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Review

# A review of homocysteine and heart failure

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**Abstract**

Chronic heart failure (CHF) is a major public health problem causing considerable morbidity and mortality. Recently, plasma homocysteine (HCY) has been suggested to be increased in CHF patients potentially representing a newly recognized risk marker. This manuscript reviews the existing literature regarding hyperhomocysteinemia (HHCY) and CHF. Clinical data indicate that HHCY is associated with an increased incidence of CHF as well as with the severity of the disease. Mechanistic studies of HHCY and CHF are rare. However, preliminary results suggest that HHCY causes adverse cardiac remodelling characterized by interstitial and perivascular fibrosis resulting in increased myocardial stiffness. In addition, HHCY seems to affect the pump function of the myocardium. The mechanisms leading from an elevated HCY level to reduced pump function and adverse cardiac remodelling are a matter of speculation. Existing data indicate that direct effects of HCY on the myocardium as well as NO independent vascular effects are involved. In conclusion, HHCY might be a potential aetiological factor in CHF. Future studies need to clarify the mechanistic role of HHCY in CHF as a useful paradigm with most interesting therapeutic implications, because HCY lowering therapy could favourably influence the prognosis in CHF patients.


*Keywords:* Homocysteine; Heart failure; Remodelling; Pump function; Incidence; Severity of disease

## 1. Introduction

Chronic heart failure (CHF) is a major public health problem causing considerable morbidity and mortality, and affecting nearly 5 million patients with about 500,000 newly diagnosed cases each year in the U.S. [1]. Additionally, CHF is the underlying cause for 12 to 15 million consultations with a physician and 6.5 million hospital days each year, thus representing one of the most frequent causes of hospitalisation [2,3]. Recent data confirm a comparable situation in Western Europe [4–12]. In the large scale epidemiological Rotterdam Study, the prevalence of CHF in the general population >55 years was found to be 3.9% [6], and increased with age reaching up to 13.0% in subjects aged 75–84 years. A comparable prevalence has been reported in the United Kingdom and south-western Europe [8,9]. According to the European Society of Cardiology the prevalence of symptomatic heart failure in Europe ranges between 0.4% and 2.0% [5]. Data from the World Health Organisation estimates a 1.4% prevalence of CHF in Europe with a total of 5.3 million affected individuals [4]. Based on data from the Rotterdam Study, the incidence rate for CHF in individuals >55 years is 14/1000 person years and the life time risk is 33% in men and 29% in women [7]. Therefore, prevention of CHF by identifying risk factors or risk indicators is a major issue. Previous studies have identified hypertension, smoking, diabetes mellitus, obesity and advancing age as the most important risk factors for CHF [13]. Recently, plasma homocysteine (HCY) has been suggested to be increased in CHF patients potentially representing another newly recognized risk marker or risk

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factor [14,15]. This manuscript reviews existing clinical and experimental data regarding hyperhomocysteinemia (HHCY) and CHF.

## 2. Clinical data

In order to ensure correct interpretation of the terminology used in the text, explanations are provided, as follows. HHCY defines the status of elevated circulating HCY levels. Since there is no internationally accepted reference range, most studies use different upper reference limits (URL). Generally, the reference range of most laboratory markers is defined as the 2.5th–97.5th percentile of presumed healthy individuals. However, due to the strong influence of the vitamin status on circulating HCY it is difficult to define an apparently healthy individual as healthy, when the vitamin status is not known [16]. Using the 97.5th percentile as the upper reference limit (URL) in adults who do not supplement vitamins or eat folate fortified food the URL ranges between 15 and 20 μmol/L [16]. Adults with a good vitamin status usually have an URL around 12 μmol/L. However, the use of a URL for HCY seems inappropriate, since cardiovascular risk and all-cause mortality increase linearly with no specific threshold level [17]. Therefore, the D.A.CH.–Liga Homocysteine e.V. recommends the use of 12 μmol/L as a cut-off for an elevated risk potential [17]. The URL of each study in the following text is shown in parentheses, if provided. The term "elevated" means that a specific HCY concentration exceeded the URL. The terms "high" or "higher" simply refer to the corresponding controls without consideration of the URL.

