Clinical Investigations

Hyperhomocysteinemia in Patients with Heart Failure Referred for Cardiac Transplantation: Preliminary Observations

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Summary

Background: Hyperhomocysteinemia is becoming recognized as a risk factor for cardiovascular disease, yet there are limited data on the prevalence of hyperhomocysteinemia in patients with heart failure.

Hypothesis: The purpose of this study was to examine the prevalence of hyperhomocysteinemia in patients with severe heart failure and to correlate serum homocysteine levels with factors that may affect homocysteine metabolism.

Methods: Serum homocysteine levels were measured at the time of cardiac transplant evaluation in 89 consecutive patients with severe heart failure. Homocysteine levels for patients with ischemic cardiomyopathy (ICM) were compared with levels obtained in patients with nonischemic cardiomyopathy (NICM), and homocysteine levels were correlated with demographic and hemodynamic parameters as well as functional status.

Results: The mean plasma homocysteine level was increased ($14.3 \pm 5.3 \mu\text{mol/l}$, normal $<9.0 \mu\text{mol/l}$) and was equivalent between patients with ICM versus NICM ($14.7 \pm 5.8 \mu\text{mol/l}$ vs. $13.8 \pm 4.5 \mu\text{mol/l}$, $p = 0.44$). Elevated homocysteine levels were seen in a large proportion (89%) of patients and were equally common to patients with NICM (94%) and ICM (85%). Serum homocysteine levels correlated with serum creatinine ($r = 0.51$, $p < 0.001$), with a history of diabetes ($p = 0.028$), and with a history of peripheral vascular disease

($p = 0.045$). Only 6% of patients were receiving folic acid therapy at the time of transplant referral.

Conclusion: Hyperhomocysteinemia is common in patients with severe heart failure, and plasma homocysteine levels are uniformly elevated regardless of the etiology of heart failure. Elevated plasma homocysteine levels are likely a consequence of heart failure-related renal insufficiency.

Key words: homocysteine, heart failure, heart transplantation

Introduction

Hyperhomocysteinemia is increasingly recognized as a risk factor for cardiovascular disease and for cardiovascular events.^{1, 2} Patients with severe heart failure are also at increased risk for cardiovascular events and cardiac death, particularly those with coronary artery disease as the source of their heart failure. Although there has been a growing recognition of homocysteine as a cardiac risk factor in patients with coronary and peripheral arterial disease, there have been few published data on the prevalence of hyperhomocysteinemia in congestive heart failure. Limited available data have suggested that homocysteine levels may be increased in patients with heart failure; however, this hypothesis is not well supported in the literature.³ The presence of hyperhomocysteinemia in patients with severe heart failure could add to the already high rate of adverse cardiovascular events in this patient population before cardiac transplantation and may increase the likelihood of coronary allograft vasculopathy after transplantation.⁴

Our impression was that many of the patients with severe cardiomyopathy who presented to our program for cardiac transplantation were at risk for hyperhomocysteinemia, but that few had undergone measurement of plasma homocysteine and even fewer were undergoing active treatment for elevated homocysteine levels. Accordingly, we analyzed plasma homocysteine levels in patients with advanced heart failure presenting for transplant evaluation, recorded the number of patients undergoing treatment for hyperhomocysteinemia, and

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correlated the observed levels with known factors that might influence homocysteine metabolism.

Methods

Patients were identified from our heart failure and transplantation clinic records following their initial new patient visit for cardiac transplantation evaluation. From these records, a series of consecutive patients presenting for evaluation between March 2001 and January 2002 were retrospectively identified and included in this analysis. Local Institutional Review Board approval was obtained to allow review of patient medical records. Patients completed either inpatient or outpatient evaluation for cardiac transplantation and underwent measurement of routine pretransplant laboratory studies including a plasma homocysteine level (Imx assay, Abbott Laboratories, Abbott Park, Ill., USA; normal value <9.0 $\mu\text{mol/l}$) the morning after arrival. Patients were in the fasting state at the time of plasma homocysteine measurement. Patient use of folic acid and/or over-the-counter multivitamins was also documented.

Cardiac transplant evaluation proceeded to include standard interventions designed to assess the patient's candidacy for transplantation, including right heart catheterization and coronary angiography if not previously done by the referring cardiologist. Patients were divided into ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM) groups based on the findings from coronary angiography. Plasma homocysteine levels were compared between groups and levels were correlated to age, gender, renal function, ejection fraction, New York Heart Association (NYHA) classification, maximal oxygen consumption (MVO_2), right heart pressures, and history of diabetes, peripheral vascular disease, or cigarette smoking. Data were analyzed by Student's *t*-test and Spearman correlation coefficients for continuous variables and chi-square analysis for categorical variables. Data are reported as mean $\pm$ standard deviation, with a 2-tailed *p* value ≤ 0.05 considered statistically significant.

