Obstructive sleep apnoea and plasma homocysteine

We read with interest the recent article by Svatikova et al., dealing with plasma homocysteine in obstructive sleep apnoea (OSA), and the accompanying editorial by Winnicki and Palatini. Although both referred to our 2001 paper on the same subject, our findings were not presented accurately. Similarly to Svatikova et al., we did not find any differences in morning levels of homocysteine between OSA patients and controls. More importantly, however, we did find a significant difference between a group of 49 OSA patients who also had ischaemic heart disease (IHD) and a group of 35 non-apnoeic patients with IHD. Sleep apnoea patients with IHD had significantly higher homocysteine levels (14.6 ± 6.77 vs. 11.92 ± 5.77 μmol/L, P < 0.03). This finding could not be accounted for by differences in age, body mass index, smoking, diabetes, medication, or a history of myocardial infarction. Moreover, in more than 50% of the patients with co-existence of OSA and IHD, homocysteine concentration was >15 μmol/L, a value shown to predict a 20% mortality within a 5-year period in IHD patients. We believe that this observation is of clinical significance.

A large body of evidence shows that endothelial function is impaired in hyperhomocysteinaemic individuals by depleting nitric oxide (NO) bioavailability. Several mechanisms were demonstrated to clarify this association, such as oxidative stress, and increased plasma asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor, in experimentally induced hyperhomocysteinaemia in humans.

Also, otherwise healthy OSA patients were found to have higher prevalence of endothelial dysfunction, reduced NO bioavailability and enhanced ADMA. It is therefore highly likely that in patients with both OSA and IHD, high homocysteine levels may further attenuate their a priori impaired endothelial function. This is further strengthened by the fact that homocysteine is a pro-oxidant molecule, therefore, hyperhomocysteinaemia in OSA with IHD may confer an added risk of mortality on top of the oxidative stress already conferred by the repeated apnoeic events. In addition, OSA patients free of cardiovascular morbidity were shown to have augmented oxidative stress that was apnoea-hypopnoea index-dependent, but more importantly, oxidative stress was further exacerbated in OSA patients with IHD. We were therefore gratified to read Winnicki and Palatini's conclusions that it is reasonable to assume that the sum of the effects of homocysteine and OSA on the cardiovascular system may be higher than the effects of each of these factors alone, which is in line with our own conclusion.

We would like also to add a note of caution in interpreting small- or large-scale observational studies on homocysteine in light of the fact that folate fortification in grain-based foods was implemented in the US in January 1998. Folate is a necessary cofactor in homocysteine metabolism and its deficiency increases circulating homocysteine levels. Several studies comparing the pre- to post-folate fortification era have clearly shown enhanced folate levels, and reduced homocysteine levels as well as a 30% decrease in the percentage of patients with high-risk homocysteine levels. This fact should be taken into account in any studies dealing with homocysteine and it’s implications for cardiovascular morbidity.

References


Lena Lavie
The Lloyd Rigler Sleep Apnea Research Laboratory
Unit of Anatomy and Cell Biology
The Bruce and Ruth Rappaport Faculty of Medicine
Technion Institute of Technology
Haifa 31096, Israel

Peretz Lavie
The Lloyd Rigler Sleep Apnea Research Laboratory
Unit of Anatomy and Cell Biology
The Bruce and Ruth Rappaport Faculty of Medicine
Technion Institute of Technology
Haifa, Israel

doip:10.1093/eurheartj/ehi486

Obstructive sleep apnoea and plasma homocysteine: reply

We very much appreciate the interest and constructive comments of Lavie and Lavie regarding our recent article on measurements of plasma homocysteine in otherwise healthy individuals with obstructive sleep apnoea. We are also very grateful for the kind and encouraging comments made in the thoughtful review by Winnicki and Palatini, which focused on our article as well as on the initial work on plasma homocysteine by Lavie et al. We have carefully reviewed all three articles and it seems...