HHCY is commonly known as a risk factor for cardiovascular (CVD), thrombotic, neurodegenerative and pregnancy-associated diseases [16–18]. Recently, new clinical issues related to HHCY have been identified. Besides osteoporosis, CHF is probably one of the most important areas of interest for HHCY. First evidence of an association between circulating HCY levels and CHF came from end-stage renal disease patients [19]. In a cross-sectional study analyzing 75 end-stage renal disease patients and 57 controls Blacher et al. reported a positive correlation between HCY and the cardiac mass index ($r=0.31$, $p<0.01$) that was independent of mechanical factors, such as blood pressure or haematocrit, and included individuals with normal and elevated HCY levels (URL in this study 13.9 μmol/L). HCY was also correlated with left ventricular end-diastolic diameter (LVEDD), posterior wall thickness and the diameter of the interventricular septum. Poyrazoglu et al. studied 27 children with chronic renal failure (CRF) as well as 16 healthy controls, and observed higher HCY levels (11.8 vs. 6.8 μmol/L; URL in this study 8.4 μmol/L, which corresponds to the 95th percentile of controls) and a higher left ventricular mass index (LVMI; 166 vs. 107 g/m$^2$) in the CRF group [20]. However, HCY and LVMI were not significantly correlated, which is probably due to the small number of subjects investigated. The co-existence of higher HCY levels (8.7 vs. 6.6 μmol/L) and a higher LVMI (96.6 vs. 83.4 g/m$^2$) was confirmed by Wocial et al. analyzing 37 subjects with mild essential hypertension and 37 controls [21].

Other trials have analyzed the frequency of HHCY in CHF patients. Cooke et al. reported elevated HCY levels in 31 CHF patients and 93 post-cardiac transplant recipients compared to 18 healthy controls (17.1 vs. 15.3 vs. 9.1 μmol/L; URL in this study 13.9 μmol/L) [22]. In agreement with these results, a high prevalence for the co-existence of HHCY (URL in this study 15 μmol/L) and CHF was also found by Ventura et al. in 600 randomly selected, hospitalised, elderly patients [15]. However, both trials did not perform a correlation analyses for HCY and commonly used markers of CHF, such as LVEDD, ejection fraction (EF), New York Heart Association (NYHA)-class and 6-min walk test. Therefore, it is not clear whether HHCY in CHF patients is just an epiphenomenon or is an indicator of an independent relation between HCY and CHF.

A major clinical impact of HHCY in CHF was first suggested by the Hordaland Homocysteine Study analyzing 587 patients with angiographically verified coronary artery disease (CAD) [23]. Patients with HCY >15 μmol/L and a reduced EF had the highest mortality of all subjects. Since HHCY is known as a cardiovascular risk marker and CAD is the most frequent cause of CHF [24], it is not clear whether HCY contributed to the high mortality of CHF patients by direct effects on the myocardium or by vascular mechanisms. The first hint for a non-vascular mechanism came from a study with 89 CHF patients referred for cardiac transplantation. Subjects with ischaemic and non-ischaemic cardiomyopathy exhibited comparable HCY levels indicating that HHCY levels do not particularly favour ischaemic cardiomyopathy [25].

Prospective data from the community-based prospective Framingham Study analyzing 2491 adults demonstrated an increased incidence of CHF in individuals with a HCY level >11–12 μmol/L. In multivariate analyses controlling for established risk factors for CHF including the occurrence of myocardial infarction during the follow-up, HCY levels above the sex-specific median value were associated with an adjusted hazard ratio for CHF of 1.93 in men and 1.84 in women. The association between HCY and risk of CHF remained significant after exclusion of individuals with any manifestation of CAD. However, this study did not provide any mechanistic insight into how HCY might affect the myocardium. Therefore it is not clear if HHCY is a mechanistically involved risk factor for CHF or only a risk indicator without any direct effects on the myocardium. A recent study by ourselves revealed that HHCY is not only related to the incidence of CHF, but also to the severity of the disease [26]. In this study we investigated 95 CHF patients and 18 healthy controls. Median HCY (URL in this study 12 μmol/L) increased stepwise with increasing NYHA-class (controls: 8.5 μmol/L, NYHA I: 10.3 μmol/