Results

In all, 89 consecutive patients were identified, 54 with ICM and 35 with NICM. The mean age was 53.6 ± 8.7 and was equivalent between the two groups. There were 19 women in the study, 8 in the ICM group and 11 in the NICM group. Mean ejection fraction was $19.8 \pm 9.5\%$ and was slightly higher in the ICM group than in the NICM group ($21.3 \pm 10.7\%$ vs. $17.6 \pm 6.8\%$, $p = 0.048$). Mean NYHA classification for all patients was 3.2 ± 0.6 , and mean maximal oxygen consumption was 13.4 ± 3.9 $\text{ml O}_2/\text{kg}/\text{min}$, consistent with the diagnosis of severe heart failure. Renal function was mildly impaired in the entire group, with a trend toward lower creatinine clearance in the patients with NICM (67.5 ± 34.4 ml/min vs. 80.7 ± 36.0 ml/min for patients with ICM, $p = 0.14$). Mean serum creatinine was 1.4 ± 1.6 mg/dl and was equivalent between the ICM

and NICM groups. A significant minority of patients (30%) had diabetes (defined as glucose intolerance requiring oral hypoglycemic agents and/or insulin), hypertension (43%), or a history of prior cigarette smoking (40%) at the time of transplant referral, with only a history of smoking being significantly different between groups (32% in patients with ICM vs. 54% in patients with NICM, $p = 0.03$). Seventeen patients had peripheral vascular disease (defined as peripheral vascular atherosclerosis documented by angiography or noninvasive imaging), 16 of whom were in the ICM group ($p = 0.002$).

The patients with ICM had extensive coronary artery disease, with 35 of 54 (65%) having significant stenosis of three major coronary vessels (defined as $>50\%$ obstruction), 14 of 54 (26%) having significant double-vessel, and 5 of 54 (9%) having significant single-vessel coronary disease. Right heart pressures were mildly elevated for the entire group, with no significant differences noted between the patients with ICM and those with NICM. Mean pulmonary capillary wedge pressure was 18.7 ± 8.7 mmHg , mean pulmonary artery systolic pressure was 42.2 ± 16.3 mmHg , and mean right atrial pressure was 8.3 ± 4.8 mmHg .

The mean homocysteine level for the entire group of patients was elevated at 14.3 ± 5.3 $\mu\text{mol/l}$. The homocysteine level was elevated in both patients with ICM (14.7 ± 5.8 $\mu\text{mol/l}$) and in patients with NICM (13.8 ± 4.5 $\mu\text{mol/l}$), and there was no significant difference in levels between the groups ($p = 0.44$). Nearly every patient (79/89 patients, or 89%) had homocysteine levels above the upper limit of normal for our laboratory, with elevated levels being equally common in the NICM group (33/35 patients, or 94%) and the ICM group (46/54 patients, or 85%). Patients taking folic acid had lower homocysteine levels than those not receiving folic acid supplementation (10.6 ± 2.1 vs. 14.7 $\mu\text{mol/l}$, $p = 0.007$). An elevated homocysteine level correlated with elevated levels of serum creatinine ($r = 0.51$, $p < 0.001$), with a history of diabetes ($p = 0.028$), and with a history of peripheral vascular disease ($p = 0.045$), (Figs. 1–3). There was no correlation, however, between homocysteine levels and patient age, gender, smoking history, NYHA classification, MVO_2 , or right heart pressures.

FIG. 1 Correlation between plasma homocysteine level and creatinine, demonstrating a direct correlation between elevated homocysteine and elevated creatinine.

FIG. 2 Relationship between plasma homocysteine and the presence or absence of diabetes. Homocysteine levels were significantly higher in diabetic than in nondiabetic patients.

FIG. 3 Relationship between plasma homocysteine and the presence or absence of peripheral vascular disease (PVD). Homocysteine levels were noted to be higher in the patients with heart failure and PVD than in those without a history of PVD.

Only 5 of 89 patients (6%) were receiving folic acid therapy at the time of transplant referral, and all of these were in the ICM group. The dose of folic acid taken by the patients with ICM who received supplementation was 1.0 mg/day for all five patients. Twelve patients (8 in the ICM group and 4 in the NICM group) were also taking over-the-counter supplemental multivitamins that may have included small doses of folic acid or B vitamins. If patients taking over-the-counter multivitamins are grouped together with those taking folic acid, there remain only 17 patients (19%) who were receiving any form of therapy for elevated homocysteine at the time of transplant referral: 13 in the ICM group and 4 in the NICM group.

