Homocysteine and atrial fibrillation: novel evidence and insights

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Abstract

Atrial fibrillation (AF) is one of the most prevalent rhythm disorders worldwide, with around 37.574 million cases around the globe (0.51 % global population). Different studies showed a high informative value of different biomarkers, including such related to the systemic inflammation, biomechanical stress and fibrosis. In this review article we aimed to study only the relation of homocysteine to the AF development. Homocysteine – is a sulfur-containing amino acid, that is produced in the process of methionine metabolism. Which is a non-canonical amino acid, that is derived from the food proteins. From the scientific point of view there is a relation between hyperhomocysteinemia and myocardial fibrosis, but these mechanisms are complicated and not sufficiently studied. Homocysteine regulates activity of the ion channels through their redox state. Elevated homocysteine level can condition electrical remodeling of the cardiomyocytes through the increase of sodium current and change in the function of rapid sodium channels, increase of inwards potassium current and decrease in amount of rapid potassium channels. High homocysteine concentration also leads to the shortening of the action potential, loss of the rate adaptation of the action potential and persistent circulation of the re-entry waves. In a series of experimental studies on mice there was an association found between the homocysteine level and activity of vascular inflammation. Elevation of homocysteine level is an independent factor of the thromboembolic events and AF relapses. Population studies showed, that homocysteine is an independent risk factor for AF. So, homocysteine is an interesting target for up-stream therapy.

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Introduction

Atrial fibrillation (AF) is one of the most prevalent rhythm disorders worldwide, with around 37.574 million cases around the globe (0.51% global population). It is expected that 6-12 million people will be suffering from atrial fibrillation in USA by the year 2050 and 17.9 million in Europe by the year 2060 [1]. AF is associated with the decreased quality of life, 5-fold increase in the stroke risk, increased risk of heart failure, dementia and mortality [2,3]. Different epidemiological studies defined main clinical risk factors of AF development, but there is a wide area that has not been studied, which include biomarkers, racial differences, influence of the diet and the environment [4].

Different study groups, that studied problem of prediction of the AF development showed a high informative value of different biomarkers. These include biomarkers of systemic inflammation, biomechanical stress and fibrosis development [5]. Several studies showed association of AF development with the biomarkers such as galectin [6], N-terminal peptide of 3rd type procollagen, C-terminal telopeptide of 1st type collagen, fibroblast growth factor [7], B-type natriuretic peptide [8], Transforming growth factor β1 [9], 25-hidroxyvitamin D, renin, metalloproteinases [10], aldosterone [11], homocysteine [12] and C-reactive protein [13].

In this review article we aimed to study only the relation of homocysteine to the AF development. Understanding of such relation opens perspectives for the development of AF risk stratification and preventive measures from the other side.

Materials and Methods

We analyzed literature for the period from 2000 to 2021 in PubMed, EMBASE, Web of Science. Following keywords were used: "atrial fibrillation", "AF", "Afib", "homocysteine", "Hcy", "hyperhomocysteinemia", "high level", "elevation", "metabolism", "myocardium", "remodeling", "ion channels", "inflammation", "thrombus", "coagulation", "risks". Articles in English were included into the review. Key data from 41 articles was synthetized and described in the article.

Results and discussions

Metabolism of homocysteine

Homocysteine is a sulfur-containing amino acid, that is produced in the process of methionine metabolism. It is a non-canonical amino acid, that is derived from the food proteins. Metabolic pathway of homocysteine is very important, because S-adenosyl methionine (SAM) it is formed in it. SAM is a donator of methyl group for methylation reactions, such as methylation of DNA and production of catecholamines. S-adenosyl homocysteine, that is produced from SAM in transmethylation reaction, is hydrolyzed to homocysteine and adenosine. This homocysteine can be methylated to methionine through the reaction dependent on folic acid and vitamin B_{12} and/or catabolized to the cysteine *via* vitamin B_6-dependent pathway. Vitamin and/or enzyme deficiency, that participate in the homocysteine metabolism and also some pathological conditions can lead to the elevation of homocysteine level in serum, which is called hyperhomocysteinemia.

