Review

Homocysteine and heart failure: a review of investigations from the Framingham Heart Study

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Abstract

High plasma homocysteine levels are associated with a moderately increased risk of cardiovascular disease, particularly of atherosclerotic events. We review the association of plasma homocysteine with heart failure, with a specific focus on a series of previously published investigations from the community-based Framingham Heart Study that evaluated the relations of plasma homocysteine levels with overt heart failure, and with its key antecedents, echocardiographic left ventricular (LV) mass and hypertension. In the Framingham sample, higher plasma homocysteine levels were associated with increased risk of new-onset heart failure in both men and women, with a more continuous and graded relation being observed in women. A positive relation between homocysteine and LV mass was observed in women, but not in men; this may underlie the stronger relations of homocysteine to heart failure risk in women. Plasma homocysteine was not associated with hypertension incidence prospectively in either sex. The relations of increased homocysteine to heart failure (in both sexes) and to greater LV mass (in women) noted in the Framingham sample should be confirmed in other community-based samples. Secondary analyses of heart failure outcomes in ongoing randomized clinical trials may provide insights into whether lowering of plasma homocysteine levels is associated with a reduction in LV mass and/or a reduction of heart failure risk.

Keywords: epidemiology; heart failure; homocysteine; left ventricular hypertrophy.

Introduction

Heart failure is a major public health problem with substantial morbidity, mortality, and economic con-

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sequences (1, 2), and the identification of modifiable risk factors is a priority. The most important risk factors for heart failure at a population level are coronary artery disease and hypertension (3). Left ventricular (LV) dilation and LV hypertrophy (LVH) are hallmarks of LV remodeling, the subclinical phenotype that frequently antedates heart failure (4). Elevated total plasma homocysteine levels have mainly been related to increased risk of atherosclerotic events (5–7). Thus, the link between elevated plasma homocysteine levels and one of the most important risk factors for heart failure (i.e., coronary disease) is well established, but the relation of plasma homocysteine levels to ''non-ischemic'' heart failure, and its chief precursors, hypertension and LVH, had not been investigated until recently.

Some experimental evidence supports a potential pathogenetic role for homocysteine in non-ischemic heart failure: cardiomyocytes do not express two key homocysteine-metabolizing enzymes (cystathionine β-synthase, in the transsulfuration pathway; and betaine-homocysteine methyltransferase, in the alternate remethylation pathway), which renders them dependent on the methionine synthase remethylation pathway (8). In experimental models, hyperhomocysteinemia had been demonstrated to induce LVH and cardiac fibrosis, findings that are reversible with folate treatment (9–11). On a parallel note, there are several plausible mechanisms by which hyperhomocysteinemia can cause heart failure indirectly by increasing the propensity for developing hypertension, via promoting increased vascular stiffness (12–14), impaired endothelial integrity (12, 15, 16), and reduced vasodilatory capacity (10, 15, 17).

We have conducted and reported previously a series of investigations on the community-based Framingham Heart Study sample that evaluated the potential association of plasma homocysteine with heart failure, echocardiographic indices of LV remodeling and high blood pressure. In these published reports, we demonstrated that elevated plasma homocysteine: 1) increases the risk of subsequent heart failure (18); 2) is associated with increased LV mass (19); 3) but is not associated with the risk of developing hypertension (20). In this review, we summarize these studies and discuss the mechanisms by which plasma homocysteine may promote heart failure.