Discussion

Our findings demonstrate that hyperhomocysteinemia is common in patients with severe heart failure referred for cardiac transplantation, and that plasma levels of homocysteine are elevated equally in those with ICM and in those with NICM as the etiology for their heart failure. This suggests that the mechanism for elevation of the homocysteine level

in our patients is common to both patients with ICM and NICM and not related to underlying atherosclerotic vascular disease alone. Limited previous evaluations of homocysteine levels in patients with heart failure have suggested that renal dysfunction may play a role in the pathogenesis of hyperhomocysteinemia, and we, in fact, found that to be true, as we noted that homocysteine levels correlated with serum creatinine. Our patients had creatinine and creatinine clearance values indicative of at least a mild degree of underlying renal insufficiency. Since renal dysfunction was present equally among the ischemic and the nonischemic patients, it could explain our finding of equally elevated homocysteine levels in each group of patients. Uremia is known to alter the metabolism of homocysteine and leads to elevations in plasma homocysteine independent of the degree of renal homocysteine excretion.⁵

A further implication of our data is the impact of high plasma homocysteine levels in patients with heart failure on the subsequent development of hyperhomocysteinemia following cardiac transplantation. Hyperhomocysteinemia is frequently present following cardiac transplantation and has been associated with coronary allograft vasculopathy, the leading cause of death after cardiac transplantation.⁶ Transplant patients are known to have impaired renal function and are therefore at high risk for the development of hyperhomocysteinemia. Heterozygous mutation of the methylenetetrahydrofolate reductase gene, a common genetic abnormality in Caucasians, has also been implicated in the development of hyperhomocysteinemia following cardiac transplantation.⁷ Many transplant cardiologists now consider homocysteine to be an important modifiable cardiac risk factor in their transplant population. Identification of patients with elevated plasma homocysteine prior to transplantation would likely assist in the management of the homocysteine levels post transplantation.

An alternative explanation for the finding of hyperhomocysteinemia in our patient population could be the presence of heart failure-related malnutrition. Cleland and others have described micronutrient deficiency in patients with heart failure, likely related to elevated central venous pressures and edema of the gastrointestinal tract with secondary malabsorption of micronutrients.⁸ In patients with heart failure and hyperhomocysteinemia, malabsorption of dietary folic acid and B vitamin intake could conceivably result in reduced serum levels of these nutrients and lead to elevated plasma homocysteine. Since we did not measure serum levels of folate, B₆, or B₁₂ in our patients, we cannot exclude deficiency of these nutrients as a cause for the elevated homocysteine levels observed. The mean body mass index for all patients was 26.9 ± 4.9 kg/m², however, and would not be consistent with a diagnosis of cachexia or malnutrition.

Limitations

Limitations of our study include its retrospective nature and the fact that serum levels of folic acid, vitamin B₆, and vitamin B₁₂ were not recorded along with the homocysteine level. We

therefore cannot exclude the presence of vitamin deficiency or malabsorption as a contributing factor to the homocysteine elevations noted. Blood samples of homocysteine were taken only once, thereby excluding the detection of diurnal or postprandial variations in the homocysteine level. There was a trend toward higher levels of homocysteine in the patients with ICM, and it is possible that a larger sample size might reveal a significant difference between the ICM and NICM groups.

Conclusion

Our data suggest that hyperhomocysteinemia is common in patients with severe heart failure and should be recognized as a cardiac risk factor. Patients with heart failure and documented hyperhomocysteinemia should be considered for therapy with folic acid since treatment is effective (we noted 28% reduction in homocysteine levels in our patients), inexpensive, without risk, and may lower the risk of adverse cardiac events. Patients with heart failure and impaired renal function, diabetes, or peripheral vascular disease should in particular be screened since the incidence of hyperhomocysteinemia in these patients appears to be quite high.

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Images in Cardiology: Partial Anomalous Pulmonary Venous Drainage in Adulthood

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A 54-year-old man with a history of aortic stenosis due to a bicuspid aortic valve underwent noninvasive cardiac assessment because of dyspnea. Despite echocardiographic evaluation, further imaging was felt necessary due to disproportionate dilatation of the right heart chambers. Further assessment was carried out with electrocardiographic-gated multislice computed tomography (CT). Three-dimensional CT reconstruction revealed a large right upper pulmonary vein (Fig. 1, arrow) draining directly into the superior vena cava (SVC). Magnetic resonance imaging provides diagnosis for this congenital abnormality, but does not have widespread availability. In contrast, multislice CT is readily available and complements existing imaging techniques elegantly.

Reference

Tan RS, Behr E, McKenna W, Mohiaddin R: Occult anomalous pulmonary venous drainage. The clinical value of cardiac magnetic resonance imaging. *Circulation* 2002;105:e27

FIG. 1 A large right upper pulmonary vein (arrow) is seen joining the superior vena cava (SVC) just proximal to the right atrium (AAo, ascending aorta; PT, pulmonary trunk).