Hyperhomocysteinemia

Hyperhomocysteinemia is divided into mild (fasting blood homocysteine level is 15-30 µmol/l), moderate (30-100 µmol/L) and severe (>100 µmol/L) [14]. Severe hyperhomocysteinemia occurs in the result of genetically conditioned deficiency of enzymes, including B12 and folic acid metabolism [15]. Severe hyperhomocysteinemia is rarely observed in the population, while mild and moderate are rather prevalent. It is likely, that the causes of mild and moderate hyperhomocysteinemia are minor mutations or B_6, B_9, B_{12} deficiency [16]. Hyperhomocysteinemia is often associated with such genetic mutations as deficiencies of 5, 10 – methylenetetrahydrofolate reductase, methionine synthase and cystathionine β-synthase. Hyperhomocysteinemia can also be conditioned by overeating and renal failure. There is a close association of hyperhomocysteinemia and homocystinuria with atherosclerosis, especially of cerebral, heart and renal arteries, venous thrombosis, chronic kidney disease, megaloblastic anemia, osteoporosis, depression, Alzheimer's disease, mental retardation, perinatal problems [17,18].

Despite a big number of studies, that shows relation of serum homocysteine level with common cardiovascular diseases such as ischemic heart disease and stroke, there is only a little amount of such studies for atrial fibrillation [19].

Impact of homocysteine on the atrial remodeling

According to most of experimental studies, structural remodeling with the following electrical remodeling of the atria lies in the basics of AF development, due to the fibrosis formation in the atrial myocardium. From the scientific point of view there is a relation between hyperhomocysteinemia and myocardial fibrosis, but these mechanisms are complicated and not sufficiently studied.

Homocysteine can bind to G-protein coupled receptors, regulate activity of phospholipase C and following formation of intercellular messengers. 1,2-diacylglycerole can involve protein kinase C, that activate a cascade of fibrotic reactions in the myocardium. Transient Receptor Potential Cation Channel Subfamily C Member 3 (TRPC3) is an irreplaceable regulation factor of fibrosis mechanisms. It facilitates fibroblast transformation into myofibroblasts with adverse collagen modulation. TRCP3 are directly activated by the phosphorylation of protein kinase C. Homocysteine can activate TRCP3 and so activate fibrotic changes in the atria.

Also progression of the fibrosis and remodeling of the myocardium lead to the activation of renin-angiotensin-aldosterone system. The last provokes apoptosis of cardiomyocytes through the tumor necrosis factor-β dependent pathway and also control monocyte and fibroblast activation through the decrease of sirtuin-1 [20]. A positive correlation was found between the serum homocysteine level and left atrial dimensions and level of C-terminal telopeptide of 1st type collagen, that indicates probable relation between the elevated homocysteine level and structural remodeling of the atria. It was shown that elevated homocysteine level (>14 µmol/L) is associated with the increased collagen/elastin ratio and elevated activity of matrix metalloproteinase (MMP). MMP activation can lead to the degradation of the intercellular proteins (connexin 43) and alteration of the conduction pathways between cardiomyocytes, that facilitates atrial remodeling [21].

Han *et al*. [22] studied an impact of hyperhomocysteinemia on the remodeling of atria and AF in mice. Heart failure was modelled in the experiment with the transverse compression of the aorta. Study group of the mice, that received diet with high homocysteine content, had significantly thicker interventricular septum, lower E/A ratio, which is a marker of diastolic dysfunction, higher E/E' ratio, which is a marker of left ventricular rigidity, higher values of end-diastolic size and myocardial mass index of the left ventricle. Acetylcholine induced AF was observed significantly more frequently in mice with high homocysteine level, this group also has higher duration of AF paroxysms. It is also interesting, that the group with high homocysteine levels also had higher incidence of ventricular flutter [22]. The last indicate probable relation of elevated homocysteine levels to the electrical instability of the myocardium.

Influence of homocysteine on the electrical remodeling of ion channels

Homocysteine can affect sodium and potassium channels in the myocytes of human atria and so increase excitability and promote arrhythmogenesis. Homocysteine regulates activity of the ion channels through their redox state [3,23,24]. Elevated homocysteine level can condition electrical remodeling of the cardiomyocytes through the increase of sodium current and change in the function of rapid sodium channels, increase of the inwards potassium current and decrease in the amount of rapid potassium channels. High homocysteine concentration also leads to the shortening of the action potential, loss of the rate adaptation of the action potential and persistent circulation of the re-entry waves. These indicate arrhythmogenic effects of the elevated homocysteine level [21].

