate macrophage activity. Furthermore, NRG-1 administration has been found to cause decreased macrophages in the myocardium and suppress the activity of IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) [10]. Vermeulen et al. [24] proved that the anti-inflammatory effects of NRG-1 are implemented through ErbB4 receptor stimulation. It has been established that NRG-4-mediated activation of ErbB4 leads to apoptosis of macrophages and suppresses the production of IL-6, IFN-γ, and TNF-α [25]. Ryzhov et al. [26] demonstrated the ability of NRG-1 to reduce TNF-α expression by activated monocytes. The anti-inflammatory effects induced by NRG-1/ErbB4 are probably based on the ability of this system to influence the synthesis of pro-inflammatory adhesion molecules by endothelial cells and inflammatory cytokines by macrophages [24, 27]. These studies show that the NRG-1/ErbB4 system plays a significant role in the regulation of inflammation in the myocardium [28].

The importance of NRG-1/ErbB signaling in maintaining adult heart health is supported by cardiovascular side effects caused by the anticancer drug trastuzumab [29]. Breast tumors overexpress ErbB2 (also called HER-2), which functions as an oncogene that increases tumor aggressiveness [30]. A humanized monoclonal antibody targeting ErbB2 (trastuzumab) was developed as an adjuvant chemotherapy drug and studied along with standard chemotherapy in women with metastatic breast cancer (comparison group: patients who received standard monotherapy with doxorubicin, epirubicin, cyclophosphamide, or paclitaxel). The addition of trastuzumab to standard chemotherapy drugs reduced tumor progression, reduced early mortality, and increased survival [31]. However, adjuvant treatment with trastuzumab resulted in high incidence of left ventricular (LV) systolic dysfunction, particularly in patients receiving concomitant anthracyclines [32]. The mechanisms of this effect are not fully understood but support the general concept that intact ErbB2 signaling plays a role in maintaining cardiac function [33, 34].

As mentioned, NRG-1, ErbB2, and ErbB4 are critical for cardiac development and for maintaining cardiac function and adaptation to physiological and pathological stresses (Fig. 1). Kuramochi et al. [35] demonstrated that reactive oxygen species enhance paracrine NRG-1beta/ErbB4 signaling in the heart, indicating that this system is involved in cardiac adaptation to oxidative stress.

During pregnancy, the heart adapts to physiological stress caused by an increase in effective circulating blood volume, resulting in LV enlargement and eccentric remodeling. LV tissue samples from pregnant rats exhibited increased levels of NRG-1 and activated ErbB2/ErbB4, indicating NRG/ErbB involvement in cardiac adaptation to physiological stress [36]. According to Moondra et al. [37], circulating NRG-1 is positively correlated with cardiorespiratory endurance. In experimental rats, after myocardial infarction (MI), exercise increases NRG-1 levels in LV tissue and ErbB2/ErbB4 activation [38]. The abovementioned studies all indicate that endogenous NRG/ErbB maintains normal myocardial function under physiological stress conditions. It has been established that a decrease in NRG-1/ErbB expression in the myocardium is associated with aging and loss of cardiomyocytes due to apoptosis, revealing that NRG-1 plays a role in the prevention of cardiovascular aging [39, 40].

Zhbanov et al. [41] determined circulating NRG-1 concentration in the blood of healthy people and studied the relationship between the concentration of this marker and sex and age. The authors determined the marker concentration using enzyme immunoassay. Median NRG-1 was 0.3 (0.121–2.24) ng/ml. NRG-1 levels were similar in individuals of different ages: 0.26 (0.17–0.37) ng/ml in patients aged 20–29 years; 0.24 (0.1–0.39) ng/ml in those aged 30–39 years; 0.31 (0.19–1.15) ng/ml in those aged 40–49 years; 0.37 (0.19–1.0) ng/ml in those aged 50–59 years; and 0.4 (0.13–0.81) ng/ml in those aged 60–69 years. No statistically significant differences were observed between NRG-1 concentrations depending on sex (p=0.145).