Plasma homocysteine and risk of congestive heart failure

Clinical evidence relating homocysteine to heart failure risk is limited. In small clinical series, patients
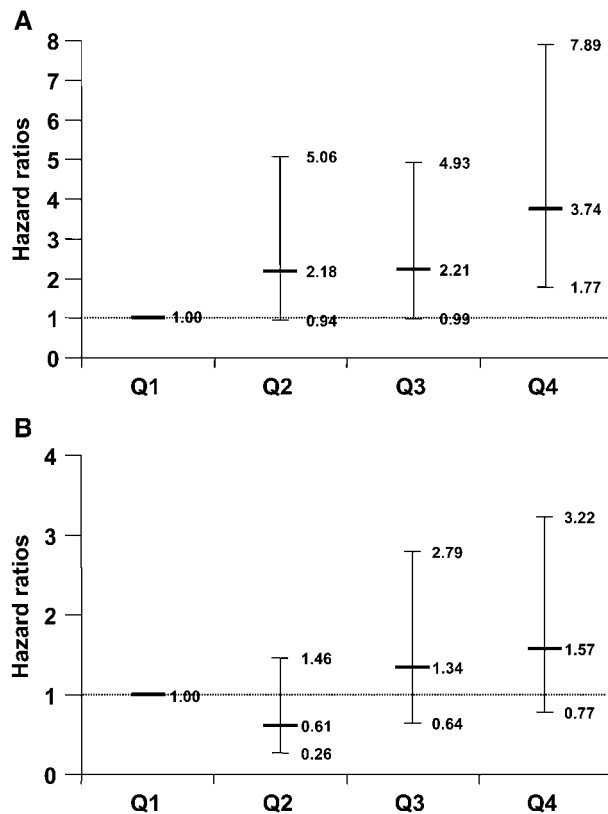
Figure 1 (A) Risk of developing heart failure in women (88 developed heart failure/1547 at risk) over 8 years by sex-specific quartiles of plasma homocysteine, adjusted for age, smoking, valve disease, systolic blood pressure, antihypertensive medication use, ECG left ventricular hypertrophy, diabetes, ratio of total cholesterol to high-density lipoprotein (HDL)-cholesterol, alcohol intake, body mass index, serum creatinine, interim recognized or unrecognized myocardial infarction, and baseline exam. Trend across quartiles, p<0.001. Above median vs. below median, p=0.008. Q4 vs. Q1–3, p<0.001. Data from reference (18). (B) Risk of developing heart failure in men (68 developed heart failure/944 at risk) over 8 years by sex-specific quartiles of plasma homocysteine, with covariates as in (A). Trend across quartiles, p=0.07. Above median vs. below median, p=0.03. Q4 vs. Q1–3, p=0.09. Data from reference (18).

with congestive heart failure have been reported to have elevated plasma homocysteine levels (21–23). Plasma homocysteine levels track with functional capacity in heart failure patients (23).

We have previously reported the relations of plasma homocysteine to incidence of heart failure in 2491 participants (mean age 72 years, 62% women) from the original cohort of the community-based longitudinal Framingham Heart Study [individuals attending the 16th (1979–1982) and 20th biennial examinations (1986–1990) who were free of heart failure or a myocardial infarction at the routine baseline examinations] (18). Plasma total homocysteine was measured using high-performance liquid chromatography with fluorimetric detection (24). During 8 years of follow-up, 156 subjects (88 women) developed a first episode of heart failure. Risk of heart failure increased by 25% (men) to 47% (women) per quartile increment in plasma homocysteine (Figure 1A, B) in multi-

variable-adjusted Cox proportional hazards analyses controlling for established risk factors for heart failure, including the occurrence of interim myocardial infarction. A plasma homocysteine level above the median value almost doubled the risk of heart failure [hazard ratio 1.93 in women (95% confidence interval 1.19–3.14) and 1.84 in men (1.06–3.17)] (18). Relations of plasma homocysteine to heart failure risk were stronger and more continuous in women compared to men (Figure 1A, B), with a doubling of heart failure risk at the second quartile and a near four-fold risk at the highest quartile (compared to the lowest quartile) in women. An increased risk of heart failure was observed only at values above the median in men. These results were maintained in analyses restricted to individuals without any manifestation of coronary heart disease at baseline (18).

A causal relationship between high plasma homocysteine levels and the development of heart failure is supported by the demonstration of a temporal sequence (high baseline homocysteine levels antedated heart failure), the strength of the association, and the consistency of results in multiple analyses. If our findings are confirmed, the observation of a doubling of heart failure risk in women with plasma homocysteine in the second quartile (levels that are generally considered normal) suggests that homocysteine may be a modifiable dietary risk factor for heart failure. To establish a causal relationship definitively, randomized clinical trials are required to demonstrate that lowering elevated plasma homocysteine levels by vitamin supplementation reduces the risk of heart failure. Secondary analyses of heart failure endpoints in ongoing clinical trials of homocysteine lowering may provide important clues in this context. In the USA, folate fortification of food has already led to a decrease in population levels of homocysteine (25), but this measure has not been taken worldwide.