Acampa *et al*. [25] mentioned that hyperhomocysteinemia is a frequent finding in patients after the heart transplant. This can promote atrial remodeling and increased risk of atrial arrhythmias in

the denervated heart. Hyperhomocysteinemia in these patients correlated with the increased P wave dispersion, which characterize heterogenous conduction in the atria and is a risk factor of AF. It was also shown that homocysteine has a direct impact on the ion channels (inhibition of I_{to} and IK_{ur}, induction of IK_1 and I_{Na}). This leads to the early post-depolarization and provocation of focal ectopic activity. Hyperhomocysteinemia also provokes biochemical damage of the extracellular matrix in the atria, leading to fibrosis and structural remodeling, that creates conditions for the re-entry mechanism [25].

Influence of homocysteine on inflammation

In a series of experimental studies on mice an association was found between the homocysteine level and increased production of transcription nuclear factor kappa B and activity of vascular inflammation. These demonstrate an ability of hyperhomocysteinemia to induce oxidative stress. These processes are potential factors of the development of the endothelial dysfunction and can be probable triggers of AF [2,9,19,26-30].

Influence of homocysteine on the thrombus formation

Results of several studies demonstrated that an elevation of homocysteine level is an independent factor of the thromboembolic events and AF relapses in patients with non-valvular AF. It is a proven fact, that homocysteine has a pro-oxidative and pro-inflammatory activity. Moderate hyperhomocysteinemia is a factor that promotes venous and arterial thrombosis, despite homocysteine is not a direct participant of coagulation or an intermediate product of thrombus formation or fibrinolysis. High homocysteine level can directly or indirectly damage vascular endothelium due to the increased oxidative stress, decreased production and bioavailability of the nitrous oxide and induction of inflammatory response. Hyperhomocysteinemia can also lead to a disbalance of coagulation and thrombogenic properties of the endothelium through the increased production of tissue factors, decreased affinity of antithrombin and inhibition of the thrombomodulin-protein C complex. Toxicity of the high homocysteine level can also activate a pathway of caspase-3/poly-adenosinphosphate-ribose-polymerase, that lead to the apoptosis of the endothelial cells. All these changes decrease resistance of the vascular wall to the thrombus formation and hypercoagulation, that correspond with the Virchow's triad, that lies in the basis of the thrombus formation pathogenesis in AF [21].

Influence of homocysteine metabolites (cysteine, hydrogen, sulfide, glutathione) on arrhythmogenesis

Transsulfuration of homocysteine is a metabolic pathway of sulfur transport from homocysteine to cysteine. This process occurs in hepatocytes and endothelial cells, that can secrete cystatione-beta synthase. Several sulfur metabolites are produced during transsulfuration including cysteine, hydrogen, sulfide and glutathione. It was proven in experiments on rats that elevated levels of hydrogen sulfide are associated with the electrical instability of the left and right atria [15,31,32].

It was also proven that cysteine has antioxidant properties and participate in the redox reaction due to the presence of thiol groups. It is also a progenitor of an important intracellular antioxidant – glutathione.

Cysteine can affect an expression of genes of inflammation, tissue fibrosis. It also can regulate activity of the ion channels, that indicates its possible relations to the arrhythmia's development including AF.

Recent studies stated that AF is a consequence of atrial fibrosis and is an initial manifestation of the atrial cardiomyopathy. Mild hyperhomocysteinemia increased collagen production in the smooth muscles of the aorta in rabbits, and at the same time increased degeneration on the elastic fibers, which is dependent on metalloproteinase. Cysteine also has properties to affect myocardial fibrosis. So, homocysteine and cysteine is related to the changes of morphological and electrophysiological properties of the atria through the promotion of inflammation and fibrosis [33-36]. All these changes can promote development of the AF.

Clinical aspects of hyperhomocysteinemia

Two large population studies, "Atherosclerosis risk in the Communities" and "Multi-Ethnic Study of Atherosclerosis" with around 7 thousand participants, showed that homocysteine is an independent risk factor for AF. Elevation of homocysteine for 1 logarithmic unit increases risk of AF by 27 % [19]. In the study of Nasso *et al*. an assessment of homocysteine level in patients after non-valvular AF was performed with the following prospective observation. Authors showed that patients with elevated homocysteine levels had more frequent relapses of AF. Higher relapse rate was observed in homocysteine level >16 µmol/L. This can indicate an importance of pharmacological correction of hyperhomocysteinemia [37].

Snezhitsky *et al*. studied prognostic significance of relation between homocysteine, structural and functional remodeling of atria and clinical presentation in patients with paroxysmal and persistent form of AF. Seventy-five patients with AF combined with ischemic heart disease (IHD) and essential hypertension (EH) without significant structural changes of the myocardium were included into the study. A comparison group included patients with IHD and EH without AF. Structural and functional condition of the heart was assessed using 2D transthoracic echocardiography. Results of the study indicates a relation between the homocysteine plasma level and left atrial dimensions and AF relapses. AF relapses were more frequent in patients with homocysteine levels >11 µmol/L [38].