L, NYHA II: 12.1 μmol/L, NYHA III: 13.5 μmol/L, NYHA IV: 17.4 μmol/L) and correlation analysis (including patients and controls) revealed significant relations between HCY, maximum oxygen uptake, 6-min walk test, N-terminal pro-brain natriuretic peptide (NT-proBNP), LVEDD and EF. After correction for age and creatinine, NT-proBNP ($r=0.434$, $p<0.001$) and LVEDD ($r=0.326$; $p<0.001$) were significantly associated with HCY. These results demonstrate that HCY is related to clinical, echocardiographic and laboratory parameters of CHF suggesting a relation between HCY and the severity of CHF. Our findings are supported by three other studies showing significant relations of HCY with left ventricular structure and function [27–29]. Cesari et al. observed an inverse relation of HCY and EF in hypertensive patients [27]. HCY was the strongest predictor for a low EF, followed by type 2 diabetes mellitus and cigarette smoking. Moreover, HCY significantly predicted cardiovascular mortality in hypertensives. An independent relation between HCY and EF has also been reported by Bokhari et al. in patients with angiographically defined CAD [28]. Data from the Framingham Study revealed significant associations of HCY with left ventricular mass and left ventricular wall thickness in women, but not in men [29]. Contrary to Cesari et al. there was no relation between HCY and the echocardiograpically assessed left ventricular function.

HCY can be degraded by two mechanisms, the remethylation pathway and the transsulfuration pathway [30,31]. Remethylation recycles HCY to methionine. This step strongly depends on folate (methyl-group donor) and vitamin $B_{12}$ (co-enzyme of methionine synthase). Vitamin $B_6$ is the co-enzyme of the cystathionine-β-synthase, centrally involved in the transsulfuration pathway. Deficiency of one or more of these B-vitamins is the most common cause for mild to moderately elevated HCY levels among adults [16,17]. This suggests that folate, vitamin $B_6$, and vitamin $B_{12}$ might also be important for CHF. However, existing data are rare. Gorelik et al. analyzed the dietary intake of 57 consecutively hospitalized CHF patients and compared them with 40 controls [32]. The dietary intake was comparable in the two groups. However, the intake of folate did not reach the daily recommended intake. Folate and vitamin $B_6$ consumption has been shown to be inversely linked to the risk of CAD [33]. But, nothing is known about folate and vitamin $B_6$ deficiencies in CHF. To obtain information about the impact of folate on CHF epidemiologic data from the USA before and after the beginning of food fortification with folate in 1998 have to be compared. Data from the Rochester Epidemiology Project clearly demonstrate that the incidence of CHF between 1991 and 2000 did not decrease [34]. However, survival after onset of CHF has increased significantly. Regarding vitamin $B_{12}$ there is one study showing a lower left ventricular ejection fraction among vitamin $B_{12}$-deficient patients [35]. Whether low left ventricular ejection fraction results in malabsorption of vitamin B-12 and vitamin B-12 deficiency, or conversely, whether vitamin $B_{12}$-deficiency depresses left ventricular function is not clear.

Besides B-vitamin deficiencies, an impaired renal function is another frequent cause of HHCY [36–40]. Moreover, renal dysfunction is a common and progressive complication of CHF. Several studies have consistently demonstrated that the presence of concomitant renal impairment is one the strongest risk factors for mortality in CHF patients [41–46]. In addition, HHCY has been shown to be an independent risk factor for CVD in renal patients [47,48]. As reported recently, HHCY in renal patients is due to reduced HCY degradation [40,49,50]. Several clinical studies have consistently demonstrated a strong correlation between the glomerular filtration rate (GFR) and HCY over a wide range of GFR [51,52]. Since urinary HCY excretion is negligible [53,54], a central role of the kidney for HCY degradation has been suggested. Besides reduced renal HCY degradation, impaired whole body HCY metabolism due to uraemic toxins is thought to be involved [40]. Even if the pathophysiology of the "cardiorenal syndrome" is not well understood [42], HHCY might be an important mechanism to explain the observed adverse clinical outcome in patients with cardiorenal syndrome [19,20]. Contrary to this hypothesis, our own data suggest that the relation between HCY and CHF is independent from renal function [26]. Additionally, Sundström et al. found a relation between HCY and left ventricular mass and wall thickness in women that was also independent from renal function [29]. However, the role of HCY in cardiorenal syndrome is insufficiently investigated. In view of its attractive and inexpensive therapeutic implications, the insufficiently investigated role of HCY in cardiorenal syndrome needs further research.

In conclusion, existing data indicate that HCY is relevantly involved in CHF. HHCY seems to be a risk factor for the incidence of CHF and blood levels are associated with the severity of the disease. This suggests a mechanistic role of HHCY in CHF. However, all of the above mentioned studies are of an epidemiological nature and do not provide any mechanistic insights.