ROLE OF NEUREGULIN-1 IN CARDIOVASCULAR PATHOLOGY

Studies on the diagnostic and prognostic value of NRG-1 in cardiac patients are scarce. Several clinical studies have demonstrated that circulating levels of NRG-1 and NRG-4 change during CVD development and progression [9, 10, 11, 40]. Shao et al. [42] revealed that NRG-1 levels are increased in patients with paroxysmal atrial fibrillation. It has been shown that increased NRG-1 levels may be associated with the induction of compensatory mechanisms in response to cardiac stress, which in turn is associated with increased inflammation, pressure overload, and the generation of reactive oxygen species [9, 10, 40]. Moreover, elevated NRG-1 levels have been noted in patients with stress-induced ischemia [43] and severe heart failure, where it is associated with the risk of death or heart transplantation [44]. Miao et al. [45] showed a statistically significant relationship between NRG-1 concentration and LV ejection fraction (EF), which supports the hypothesis that NRG-1 plays a role in compensatory cardiac responses.

According to Tian et al. [46], NRG-1 and NRG-4 levels are negatively associated with coronary heart disease (CHD) severity and coronary collateral circulation [47]. This can

be due to decreased synthesis or secretion of NRG-1 and NRG-4 by endothelial cells [48, 49], which is associated with endothelial dysfunction in CHD [50]. Additionally, an association between higher NRG-4 levels and a lower risk of acute coronary syndrome has been described [51].

Increased NRG-1 activity in heart failure is one of the adaptive pathways in this disease, as it counteracts cardiac remodeling and disease progression. Treatment of experimental animals with recombinant NRG-1 reduced fibrosis severity and heart failure progression [52].

A positive effect of NRG-1 on atherosclerosis, diabetes mellitus (DM), glomerular sclerosis, and pulmonary hypertension (PH) was also noted. Thus, NRG-1 is a pleiotropic factor that influences various physiological and pathophysiological processes [53].

Neuregulins in atherosclerosis and related diseases

There is growing evidence that NRG-1 supports normal vascular function through signaling in endothelial cells, smooth muscle cells, and macrophages, and abnormalities in signaling may be associated with atherosclerosis [9, 10, 11, 40].

Panutsopoulos et al. [54] performed immunohistochemical analysis of coronary arteries with atherosclerotic lesions and revealed increased NRG-1 expression in macrophages.

Moreover, Xu et al. [55] reported that NRG-1 reduced dose-dependently cholesteryl ester accumulation in monocytic macrophages *in vitro*, and administration of human recombinant NRG-1 (rhNRG-1) to apolipoprotein E-deficient mice (ApoE –/–) resulted in a significant reduction in the atheromatous plaque area in the aorta.

Neuregulin-1 can improve myocardial glucose uptake and utilization by activating the phosphorylation of the myocardial ErbB4 receptor in rats with MI [56].

Wang et al. [57] demonstrated that NRG-1 can reduce reactive oxygen species production by inhibiting NADPH oxidase 4 through the mitogen-activated protein kinase (ERK1/2) signaling pathway and the NLRP3/CASP-1 (cryopyrin/caspase-1) pathway, which helps inhibit oxidative damage and reduce inflammation in cases of ischemic reperfusion injury.

Zeng et al. [58] determined the concentration of NRG-1 in the blood serum of patients with unstable angina and type 2 DM and healthy individuals. NRG-1 levels in patients with type 2 DM and healthy individuals were not significantly different. Simultaneously, in patients with unstable angina, NRG-1 concentration tended to increase.

Huang et al. [47] examined the circulating levels of NRG-1 in patients with CHD with coronary artery stenosis ⩾90% (as determined by coronary angiography). The condition of the coronary bed was assessed using the Rentrop–Cohen scale. Statistical analysis showed that NRG-1 could significantly predict collateral condition.

Geisberg et al. [43] studied the blood NRG-1 concentration in patients with obliterating atherosclerosis of the coronary arteries of varying severity, which was assessed using Duke angiographic criteria (mild, 2 points; moderate, 4–6 points; severe, 8–12 points). NRG-1 concentration in healthy people and patients with the mild form did not differ significantly. It was established that as disease severity increased, the level of NRG-1 decreased significantly.

Neuregulin-1 in myocardial hypertrophy and fibrosis

The formation of fibrous tissue after MI is critical for maintaining cardiac structure [10, 11]. A study reported antifibrotic effects in a mouse model when treatment with rhNRG-1 attenuated the adverse effects of angiotensin II by suppressing fibroblast activity [24]. In ErbB4-deficient mice, exposure to angiotensin II resulted in increased myocardial fibrosis, indicating that fibroblast activity is attenuated by active NRG/ErbB4 [24]. Additionally, NRG-1 has antifibrotic effects by inhibiting macrophage activation and preventing bleomycin-induced (a cytotoxic drug, glycopeptide antibiotic) fibrosis of the heart, lungs, and skin *in vivo* [24]. A study by Dugaucquier et al. [59] showed the role of endothelial autocrine NRG-1/ErbB4 signaling in modulating hypertrophic and fibrotic responses during early cardiac remodeling. According to Shakeri et al. [60], NRG-1 administration prevents cardiac and renal hypertrophy and fibrosis caused by endothelial nitric oxide synthase (eNOS) deficiency; NRG-1 expression is regulated by microRNA-134.