Plasma homocysteine and left ventricular mass and function

Experimental and clinical data support the concept that plasma homocysteine levels influence LV remodeling. Elegant work by Joseph and others has demonstrated that hyperhomocysteinemia is associated with concentric ventricular hypertrophy in experimental models of pressure and volume overload (9, 11, 26–28). However, other workers have reported LV dilation and wall thinning as the initial phenotype upon acute exposure to increased homocysteine levels (29). Homocysteine-induced atrial remodeling has also been demonstrated in experimental animals (30).

Clinical data relating plasma homocysteine to LV function are more limited and have yielded inconsistent results. Negative (31–33), positive (34), and no association (35) of plasma homocysteine with LV ejection fraction have been reported in referral samples of patients with coronary artery disease. Hermann and colleagues have reported a positive correlation of plasma homocysteine with LV internal dimensions and an inverse relation to ejection fraction in a series
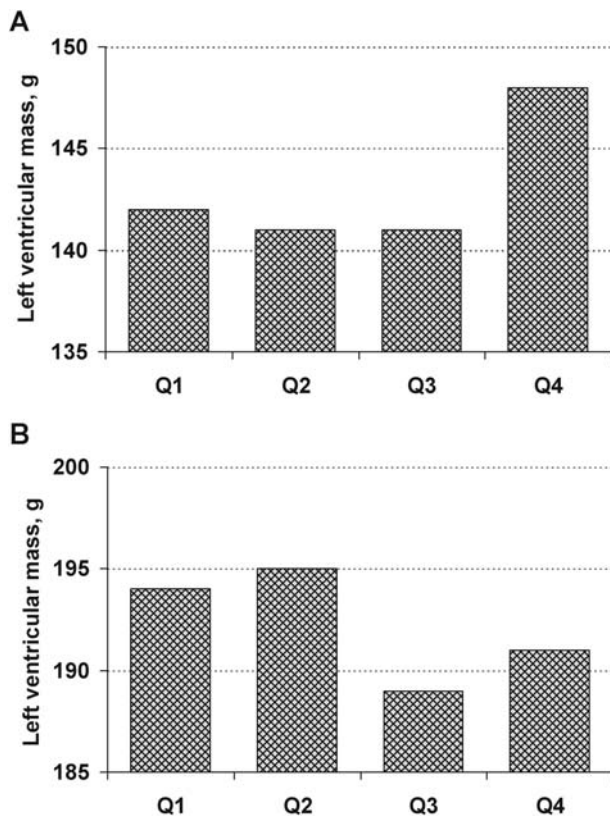
Figure 2 (A) Left ventricular mass (g) in women (n = 1552) by sex-specific quartiles of plasma homocysteine, adjusted for age, height, weight, total/HDL-cholesterol ratio, systolic blood pressure, antihypertensive treatment, diabetes, valve disease, heart rate and serum creatinine. Trend across quartiles, p = 0.04; Q4 vs. Q1–3, p = 0.0003. Data from reference (19). (B) Left ventricular mass (g) in men (n = 1145) by sex-specific quartiles of plasma homocysteine, with covariates as in Figure 2A. Trend across quartiles, p = 0.16. Data from reference (19).

of patients with overt heart failure (23). Hyperhomocysteinemia has been related to LVH in a small sample of end-stage renal disease patients (36), but no such association was noted in another sample of hypertensive persons (37).

We have reported previously the cross-sectional relations of plasma total homocysteine to echocardiographic LV structure and function in the Framingham Heart Study sample (19). In that report, we evaluated 2697 Framingham Offspring Study participants (mean age 58 years, 58% women) who attended the sixth examination cycle (1995–1998) and who were free of heart failure and previous myocardial infarction. In multivariable analyses adjusting for clinical covariates, plasma homocysteine was significantly and positively related to LV mass and wall thickness, and borderline significantly to relative wall thickness in women (1.92 g, 0.01 cm, and 0.29% increase, respectively, for a 1-SD increase in ln[homocysteine], p = 0.01–0.08), but not in men (p = 0.11–0.44) (19). LV mass and wall thickness were higher in the fourth quartile of plasma homocysteine compared to the lower three quartiles in women (p = 0.0003–0.02), but not in men (p = 0.25–0.78) (Figure 2A, B) (19). It is

worth noting that the cut-off point for the highest quartile was 10.3 μmol/L in women, which is lower than the clinically used upper limit of normal of 14 μmol/L. The relations of plasma homocysteine to echocardiographic LV measures in women did not vary with menopausal status (19).

