Acquired Hyperhomocysteinemia in Heart Transplant Recipients

The etiology and clinical significance of hyperhomocysteinemia are under intense investigation. Although non-genetic (1) and genetic (2–4) factors influence plasma homocysteine concentrations, the etiology of moderate to severe hyperhomocysteinemia (15–50 μmol/L), commonly found in patients with coronary artery disease, cerebrovascular disease, peripheral vascular disease, and in patients with end-stage renal disease, is often unclear. The causes are likely to be multifactorial, involving both acquired and genetic components. There is strong evidence that hyperhomocysteinemia is an independent risk factor for cardiovascular disease (1, 5–7), but there are conflicting reports as well (8–10). Some individuals cannot afford to wait the several years it may take before definitive results are available from intervention studies. These include patients with end-stage renal disease, renal transplant recipients, and heart transplant recipients. Immediate treatment of their hyperhomocysteinemia may be more prudent.

Homocysteine is an easily modifiable risk factor that responds well to benign intervention strategies using water-soluble B complex vitamins (11–13). It is derived from methionine in a three-step pathway (14). Homocysteine may be cytotoxic, and low intracellular steady-state concentrations are maintained by remethylation back to methionine (to complete the cycle), conversion to cystathionine in the transsulfuration pathway, and export to the circulation. The transsulfuration pathway appears to be highly organ-specific (14), and the betaine-dependent remethylation pathway is found only in the liver and kidneys (15). The transsulfuration pathway requires pyridoxal phosphate (B₆), whereas the ubiquitous remethylation pathway requires pyridoxal phosphate (B₆), flavin adenine dinucleotide (B₂), cobalamin (B₁₂), and folate.

Nutritional deficiency is one of the causes of acquired hyperhomocysteinemia. Patients respond well to vitamin therapy and usually normalize total plasma homocysteine (tHcy)¹ within a few weeks after initiation of vitamin treatment (16). Unfortunately, undiagnosed B₁₂ and folate deficiencies appear to be prevalent in this country, particularly in the elderly (17), and in the original Framingham cohort, nearly 70% of the cases of hyperhomocysteinemia could be related to suboptimal B complex vitamin status (18).

A newly recognized form of acquired hyperhomocysteinemia is associated with heart transplantation (19–21). The first report on hyperhomocysteinemia in heart transplant recipients appeared in 1994 from Ambrosi et al. (19). Berger et al. (20) determined tHcy in 44 consecutive patients before, and 3, 6, and 12 months posttransplantation and found that mean tHcy increased 70% and remained high for up to 1 year. Gupta et al. (21) studied 189 heart transplant recipients and reported that 68% had hyperhomocysteinemia. In this issue, Cole et al. (22), studying a group of 72 cardiac transplant recipients, extend this work with a detailed analysis of determinants. The patients in their study all had tHcy concentrations above 15 μmol/L, the upper limit of the normal range. The mean time from transplant in this group was 3.95 ± 3.14 years, and the mean tHcy concentration was 25.4 ± 7.4 μmol/L. In a linear regression model, more than 50% of the variation in tHcy could be explained by four independent variables: time since transplant, serum creatinine, log serum folate, and trough whole blood cyclosporine concentrations. Cyclosporine was the strongest predictor of tHcy.

Berger et al. (20) reported lower plasma folate and B₁₂ values as well as reduced glomerular filtration rates in patients 3 months after transplant. Folate and B₁₂ deficiencies were found in 11% and 18%, respectively, of 106 patients in the study by Gupta et al. (21). These studies as a whole suggest that suboptimal B₁₂, folate, and B₆ contribute to increases in tHcy. Renal function may also play an important role because cyclosporine and other immunosuppressives are nephrotoxins.

Acquired hyperhomocysteinemia is associated with end-stage renal disease, as described nearly 20 years ago by Wilcken and Gupta in Australia (23). Patients with end-stage renal disease and renal transplant recipients are at high risk for developing occlusive arterial disease (24, 25). Numerous studies have documented mild to intermediate hyperhomocysteinemia in the majority of these patients (26, 27). Although impaired renal function is a major determinant of increased tHcy in end-stage renal disease and is probably an important determinant in organ transplant recipients, the mechanisms are complex. It is estimated that 55 μmol of homocysteine enters the circulation every hour (1.32 mmol/day) in healthy individuals, but that only 0.25 μmol/h (0.006 mmol/day) is excreted in the urine (28). Thus, if the kidney is to play a major role in homocysteine elimination, it must do so by metabolism. Indeed, Bostom et al. (29) have shown by arteriovenous difference that nondiseased rat kidneys remove ~20% of circulating homocysteine. By extrapolation they estimated that renal uptake and metabolism could account for ~70% of the daily elimination of tHcy in humans (27). However, van Guldener et al. (30) recently found no net arteriovenous differences in tHcy and “free homocysteine”, i.e., non-protein-bound homocysteine, in human subjects undergoing cardiac catheterization and suggested that the hyperhomocysteinemia of end-stage renal disease must be caused by impaired extrarenal metabolism. Gutfursen et al. (28) estimate that tHcy clearance is reduced by 70% in patients with chronic renal failure. It is well known that the failing kidney can

¹Total plasma homocysteine (tHcy) refers to the sum of the species of homocysteine components in plasma or serum. These include homocysteine with its sulfhydryl (–SH) group and oxidized forms with disulfide (–SS–) bonds. The latter include homocysteine, the homocysteine-cysteine mixed disulfide, and protein-bound homocysteine. Assays for tHcy utilize disulfide bond-reducing agents and thus determine both oxidized and reduced homocysteine.
drastically alter circulating concentrations of amino acids other than homocysteine (31). For example, arteriovenous studies show that nondiseased kidneys release serine into the circulation (~46% increase in concentration) (30), whereas in kidney failure the plasma serine concentration decreases ~50% (31). Serine is an essential amino acid substrate for both the remethylation and transsulfuration pathways of homocysteine metabolism. A reduction of intracellular serine concentration could impair homocysteine turnover and lead to greater export. However, in a study of four patients with end-stage renal disease, 3 or 4 g of serine taken daily for 1 week had no effect on tHcy (32).

In heart transplant recipients surviving beyond 1 year, cardiac allograft vasculopathy is the major cause of death (33). Both intramyocardial and epicardial arteries are affected by an unusually accelerated form of coronary disease. It is thought that vascular injury may be caused by adverse stimuli, not the least of which is an immunemediated attack on the allograft. Does homocysteine play a role? We do not know. However, Ambrosi et al. (34) recently reported that hyperhomocysteinemia is more frequent in heart transplant recipients with graft vasculopathy.

Should heart transplant recipients be routinely treated for hyperhomocysteinemia? On the basis of studies published to date, we know that 50–100% of these patients will develop hyperhomocysteinemia shortly after transplantation. A safe and effective treatment to normalize tHcy in most of these patients would be a daily cocktail of folic acid (1 mg), vitamin B_{12} (0.5 mg), and vitamin B_{6} (10 mg). Clearly the time is ripe for a clinical trial in heart transplant recipients, but can they afford to wait for the outcome?

References


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