EDITORIAL

Is homocysteine a mediator of atrial dysfunction or just another marker of endothelial dysfunction?

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This editorial refers to ‘Circulating homocysteine levels in patients with radiofrequency catheter ablation for atrial fibrillation’ by M. Shimano et al., on page 961

Atrial fibrillation (AF) is a common and increasingly prevalent arrhythmia that is associated with a significant increase in risk for stroke (five- to seven-fold) and mortality (~two-fold). Stroke risk is a primary concern in the management of AF patients. Structural factors contribute to increased stroke risk. Left atrial enlargement, reflecting either mitral regurgitation or impaired left ventricular (LV) function, promotes persistent AF as a result of increased area for re-entrant electrical activity. Left atrial enlargement and AF are associated with endocardial changes that lead to increased risk of left atrial thrombus formation, with the consequent increment in risk for thrombo-embolism and stroke, and thus is a strong predictor of a poor clinical prognosis.2

Left atrial enlargement occurs in response to LV dysfunction as a result of both haemodynamic influences and active remodelling of the atrial wall. Matrix metalloproteinases (MMPs) facilitate the disruption of collagen filaments that hold myocytes closely together. Several of the MMPs (MMP2, MMP9) are activated in response to oxidant stress. Left atrial enlargement and AF are associated with endocardial changes that lead to increased risk of left atrial thrombus formation, with the consequent increment in risk for thrombo-embolism and stroke, and thus is a strong predictor of a poor clinical prognosis.2

Homocysteine (Hcy) is an amino acid metabolite of cysteine or methionine; circulating Hcy levels are elevated in patients with coronary artery disease. Hyperhomocysteinaemia occurs under conditions of oxidant stress, and much of the circulating Hcy is oxidized and protein-bound, as a result of depletion of circulating reduced glutathione.6 In 2004, Marcucci et al.7 reported that patients with non-valvular AF had increased plasma Hcy levels, but did not probe the relationship between plasma Hcy levels and atrial dimensions. Shimano et al.8 presented a study in which they evaluated plasma levels of Hcy in a series of patients scheduled to undergo catheter ablation of AF. Their results confirm those of Marcucci et al., documenting a significant increase in plasma Hcy in the patients with persistent (but not paroxysmal) AF. Importantly, they also extend this analysis and show an impressive correlation between plasma Hcy levels and left atrial diameter. This is suggestive of a mechanistic link between Hcy and atrial MMP activity. The plasma collagen degradation peptide (CITP) data provided further supports this mechanistic association.

Remodelling of the extracellular matrix around atrial myocytes is an important step in the development of atrial arrhythmias in the setting of heart failure, facilitating conduction slowing and heterogeneity. Recent studies show that, subsequent to rapid ventricular pacing (resulting in increased left atrial dimension), there is a profound accumulation of extracellular matrix in the left atrium.9 In this setting of impaired LV function, it was the interstitial fibrosis, rather than the electrical remodelling that results from rapid atrial rates, that was the primary determinant of the duration of AF episodes.9

In characterizing their patient groups, Shimano et al. have provided an additional intriguing insight. They note a step-wise decrement in high-density lipoprotein (HDL) cholesterol levels from control to paroxysmal AF and to persistent AF, suggesting an inverse relationship between plasma HDL and Hcy levels. Paraoxonase 1 (PON-1) is an enzyme with putative antioxidant and cardioprotective properties; this enzyme binds to HDL particles.10 One Hcy metabolite, the thioester Hcy-thiolactone, can damage proteins by post-translationally modifying lysine residues.11 This modification has been suggested to contribute to Hcy-associated cardiovascular disease in humans. Paraoxonase 1 has Hcy thiolactonase (HTase) activity that can hydrolyse Hcy-thiolactone to Hcy. In the setting of low HDL levels, plasma PON-1 activity is likely reduced. On the basis of the existing data, it is impossible to determine causality; however, it is possible that the
elevated Hcy levels in the AF patients are related (via PON-1) to the low HDL levels.

The links between hyperhomocysteinaemia and endothelial dysfunction are clear and suggest that elevated Hcy may contribute to the increased stroke risk in patients with persistent AF. It is also likely that elevated Hcy levels contribute to atrial structural and perhaps electrical remodelling in AF. Here, Shimano et al. have documented a significant difference in the atrial size and in cardiovascular events in patients with elevated plasma Hcy levels. Unfortunately, recent efforts to treat hyperhomocysteinaemia using vitamin supplement (folate/B6) therapy have yielded little clinical benefit. Similarly, efforts to treat cardiovascular disease using antioxidant vitamins have been mostly unsuccessful. The lack of success using direct interventions suggests either that we still do not adequately appreciate the complexity of the underlying systems or that there is a great pharmacokinetic challenge in maintaining constant and appropriate plasma levels of these small molecules. Additional translational and fundamental studies are required to resolve this conundrum.

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References