

Homocysteine and Nighttime Blood Pressure Dipping—Is There a Connection?

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Increased plasma level of homocysteine is a risk factor for neural tube defects and has been associated with many noncommunicable diseases, including cardiovascular and cerebrovascular diseases, type 2 diabetes, and cancer.^{1–3} Homocysteine is a major independent biomarker for endothelial dysfunction, as it leads to an imbalance between blood endothelin-1 and nitric oxide levels, affects the proliferation of smooth muscle cells, and induces subclinical inflammation—thereby contributing to increased vascular endothelial damage and atherosclerosis in clinical patients.⁴ The role of homocysteine in endothelial dysfunction is thought to be mediated by mechanisms including oxidative stress, nuclear factor-kb activation, inflammation, and inhibition of endothelial nitric oxide synthase.⁵ It is also well documented that homocysteine is capable of triggering neuronal damage *via* oxidative stress, and may exert several functions as potential neurotransmitter.⁴ The contribution of homocysteine toward sympathetic nervous system activation is still controversial with animal studies suggesting that acute homocysteine administration does not lead to sympathetic activation,⁶ whereas others found that hyperhomocysteinemia did induce dysfunction of the autonomic system.⁷

Homocysteine is formed through demethylation of methionine, which donates a methyl group in many biochemical reactions. It is metabolized through 2 enzymatic pathways: trans-sulfuration and re-methylation. Homocysteine can be re-methylated to methionine through a vitamin B12-dependent reaction catalyzed by methionine synthase, in which 5-methyltetrahydrofolate donates the methyl group. In re-methylation, homocysteine typically receives a methyl group from 5-methyltetrahydrofolate (the main circulating form of folate in plasma) in a vitamin B12-dependent reaction, catalyzed by the enzyme methionine synthase. 5-Methyltetrahydrofolate is formed by the reduction of 5,10-methylenetetrahydrofolate, *via* the enzyme methylenetetrahydrofolate reductase (MTHFR).⁸ The TT

genotype of the MTHFR enzyme causes thermolability of the enzyme, reduces enzyme activity, and impairs the formation of 5-methyltetrahydrofolate, which might explain as to why the TT genotype is associated with increased homocysteine levels when folate status is relatively low.⁸

Elevated homocysteine levels and hypertension might act synergistically to increase the risk of stroke, compared with either condition alone.⁹ People of certain ethnic groups experience a disproportionately greater burden of cardiovascular diseases including coronary heart disease and stroke. For example, Chinese and Japanese exhibit consistently high rates of stroke but not coronary heart disease.¹⁰ China also lacks folic acid food fortification or the widespread use of folic acid supplementation. According to one national survey, approximately 75% of hypertensive adults were found to have elevated homocysteine levels (>10 $\mu\text{mol/l}$).¹¹ This necessitates further investigation into the interactions of homocysteine and hypertension in the Chinese population.

In this issue of the *American Journal of Hypertension*, Zhan *et al.*¹² investigate for the first time the cross-sectional relationship between homocysteine and circadian BP variation in an older Chinese cohort of hypertensive adults. While a recent study indicated a plausible relationship between homocysteine and circadian BP by demonstrating homocysteine-lowering intervention with folic acid therapy to decrease nocturnal systolic BP¹³; Zhan *et al.*¹² investigated this association in a hypertensive population-based study. A total of 493 hypertensives who were on BP-lowering medications underwent ABPM and were subclassified into dippers and nondippers. Fasted blood samples were used to determine plasma homocysteine by enzymatic methods using test kits. MTHFR C677T polymorphisms were detected using an ABI 7500 Real-Time PCR System using the TaqMan assay. The authors further subclassified participants into 390 hypertensive adults with CC/CT genotypes of MTHFR and 79 TT genotypes. Plasma homocysteine in nondippers was significantly higher than dippers (13.5 vs.

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12.3 $\mu\text{mol/l}$; $P < 0.001$). Simple linear analysis showed that homocysteine significantly correlated with nocturnal systolic ($r = -0.145$, $P = 0.001$) and diastolic BP fall ($r = -0.141$, $P = 0.002$). Multivariate logistic regression analysis further identified homocysteine as an independent factor which correlated with nondipping BP status in hypertensive adults (odds ratio: 1.873, 95% confidence interval: 1.171–2.996, $P = 0.009$). The percentage of dipping BP status was 19.4% or 8.8% and the percentage of nondipping BP status was 80.5% or 91.1% in CC/CT or TT genotypes, respectively, and the difference between CC/CT and TT genotypes was significant ($P = 0.024$). Collectively, these findings provide evidence that high homocysteine levels correlate with elevated nighttime blood pressures (BPs) in Chinese hypertensive adults. Of course, these observational and cross-sectional study findings will need to be confirmed in much larger prospective studies, to not only determine the feasibility of homocysteine-lowering intervention with folic acid therapy on a large-scale basis, but also to understand the variability across different population subgroups with different BP phenotypes, and the generalizability of such interventions across different populations. Nonetheless, they do shed light on the possible interactions between homocysteine and nighttime BP dipping.

The findings presented by Zhan *et al.* are noteworthy, particularly as homocysteine is associated with cardiovascular disease,⁴ especially stroke⁸ which is the leading cause of long-term disability in the United States.¹⁴ For now, however, the findings by Zhan *et al.* raise more questions than answers. First, what are the possible mechanisms through which homocysteine interacts with nighttime BP dipping within the different MTHFR genotypes? One would expect sympathetic nervous system activity to be involved in reduced nighttime BP dipping. Second, is there a dose–response relationship between lowering homocysteine levels by folic acid intake either through food fortification or medications and nighttime BP dipping? If so, which BP phenotypes and at what stage of hypertension would benefit the most from such an intervention? Third, does folic acid intake affect cardiovascular outcomes through mechanisms independent of homocysteine—due to its antioxidant properties? The answers to which need to be clarified in future studies.

In conclusion, in a cross-sectional study of hypertensive Chinese adults, a connection between homocysteine and nighttime BP dipping was found. This study potentially exposes a new target to treat nondipping nighttime BP patterns in hypertensive individuals. Further studies are needed to pin-point the physiological mechanisms for this observation, and to determine whether combined treatment consisting of antihypertensive medications and folic acid have

a greater beneficial effect when compared with that of anti-hypertensive medications alone in mitigating cardiovascular disease.

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