



Does recurrent endogenous hypoxia protect the heart?

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Obstructive sleep apnea (OSA) is characterized by episodic airway obstruction resulting in intermittent hypoxia and disrupted sleep. The associated activation of the sympathetic nervous system may lead to acute blood pressure elevation and metabolic disturbances, including lipolysis and insulin resistance (1). Accordingly, OSA is associated with increased incidence of hypertension and type 2 diabetes, as well as with coronary artery disease (2-4). Moreover, OSA has been associated with subclinical myocardial injury, expressed as low-grade chronic elevation of circulating concentrations of cardiac troponin T (5,6) measured by high sensitivity assays. Whereas cardiac troponins measured with high sensitivity assays are closely related to the incidence of heart failure and cardiovascular death (7) in the general population and in patients with OSA, the relationship may be stronger in women than in men (8,9).

Experimentally induced intermittent hypoxia in animal and human myocardium models has been associated with reduced infarct size (10,11). Theoretically, a condition like OSA, which is characterized by repeated episodes of intermittent hypoxia, could therefore be associated with reduced myocardial injury. This was the underlying rationale for a study recently published in *Chest* by Sánchez-de-la-Torre *et al.* (12). The study compared peak troponin I concentrations in patients hospitalized with ACS in patients with and without OSA and report significantly lower peak troponin I levels in patients with OSA than those without OSA (12). The authors interpret these findings as an indication of reduced myocardial injury in patients with OSA, postulating that OSA has a cardio-protective effect

mediated by ischemic preconditioning.

This concept is interesting. Unfortunately, the study by Sánchez-de-la-Torre *et al.* has several limitations that need to be taken into account when interpreting the results. The patients included were participants in a randomized clinical trial of ACS patients with non-sleepy OSA. Study inclusion and exclusion criteria imply that patients included in a randomized clinical trial commonly are not representative of patients in general, and in this case exclusion of OSA patients with sleepiness suggest selection bias and lack of external validity. Moreover, the high proportion of patients (89 out of 127) with apnea-hyponea index (AHI) of 15 or greater, i.e., moderate to severe OSA, also suggests a strong selection bias. It remains unclear why not a higher number of patients included in the main trial were included in this substudy analysis and why 81 of 119 patients in the non-OSA group were randomly excluded from the statistical analysis.

Although the investigators observed significantly lower median peak troponin I concentration in the OSA *vs.* non-OSA group, the difference was not very robust ($P=0.04$), suggesting that the result could be a chance finding. When infarct size was estimated based on the area under the curve of serial troponin values, the difference was borderline significant ($P=0.049$). Moreover, when patients were categorized according to OSA severity, the association with estimated infarct size was not significant ($P=0.08$). The lack of a dose-response relationship does not strengthen the theory of a cardioprotective effect of OSA.

If OSA leads to a state of endogenous ischemic preconditioning that is clinically important, the prognosis of

OSA patients with ACS would be improved. Unfortunately, few studies have investigated in-hospital morbidity and mortality in ACS patients according to OSA status, but an unfavorable effect was demonstrated in a small study by Correia *et al.* (13). That investigation included 168 patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI). During the primary hospitalization 22 cardiovascular events occurred in the patients who had high probability of OSA according to the Berlin Questionnaire *vs.* none in the low-probability group (13), contradicting the hypothesis that the presence of OSA is beneficial during acute ischemic events.

However, the findings of Sánchez-de-la-Torre *et al.* are supported by a prior study measuring cardiac troponin T concentrations in patients with acute myocardial infarction (14). In that study 77% of patients had evidence of OSA, defined as an AHI of 5 or greater. In crude analysis, there was no significant difference in peak troponin T, although there was a significant association between OSA and lower peak cardiac troponin T levels in an adjusted multivariable model. Although these findings seem to suggest that OSA is associated with cardio-protection, drawing a firm conclusion based on these small studies may be premature. Both were cross sectional observational studies, suggesting that residual confounding and selection bias may represent problems, and none of them reported follow-up data. Moreover, patients with extensive coronary artery disease may more commonly suffer a NSTEMI than a STEMI. Supporting this, OSA patients had significantly more stents implanted than non-OSA patients in the study by Sánchez-de-la-Torre *et al.* This observation suggests that patients with OSA may have more extensive atherosclerosis, which again preferentially results in smaller infarctions.

The fact that the prevalence of NSTEMI *vs.* STEMI was different in the OSA compared to the non-OSA groups may also have confounded the results. Patients with STEMI typically have higher peak troponin values than patients with NSTEMI. Both studies included more patients with NSTEMI in the OSA group compared to in the non-OSA group [52.8% *vs.* 39.5% (12) and 61% *vs.* 41% (14)]. Although these differences were not statistically significant, it may have contributed to the lower peak troponin concentrations observed in the OSA group. Furthermore, the underlying assumptions that cardiac troponins represent an accurate index of infarct size in acute coronary syndrome patients with NSTEMI may not hold true. The correlation between cardiac troponin levels 12–24 hours after symptom onset and infarct size assessed by

cardiovascular magnetic resonance is primarily established in STEMI patients, and shown to be modest (15,16).

Despite the many limitations the studies raise an important and interesting question; is it likely that recurrent endogenous hypoxia is beneficial for the heart? Since Murry *et al.* published their reports more than 30 years ago showing that the size of myocardial infarction in dogs may be reduced due to ischemic preconditioning (17) the effect of ischemic preconditioning and potential therapeutically use of this procedure have been debated (10,11,18–20). Ischemic preconditioning is a general phenomenon that affects many organ systems including the heart, brain, kidney liver and lungs. Multiple small-scale studies have shown promising results when ischemic preconditioning has been performed before surgery (11), reflected in reduced postoperative troponin or creatinine kinase concentrations (21–23). However, recently the results of two large-scale multicenter, randomized, double-blind clinical trials of remote ischemic preconditioning before surgery were reported; no beneficial effect was observed for clinical endpoints, including postoperative troponin increase (19,20). The reason why the findings from experimental animal models are not translated into clinical benefit is yet not know. A limitation in both studies was the frequent use of propofol, an anesthetic agent that might reduce the effect of ischemic preconditioning (24). Also the effect of preconditioning is likely to be affected by age, gender, comorbidity and drugs used, all frequent conditions in patients with cardiac disease that may confound possible positive effects of preconditioning. Obviously, more studies are needed to clarify the clinical benefit both for exogenously and endogenously induced ischemic preconditioning.

In summary, the hypothesis that patients with OSA have smaller infarct size independently of infarct type remains unconfirmed, and must be tested in larger prospective studies of unselected patients with ACS using high sensitive troponin assays and including balanced patient groups regarding myocardial infarct type. Based on the current evidence, it remains unclear whether the recurrent endogenous hypoxia seen in OSA patients protects the heart.

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