Shiraishi et al. [61] studied *in vitro* and *in vivo* the cellular and molecular mechanisms of the formation of post-infarction fibrous tissue, especially related to the regulation of cellular senescence and apoptosis. $CD206^{+}F4/80{+}CD11b^{+}$M2-like macrophages collected from mouse hearts on post-MI day 7 showed increased NRG-1 expression. ErbB2 and ErbB4 are expressed on cardiac fibroblasts in the MI zone. Macrophage-derived NRG-1 suppressed both hydrogen peroxide-induced senescence and fibroblast apoptosis, whereas blockade of ErbB function significantly accelerated both processes. NRG-1/ErbB/PI3K/AKT signaling was activated in damaged cardiac fibroblasts. Systemic blockade of ErbB function in mice with MI increased senescence and apoptosis of cardiac fibroblasts and exacerbated inflammation. Furthermore, increased accumulation of M2-like macrophages led to progression of post-infarction fibrosis in mouse hearts. The molecular mechanism of the regulation of fibrous tissue formation in MI has been shown to attenuate apoptosis and senescence of cardiac fibroblasts through NRG-1/ErbB/PI3K/AKT signaling activation. Thus, regulation of NRG-1/ErbB signaling significantly affects fibrous tissue formation in the infarcted heart of adult mice and is critical for suppressing the progression of aging and apoptosis of cardiac fibroblasts.

The role of NRG-1 has been shown to be involved in the induction of cardiac hypertrophy. Rats treated with rhNRG-1 had significantly increased post-MI LV wall thickness and increased NT-pro-BNP levels in a dose-dependent manner [62].

Myocardial stiffness and neuregulin-1

Titin, a major component of sarcomeres, is involved in passive myocardial stiffness and stress-sensitive signaling [63]. Titin is a structural microfilament of the sarcomere and is represented by two main isoforms: less rigid (N2BA) and more rigid (N2B) [63]. The main function of titin is to ensure the retraction of myosin fibrils relative to microfilaments during myocyte relaxation [64]. The change in titin function is caused by disturbances in the processes of phosphorylation of the N2B and PEVK regions, in which protein kinases (a subclass of kinase enzymes) play a significant role [63]. Borbély et al. [65] proved that in CHF patients with preserved LV EF (CHFpEF), N2BA synthesis is increased.

Studies on the role of NRG-1 in myocardial stiffness are limited. According to Hopf et al. [66], rhNRG-1 administration into isolated rodent cardiomyocytes led to normalization of the phosphorylation of N2B and the PEVK region of titin. Adão et al. [67] established that NRG-1 suppressed the activity of protein kinase C, which contributed to the normalization of the phosphorylation of the PEVK region and increased cytosolic calcium reuptake in muscle cells. Consequently, a decrease was noted in the passive stiffness of both ventricles of the heart.

Neuregulin and heart failure

Ky et al. [44] studied the associations of circulating NRG-1β with disease severity and clinical outcomes in CHF (899 outpatients). NRG-1β was significantly elevated in patients with more severe disease (median 6.2 ng/mL for New York Heart Association (NYHA) grade IV versus 4.4 ng/mL for grade I; p=0.002). NRG-1β was independently associated with an increased risk of death or heart transplantation over a median followup period of 2.4 years. The strongest associations were noted in patients with cardiomyopathy of ischemic origin (p=0.008) and NYHA grade III–IV heart failure (p=0.01). The authors demonstrated that NRG-1 and NT-proBNP analysis together provided a more accurate risk stratification than either biological marker alone.

Moreover, Miao et al. [45] showed no changes in NRG-1 concentrations depending on NYHA grade in patients with ischemic CHF (n=239). During one year, no association was noted between the concentration of this marker and prognosis. Thus, the prognostic value of NRG-1 in patients with heart failure remains controversial and requires further research.