## 3. Experimental findings

To understand the mechanistic role of HHCY in CHF, experimental studies are needed. However, there are only a few studies available providing only preliminary insights. Most of the existing work has been done by the group of Kennedy and Joseph. In a first animal study they treated spontaneously hypertensive male rats with a homocysteine enriched diet or a homocysteine enriched and folate, choline and methionine deficient diet to induce an intermediate (IH) or severe (SH) HHCY, respectively [55]. The mean HCY levels were 4.3 μmol/L in control animals, 47.1 μmol/L in the IH group and 202.8 μmol/L in the SH group. After 10 weeks of treatment they observed a stepwise increase of

total, perivascular and interstitial collagen and mast cells in the myocardium with increasing HCY levels indicating adverse cardiac remodelling. Moreover, HHCY caused an elevated left ventricular diastolic pressure suggesting diastolic dysfunction. Relative heart weight, cardiac myocyte diameter, blood pressure and systolic function did not differ between groups. In a later study, they repeated the experiment with normotensive rats [56]. However, this study included only a control and an IH group and confirmed the results observed in hypertensive rats. In addition, this trial revealed an increased ventricular weight, an increased myocyte size and thickening of the posterior wall and the interventricular septum. The echocardiographically assessed systolic pump function was reduced. At the end of the treatment period, hearts were explanted and perfused in a Langendorff system. Organs from treated animals exhibited an upward shift in left ventricular diastolic volume–pressure curve indicating diastolic dysfunction. Contractile and relaxation functions were unchanged. These two studies clearly indicate a direct adverse function of HHCY on cardiac structure and function. Walker et al. reported reduced systolic and diastolic function in rats after two weeks of daily HCY injections, leading to a twofold increase in circulating HCY [57]. In our own study, we fed normotensive rats with a homocysteine enriched IH diet (comparable to that used by Joseph et al.) for 12 weeks (unpublished data). Additionally, we included a group with a moderate HHCY (MH) induced by methionine enriched chow. Contrary to Joseph et al. we did not find significant changes in heart weight, ventricular mass and echocardiographically measured wall thickness. However, the IH group exhibited significantly higher tissue levels of brain natriuretic peptide (BNP), a new laboratory marker of heart failure. This finding was confirmed by increased cellular mRNA concentrations (1.8-fold) indicating adverse effects of HCY on the myocardium.

In addition to morphologic changes and reduced diastolic function, in ex vivo perfused rat hearts, Joseph et al. demonstrated an acute, endothelium-derived negative inotropic effect of HCY that was not mediated by NO [58]. No effect on contractility was observed in isolated papillary muscles superfused with increasing concentrations of HCY. The susceptibility of coronary endothelium to HCY derived adverse effects can at least partly be ascribed to the reduced HCY degradation capacity due to the missing transsulfuration pathway in these cells [59].

The increased mast cell number in HHCY rats seems to have a dual function. On the one hand mast cells secrete various mediators of cardiomyocyte and fibroblast function and are thought to play a role in the remodelling of the myocardium [56]. On the other hand, a recent study with mast cell deficient rats demonstrated a protective role of mast cells. The HHCY induced changes were much worse in mast cell deficient rats than in mast cell competent rats [60].

Taken together, mechanistic studies of HHCY and CHF are rare. However, existing data suggest that HHCY causes adverse cardiac remodelling characterized by interstitial and perivascular fibrosis resulting in increased myocardial stiffness. In addition, HHCY seems to affect the pump function of the myocardium. The mechanisms leading from an elevated HCY level to reduced pump function and adverse cardiac remodelling are still a matter for speculation. First evidence indicates that NO independent vascular effects are involved. Besides acute effects [58], the HHCY derived endothelial dysfunction might induce an increased expression of adhesion molecules followed by immigration and activation of inflammatory cells, secretion of chemokines, an altered fibroblast and cardiomyocyte function and an increased collagen synthesis. Moreover, HCY could directly affect fibroblasts and cardiomyocytes [55]. A potential mechanism whereby HHCY might affect cardiac remodelling is the activation of matrix metalloproteinases (MMP). The role of MMPs in CHF and cardiac remodelling has been shown by various in vivo and in vitro studies [61–67]. Moreover, HHCY has been found to induce MMPs in vascular tissue [68–70]. The primary events and signalling mechanisms of HCY that affect endothelial, fibroblast and inflammatory cell function in the heart may include oxidative stress and the protein kinase C pathway [71].

Lastly, existing clinical and experimental data indicate that HHCY might be a potential aetiological factor in CHF. However, the cellular mechanisms behind the adverse effects of HHCY on cardiac remodelling and pump function are not understood at the moment. Future studies need to clarify the mechanistic role of HHCY in CHF as a useful paradigm with interesting therapeutic implications, because HCY lowering therapy could favourably influence prognosis in CHF patients.

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