The observations of a stronger relation between homocysteine and LVH in women than in men are intriguing, and may underlie the stronger relations of plasma homocysteine to congestive heart failure (18) and other cardiovascular disease (38) in women relative to men noted previously, as LVH is a strong risk factor for coronary events and sudden death, in addition to being a key antecedent of heart failure.

Plasma homocysteine and risk for hypertension

Several cross-sectional studies have demonstrated an association of plasma homocysteine with systolic and diastolic blood pressure, and with hypertension (39–42), and homocysteine-lowering treatment has been associated with a reduction in systolic and diastolic blood pressure in intervention studies (43, 44).

Given the lack of prospective data relating plasma homocysteine to future incidence of hypertension, we conducted and reported the relations of baseline plasma total homocysteine levels to subsequent hypertension incidence and blood pressure increase in the Framingham Sample (20). We investigated a sample of participants attending the 16th (1979–1982) or 20th (1986–1990) original cohort examinations, or the fifth offspring cohort examination (1991–1995) (20). The study sample consisted of 2137 participants (mean age 58 years, 58% women) free of hypertension, myocardial infarction, heart failure, atrial fibrillation, or renal failure at baseline. In contrast to the above two studies of heart failure and LV measures, no effect modification by sex was observed regarding the relation of plasma homocysteine to hypertension incidence, so sex-pooled analyses were performed. During 4 years of follow-up, 396 persons (17.6%) developed hypertension and 942 persons (41.9%) had progressed to a higher JNC VI blood pressure stage [optimal (systolic < 120 mm Hg and diastolic < 80 mm Hg), normal (systolic 120–129 mm Hg or diastolic 80–84 mm Hg), or high normal blood pressure (systolic 130–139 mm Hg or diastolic 85–89 mm Hg)] (45). Crude rates of hypertension incidence increased across homocysteine quartiles. However, plasma homocysteine was not significantly related to hypertension incidence or blood pressure progression in age- and sex-adjusted models [OR per SD increment in ln[homocysteine] of 0.98 (0.87–1.11) and 1.05 (0.96–1.16), respectively] or in multivariable-adjusted models [OR per SD increment in ln[homocysteine] of 0.92 (0.81–1.06) and 1.07 (0.97–1.18), respectively] (20).

Thus, in our prospective study, plasma homocysteine levels were not related to hypertension incidence after adjustment for age, sex and other important covariates (20). Our observations provide

modest evidence against the hypothesis (based on cross-sectional studies; 39–42) that higher plasma homocysteine levels are causally related to elevated blood pressure. Other evidence against a causal relation between homocysteine and hypertension incidence is provided by experimental studies in which diet-induced hyperhomocysteinemia has been demonstrated to lower blood pressure (46).

Gender-related differences in the relations of homocysteine to left ventricular mass and heart failure

As summarized above, we have reported a more continuous relation between plasma homocysteine level and heart failure risk in women than in men (Figure 1A, B) (18). This observation needs to be confirmed, and the mechanisms behind the observation remain to be explained. We also observed a stronger relation of plasma homocysteine level to LV mass and wall thickness in women than in men (Figure 2A, B) in a separate report (19), which may explain the stronger relation to heart failure in women. Gender-related difference in the relation of homocysteine to LV mass may also partly explain the previously reported higher risk of atherosclerotic events associated with hyperhomocysteinemia in women compared with men (38), because LV mass is also a risk factor for myocardial ischemic events, arrhythmias and sudden death.