Zhbanov et al. [68] assessed NRG-1β levels in 47 patients with CHFpEF and the relationship of this biological marker with the patient's grade, echocardiography parameters, and risk of adverse cardiovascular events (CVE). The control group consisted of 40 healthy individuals. The median concentration of NRG-1β was 0.969 ng/ml and 0.379 ng/ml in in the group of patients and group of healthy individuals, respectively, and was statistically significantly higher in patients (p=0.003). No reliable correlations between the levels of the studied biomarker and 6MWT (6-minute walk test) or echocardiographic parameters of LV diastolic function have been established. The average followup time was 456 days. Twenty-one adverse CVEs were recorded, including 2 cardiovascular deaths and 19 hospitalizations for decompensated heart failure. Patients with high NRG-1β concentration had a higher incidence of adverse CVEs.

The same authors conducted an observational prospective study to determine the level of NRG-1β in CHF patients, including 47 patients with CHFpEF, 39 patients with low EF (CHFlEF), and a control group consisting of 40 healthy volunteers [69]. In addition, we studied the association of NRG-1β with indicators of systemic inflammation (high-sensitivity C-reactive protein (hsCRP), IL-6, vascular endothelial adhesion molecule type 1 (sVCAM-1), stimulating growth factor (ST2)) and myocardial fibrosis factor (matrix metalloproteinase 9 (MMP-9)), galectin-3 (Gal-3), transforming growth factor beta (TGF-β)), and clinical outcomes. Patients with heart failure were followed up for 24 months. In the CHFpEF, CHFlEF, and control groups, the median concentration of NRG-1β was 0.969 ng/ml, 0.63 ng/ml, and 0.379 ng/ml, respectively. In the CHFpEF group, the concentration of NRG-1β was statistically significantly higher than that in the control group and did not differ from that in the CHFlEF group. In patients with heart failure, the levels of all biological markers of systemic inflammation studied were significantly higher than those in healthy controls. ST2, TGF-β, and IL-6 levels were higher in patients with CHFlEF than in those with CHFpEF. Concentrations of hsCRP, sVCAM-1, MMP-9, and Gal-3 did not differ between the groups of patients with heart failure. In patients with CHFpEF, NRG-1β concentration was significantly associated with biomarkers of systemic inflammation (hsCRP (r_S=0.378; p=0.023), IL-6 (r_S=0.378; p=0.014)) and fibrosis (TGF-β (r_S=0.603, p=0.001)). In patients with CHFpEF, but not CHFlEF, who had elevated concentrations of NRG-1β and IL-6, the rate of hospitalization for decompensated heart failure was significantly higher than that in patients with low concentrations of these markers. The association of NRG-1β with outcomes remained statistically significant when sex, age, and NT-proBNP were included in the model.

Hage et al. [70] studied NRG-1 concentrations in patients with CHFpEF and CHFlEF and in healthy people. It was revealed that patients with CHFpEF are characterized by significantly higher concentrations of the studied biomarker than those with CHFlEF. In addition, patients with heart failure had significantly lower NRG-1 scores than healthy individuals. In patients with CHFlEF, a high concentration of this marker was associated with worse outcomes and did not depend on the cause of CHF. In patients with CHFpEF, the dependence of marker concentrations on disease outcomes was associated with the presence of ischemia, and in patients without ischemia, higher marker concentrations predicted favorable outcomes.

The results of the analyzed studies support NRG-1 involvement in the regulation of key aspects of the development and progression of heart failure.

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USE OF RECOMBINANT NEUREGULINS IN HEART FAILURE

Recombinant human neuregulin-1 (rhNRG-1), also called neucardin, is a 61-amino acid peptide that acts directly on damaged cardiac muscle cells [9].

Jabbour et al. [71] conducted the first human study aimed at studying the effect of rhNRG-1 in patients with CHF. Fifteen patients (age: 60±2 years; NYHA grade II–III; LV EF <40%) received rhNRG-1 infusion daily for 11 days against optimal drug therapy. Immediately after a 6-h rhNRG-1 infusion, cardiac output increased by 30% (p <0.01). Pulmonary artery wedge pressure and systemic vascular resistance decreased by 30% and 20%, respectively, after 2 h (p <0.01). Further, norepinephrine levels in the blood decreased by 47% and aldosterone by 55% (p <0.001). The LV EF increased by 12% after 12 weeks, from 32.2%±2.0% (baseline) to 36.1%±2.3% (p <0.001). The therapy was well-tolerated.