Wang *et al.* included 717 patients with acute ischemic stroke. All patiens were divide into two groups – with and without AF. Patient with non-valvular AF had significantly higher serum levels of homocysteine and thyroxine when compared to the patients without AF. While there was no relation between the homocysteine level and the thyroid gland dysfunction [39].

Svenningson *et al*. studied relation between homocysteine and transsulfuration products with the AF incidence in the general population. 3535 patients were included into the study, average observation period was 7.4 years. For the period of observation 10.2% of patients developed AF. Patient who had AF also had significantly higher levels of homocysteine and cysteine when compared to the patients without arrhythmia. There was no relation between the cystatione level and AF incidence [40].

Two recent meta-analysis showed a clear relation between the elevated homocysteinemia and development of atrial fibrillation. A meta-analysis of Rong *et al*. showed that both patients with paroxysmal and persistent AF had higher levels of homocysteine. Also, patients with elevated homocysteine level had a significantly higher risk of AF development as well as a higher recurrence rate [41]. Higher incidence of AF in patients with elevated homocysteine levels were also demonstrated in the meta-analysis of Dong *et al*. [42].

Genetic aspects of hyperhomocysteinemia and AF

Chen *et al*. [12] studied a relation of different genes polymorphism with the risk of AF development. Study was performed in the model of genome-wide association search, where different genes were related to the homocysteine level. Eighteen genes responsible for the hyperhomocysteinemia were identified in total; four genes were excluded as there was no significant relation with the hyperhomocysteinemia - rs12921383, rs1801133, rs2851391, and rs957140, 5 others – because of their relation with other risk factors of AF: rs154657 was related to arterial hypertension, rs2251468 – with cholesterol level, C-reactive protein and ischemic heart disease, rs548987 was associated with the body mass index, rs7422339 was associated with weight, cholesterol and blood pressure, rs9369898 – with cholesterol level. So, only 9 genes had a reliable relation with the homocysteine level without clear relation to other risk factors: rs12134663 – methylenhidrofolate reductase, rs12780845, rs1801222 - cubilin, rs2275565 – 5-methyltetrahidrofolate-homocysteine methyltransferase, rs234709 – cystation-beta syntase, rs42648 – guanosine-5'-triphosphate binding protein 10 10, rs4660306 – methylmalonic aciduria and type C homocysteinuria, rs7130284 – NADPH-oxidase 4, rs838133 – fucosyltransferase 2. There was no significant associations between any of these 9 genes and AF development. Authors made a conclusion that further studies are needed with the larger sample [40].

Marcucci *et al*. assessed level of homocysteine, vitamins B_6, B_9 and B_{12}, polymorphism of methyltetrahidrofolate reductase (MTHFR) gene in C677T position in patients with non-valvular AF. According to the study results homocysteine level was significantly higher in the group of patients with AF when compared to those without arrhythmia. There was also a difference in the vitamin B6 level, but no difference in the levels of vitamin B_9 and B_{12}. There was no difference in the prevalence of MTHFR gene polymorphism in C677T position between the group with and without non-valvular AF. A risk of AF was significantly higher in patients with homocysteine concentration >19.6 µmol/L when compared to concertation <11.9 µmol/l. There were also associations between the homocysteine level and left atrial dimensions. Homocysteine level was higher and +/+ allele of C677T was more prevalent in patients with ischemic events in the medical history [43]. So, we can see, that genetic factor can play an important role in the development of hyperhomocysteinemia. These changes usually involve genes of the homocysteine metabolism.

Conclusions

AF is the most common rhythm disorder, which is associated with the decreased quality of life, higher incidence of stroke, heart failure, dementia and mortality. Its prevalence in the population is constantly growing. All these requires new methods for the stratification of AF development risk. Different biomarkers are studied as a potential target for interventions. According to the data from various studies elevated homocysteine level increase risk of AF through different mechanisms, which include inflammation, oxidative stress, remodeling of the left atrium and ion channels, thrombosis. This problem requires further investigation and development of pharmacological treatment for hyperhomocysteinemia as one of the types of up-stream therapy. Up-stream has o goal of prevention and slowing down the AF development through the impact on different pathogenetic mechanisms of arrhythmia development.

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