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The Injury Theory, Endothelial Progenitors, and Sleep Apnea

Since the original views of the endothelium as a single-cell lining of the vascular tree, it has become apparent that such views are not only obsolete, but that the vascular endothelium is a complex, dynamic, and constantly changing surface that is locally and systemically responsive to a variety of stimuli. As a consequence of the unique biological repertoire of the endothelial cell, reprogramming will occur during exposures to stimuli such as those elicited by obstructive sleep apnea (OSA) or by acute myocardial infarction (AMI), and will ultimately generate an impressive array of responses aiming to maintain vascular homeostasis (1). According to the theory positing that atherosclerosis embodies a prototypic injury response (2), chronic exposure to cardiovascular risk factors, such as might occur in the context of OSA, will inevitably alter the regulatory functions of the endothelium, and progress toward proinflammatory activation and propagation, ultimately leading to endothelial cell senescence and apoptosis. As a consequence of such pathways, the endothelium will not only display altered functionality, but will also lose its integrity, and thus should be associated with worse outcomes during acute ischemic events prompted by vascular occlusion. The epidemiological data linking OSA to adverse cardiovascular outcomes would indeed support this view, such that treatment of OSA should ultimately be a viable mechanism to palliate this *a priori* inevitable course of events (3–6).

However, more detailed analyses of recent studies appear to raise some question marks, insinuating the concept that OSA may not be exclusively associated with activation of deleterious pathways. In fact, the repetitive exposure to intermittent hypoxia, which is a characteristic of OSA, could play a cardioprotective effect in ischemic heart disease. A meta-analysis of remote ischemic preconditioning in cardiac surgery, percutaneous coronary intervention, and vascular surgery showed that remote ischemic preconditioning reduced the incidence of periprocedural myocardial infarctions and the release of troponin (7). However, there was no evidence that this procedure reduced mortality associated with ischemic events or major adverse cardiovascular events (7). Moreover, remote ischemic conditioning studied during, instead of before, an evolving ST-elevation myocardial infarction was also effective in increasing myocardial salvage (8). In this contextual setting,

and specifically addressing cardiovascular disease in patients with OSA, Marin and colleagues initially pointed out that the global outcomes of AMI were not different in patients with and without OSA (9). Similarly, the risk of microvascular perfusion deficits after primary percutaneous coronary intervention was not affected by OSA (10), and the overall risk of hypertension or serious adverse cardiovascular events did not seem to be modified by continuous positive airway pressure treatment (11), or even by OSA itself (12). Interestingly, two very recent reports provide apparently conflicting results: whereas Correia and colleagues reported that the probability of OSA remained an independent predictor of events in patients admitted for non-ST-elevation myocardial infarction (13), Shah and collaborators showed that patients with OSA had less severe cardiac injury during a nonfatal AMI compared with patients without OSA (14).

How do we reconcile these *a priori* contradictory findings? In this issue of the *Journal*, Berger and colleagues (pp. 90–98) propose a different scenario, whereby patients with OSA are essentially better prepared to harness the recruitment of endothelial progenitor cells (EPCs) when an AMI comes knocking at the door (15). This is an emerging field aiming to investigate whether adult stem cells play a role in the protective/reparative responses to end-organ morbidities experienced by patients with OSA (16). Contrary to other adult stem cells that have been investigated only in animal models of OSA—that is, very small embryonic-like stem cells and mesenchymal stem cells—there is already available knowledge on how EPCs are activated and mobilized in patients with OSA (16). EPCs are a complex and heterogeneous group of cells that functionally and structurally show elements of vascular ontogeny and differentiation, and support endogenous angiogenesis. Based on their origin and differentiation spectrum, multiple adult cell types have been identified as possessing vascular progenitor potential (17), and some of these cells have already been used in interventional trials for AMI with increased likelihood for early-stage, rather than late-phase, favorable outcomes (18, 19). Berger and collaborators show that (1) in patients with OSA(+)-AMI, increased recruitment of EPCs and angiogenic T cells occurs compared with patients with OSA(–)-AMI; (2) plasma levels of stromal-derived factor-1 α (SDF-1 α), the major chemokine associated with migration and recruitment of EPCs from the bone marrow, were paradoxically inversely correlated with the EPC counts in OSA+AMI; and (3) exposure of EPCs from healthy subjects to

intermittent hypoxia *in vitro* for a short period of time leads to enhanced angiogenic proliferation and tube formation.

In adult patients with OSA, circulating EPCs are either low or normal (20, 21), whereas in children with OSA they are either low, in which case endothelial function is altered, or high, in which case endothelial function is preserved (22). However, it is well established that AMI or any other acute ischemic event will activate signaling cascades that ultimately trigger the activation, recruitment, and homing of EPCs (23). Thus, it would be conceivable that repetitive short ischemic events, which could trigger myocardial pre- or postconditioning, may have occurred in the context of the underlying OSA, and may have improved recruitment of EPCs to the circulation. Such a possibility, however, has not been confirmed by a recent study of patients with stent thrombosis-elevation myocardial infarction or in patients with preexisting angina prior to AMI (24, 25). Another possibility would be that the OSA(+)-AMI patients would have more extensive infarcts and reduced left ventricular ejection fraction, which would promote increased mobilization of EPCs (26), and yet such a possibility was negated by the authors, who reported that the infarct size was similar in the two groups. However, the time course of EPC response displays increases in EPC counts starting within a few hours of AMI, peaking at 5–7 days, and then decreasing to basal levels (27). Because a time course for EPCs, their subtypes (early vs. late outgrowth) and their specific vasculogenic properties was not undertaken, it is difficult to determine whether the time frames of EPCs in OSA(+)-AMI and OSA(–)-AMI indeed differ. Thus, the mechanisms underlying the putatively increased mobilization of EPCs reported herein among patients with OSA(+)-AMI remain unclear, particularly considering the paradoxically lower plasma levels of SDF-1 α . Could it be that SDF-1 α gradients will develop earlier in OSA during AMI? Could it be that the increased vascular endothelial growth factor immunoreactivity in monocytes of patients with OSA(+)-AMI is functionally more important for EPC-related angiogenic activity? The latter seems to be the case, particularly in the context of acute hypoxia, during which, similar to the findings reported by Berger and colleagues, reduced SDF-1 α also seems to occur (28). Would the AMI short-term and long-term outcomes be worse in patients with OSA if the repair mechanisms represented by increased EPC responses were not present?

In summary, there is no doubt that the provocative findings by Berger and collaborators have prompted a multitude of questions that definitely merit further exploration. In the interim, their message is that OSA seems to generate a constellation of processes that includes both increased long-term endothelial vulnerability and improved acute injury-related endothelial defenses.

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