The mechanisms behind the gender differences in the relation of homocysteine to LV measures and heart failure remain to be elucidated. Women respond to pressure overload with a greater degree of increase in LV wall thickness and concentric hypertrophy than men do (47), which may be explained by molecular differences in the LV remodeling process (48). Homocysteine is an Na^+-K^+-ATPase inhibitor, like digoxin (49). In the Digitalis Investigation Group heart failure study, digoxin treatment was associated with more adverse outcomes in women than in men (50). We speculate that inhibition of the Na^+-K^+-ATPase by homocysteine could possibly lead to LV remodeling and heart failure to a greater extent in women than in men (18). Estrogen may favorably influence LV geometry (51), and may also lower plasma homocysteine levels (52), which theoretically could render postmenopausal women with lower estrogen levels more prone to adverse effects of homocysteine on LV remodeling. However, the relations of plasma homocysteine to LV measures did not vary with menopausal status in our report. It is unclear, therefore, if endogenous estrogen effects can explain the gender differences observed in our studies.

It is intriguing that the gender differences for relations of homocysteine to LV measures and heart failure incidence were not as evident for other outcomes in the Framingham Heart Study cohorts, such as for hypertension (20), carotid artery atherosclerosis (53), stroke incidence (54), or cardiovascular mortality (55).

Mechanisms behind the relations of homocysteine to left ventricular mass and heart failure

Elevated homocysteine levels may promote heart failure through several mechanisms. Based on our observations, it is likely that increased LV mass may be along the causal the pathway between hyperhomocysteinemia and heart failure, at least in women.

Elevated homocysteine levels may be causally related to increased LV mass through vascular and non-vascular mechanisms. Homocysteine stimulates growth and collagen production by vascular smooth muscle cells and inhibits endothelial cell growth (12, 14, 56). Homocysteine also promotes oxidative stress and stimulates matrix metalloproteinase production (a family of collagen-degrading enzymes) (17), which promotes endothelial dysfunction (15, 16), ultimately leading to atherosclerosis. In addition to the vascular effects, homocysteine may have direct adverse myocardial effects, mainly affecting the cardiac extracellular matrix (9, 10). Homocysteine induces cardiac fibrosis (by increasing transforming growth factor-β1; 26) and modulates cardiac matrix metalloproteinase activity (9, 10), which may promote diastolic dysfunction (9). Inflammatory cell infiltration may play a critical role in homocysteine-induced ventricular remodeling; a protective influence of myocardial mast cells has been proposed in experimental hyperhomocysteinemia (27).

In addition to the homocysteine→increased LV mass→heart failure pathway, there are other mechanisms by which homocysteine may promote heart failure, mainly by increasing the risk of coronary atherosclerosis (57, 58) and myocardial infarction (59) [a key precursor of heart failure; (3)]. Alternatively, homocysteine may cause myocardial ischemia (and resultant myocardial dysfunction) by promoting endothelial dysfunction of coronary arteries (15, 60, 61). Furthermore, homocysteine is a source of increased oxidative stress, which may lead to myocardial dysfunction (62). In experimental models, homocysteine increases reactive oxygen species, generates nitrotyrosine, activates latent matrix metalloproteinase, and decreases the levels of endothelial nitric oxide, thioredoxin, peroxiredoxin and peroxisome proliferator-activated receptor-γ activity (28, 63). Additionally, in experimental settings homocysteine has been reported to have a negative inotropic effect on cardiac myocytes via its potential effect on voltage-dependent calcium influx, sarcoplasmic reticular calcium release and reuptake, calcium efflux (via the Na/Ca exchanger), and myofilament calcium sensitivity (64).

Conclusion

In this review, we have summarized previously published investigations of the Framingham cohort that suggest that an increased plasma homocysteine level is an independent risk factor for the development of heart failure in both men and women, with a stronger and more continuous relation noted in women. We

have also reported stronger relations between plasma homocysteine and LV mass in women compared to men. We observed no association of baseline plasma homocysteine levels with hypertension incidence or with longitudinal blood pressure tracking. Our published observations support the notion that increased LV mass may mediate in part the risk of heart failure associated with hyperhomocysteinemia, especially in women. These findings warrant confirmation in other epidemiological studies, and their clinical importance can be assessed in secondary analyses of homocysteine-lowering intervention studies.

Acknowledgements

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