Gao et al. [72] assessed the safety and efficiency of rhNRG-1 in 44 patients with grades II or III CHF. Patients received placebo or rhNRG-1 at doses of 0.3, 0.6, or 1.2 mcg/kg per day for 10 days in addition to standard therapy. The followup period was 90 days. Despite the lack of statistically significant differences from the placebo, the LV EF increased significantly (by 27.11%±31.12%) (p=0.009) on day 30 after treatment with rhNRG-1 in the 0.6 μg/kg group, whereas in the placebo group, it increased only by 5.83%±25.75% (p=0.49). Additionally, on day 30, LV end-systolic volume (-11.58%±12.74%; p=0.002) and LV end-diastolic volume (-5.64%±10.03%; p=0.05) decreased in the group receiving 0.6 mcg/kg per day. LV end-systolic and end-diastolic volume levels continued to decrease on day 90 (–20.79%±17.03% and –14.03%±13.17%, respectively), which was accompanied by a sustained increase in LV EF. This shows that short-term treatment with rhNRG-1 results in a longterm reduction in cardiac remodeling. The authors have proven that the effective dose is tolerable and safe for patients with CHF.

Cimaglermin®, a new investigational drug, also known as glial growth factor 2 (GGF2) and neuregulin-1β (NRG-1β), was analyzed in a study by Lenihan et al. [73]. In patients with systolic heart failure receiving optimal medical therapy according to current guidelines, a dose-dependent improvement in LV EF was registered within 90 days after infusion. This drug is not registered in Russia.

Zhou et al. [74] established that treatment of rats with rhNRG-1 improved survival rates. Hemodynamic measurements revealed stabilization of mean arterial pressure, isovolumetric relaxation, decreased LV end-diastolic pressure, and decreased troponin, TNF-α, IL-1β, and IL-6 levels in the rhNGR-1 treatment group.

Evidence of NRG-1 suppression of inflammatory cytokines indicates that NRG-1 has a protective effect in septic cardiomyopathy by reducing cardiac damage. Kang et al. [16] investigated the effects of NRG-1 on sepsis, particularly the effect of NRG-1 on endothelial cells. The inhibitory effect of NRG-1 on the cell adhesion molecule ICAM-1, vascular endothelial growth factor (VEGF), and nitric oxide has been demonstrated.

Mendes-Ferreira et al. [75] demonstrated that treatment with rhNRG-1 reduces PH by reducing pulmonary artery remodeling and endothelial dysfunction and by restoring right ventricular (RV) function.

According to Adão et al. [67], rhNRG-1 reduces the development of passive tension in the RV and LV during monocrotaline-induced PH (monocrotaline is a macrocyclic pyrrolizidine alkaloid). This is associated with increased phosphorylation of phospholamban and decreased expression of maladaptive cardiac remodeling markers. Furthermore, rhNRG-1 therapy reduced RV remodeling and passive cardiomyocyte tension in animals with RV hypertrophy caused by pulmonary artery ligation.

Xiao et al. [76] injected lentivirus carrying the NRG-1 gene into the infarcted areas of rats. Four weeks later, lentivirus-mediated gene transduction promoted NRG-1 gene and protein expression. NRG-1 overexpression increased the number of microvessels in the ischemic myocardium. In addition, it was revealed that NRG-1 can increase the expression of the apoptosis regulators Bcl-2 and VEGF-A while simultaneously decreasing the expression of the apoptosis activator Bax. NRG-1 overexpression activates the PI3K/AKT pathway and increases the phosphorylation of AKT and eNOS. The authors concluded that NRG-1 gene transduction may improve cardiac function by promoting angiogenesis and preventing apoptosis.

VEGF and angiopoietin (Ang)-1 regulate myocardial angiogenesis through the NRG-1/ErbB signaling pathway [9], and VEGF or Ang-1 may significantly influence the expression and secretion of NRG-1 in cardiac microvascular endothelial cells [77]. NRG-1 treatment significantly increased the expression of VEGF and Ang-1 in coronary artery smooth muscle cells [78].

CONCLUSION

Currently, several countries worldwide have an arsenal of modern technologies for identifying new laboratory biological markers; therefore, it is advisable to develop a multimarker model. This requires the improvement of bioinformatics technologies crucial for analyzing a large database. The presented literature review indicates the potentially important diagnostic and prognostic value of NRG-1 assessment as a biomarker. Further scientific and clinical studies are required to demonstrate the possibility of using this marker as an additional laboratory tool for the diagnosis, risk stratification, and prediction of cardiovascular accidents in patients with cardiovascular diseases. Moreover, the therapeutic effect of recombinant NRG-1 on reducing morbidity and mortality in cardiac patients remains to be assessed in more detail.

ADDITIONAL INFORMATION

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