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CROSSTALK

CrossTalk opposing view: Most cardiovascular diseases in sleep apnoea are not caused by sympathetic activation

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Abbreviations AngII, angiotensin II; ET-1, endothelin-1; HIF, hypoxia inducible factor; IH, intermittent hypoxia; NF-κB, nuclear factor-κB; NOS, nitric oxide synthase; OSAS, obstructive sleep apnoea syndrome; ROS, reactive oxygen species; RVLM, rostral ventrolateral medulla; SA, sympathetic activation.

Obstructive sleep apnoea syndrome (OSAS) is highly prevalent in adults and constitutes an independent risk factor for cardiovascular morbidities including arterial hypertension, coronary artery disease, heart failure and stroke (Somers *et al.* 2008). However, the underlying mechanisms are complex and not entirely understood. Earlier studies have mostly focused on sympathetic activation (SA) resulting from the apnoeic events during sleep. Increased SA was documented in OSAS during both sleep and wakefulness (Carlson *et al.* 1993). Sympathetic activation combined with the apnoeas-related swings in intrathoracic pressure were suggested to promote hypertension in OSAS (Somers *et al.* 2008). In recent years research has focused on intermittent hypoxia (IH)-related oxidative stress and concomitant inflammation. This was based on the notion that the recurrent nocturnal cycles of hypoxia–re-oxygenation are analogous to cycles of ischaemia–reperfusion, thus promoting increased reactive oxygen species (ROS) resulting in oxidative stress and tissue injury (Lavie, 2003).

A large body of evidence supports increased ROS/oxidative stress in OSAS. It was shown in leukocytes (Dyugovskaya *et al.* 2002), and in lipids and proteins of plasma, and could be moderated by treatment. Increased oxidative stress was also shown in animal models mimicking sleep apnoea (Lavie & Lavie, 2009).

Excess ROS affects the vasculature by directly and irreversibly damaging various bio-molecules, resulting in altered biological functions. ROS can also disrupt key signalling pathways in the arterial wall by promoting inflammatory/immune functions through nuclear factor-κB (NF-κB) activation and its downstream genes, namely, adhesion molecules and inflammatory cytokines (Lavie & Lavie, 2009). Up-regulated NF-κB (Htoo *et al.* 2006), adhesion molecules and inflammatory cytokines were noted in leukocytes as well as in plasma of OSAS patients (Lavie, 2003; Lavie & Lavie, 2009). Moreover, OSAS blood leukocytes and endothelial cells display an activated pro-inflammatory/pro-thrombotic phenotype with increased avidity and cytotoxicity towards endothelial cells (Dyugovskaya *et al.* 2002, 2003, 2008). Notably also, leukocytes from healthy subjects exposed to IH *in vitro,* which is devoid of SA, expressed a pro-inflammatory/pro-thrombotic phenotype (Dyugovskaya *et al.* 2002, 2008, 2011). Thus, the increased ROS in OSAS induces inflammation which in turn increases ROS formation, hence, creating a vicious cycle of oxidative stress/inflammation promoting endothelial dysfunction and atherosclerosis, and consequently cardiovascular sequelae (Lavie, 2003).

Which of the two pathophysiological mechanisms, sympathoexcitation or oxidative stress/inflammation, is the key player inducing most of the cardiovascular sequelae in OSAS? We argue that ROS/oxidative stress is the initiator and therefore mainly responsible for the cardiovascular morbidities. Our argument relies primarily on a large body of evidence demonstrating that increased ROS, produced in various tissues, induces SA and concomitant hypertension. Also, oxidative stress was shown to promote endothelial dysfunction and atherosclerosis. Additionally, oxidative stress is a prominent feature of co-morbidities which frequently aggregate with OSAS and may therefore amplify its cardiovascular impact.

Sympathetic activation is enhanced by oxidative stress and attenuated by antioxidants

The mechanisms by which oxidative stress induces SA and hypertension were primarily described in rodents using neuronal, renal and vascular tissues. Cumulative evidence implicated increased ROS production in the development of hypertension through increased sympathetic outflow in various autonomic

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brain nuclei (Datla & Griendling, 2010; Hirooka, 2011; Chan & Chan, 2012), and in cardiac-autonomic signalling (Danson & Paterson, 2006). Angiotensin II (AngII) is a potent stimulant for ROS formation. Its overproduction was shown to contribute to the development of hypertension and cardiovascular diseases through ROS. Systemic and direct infusion of AngII to the rostral ventrolateral medulla (RVLM) increases NADPH oxidase-dependent ROS production and hypertension. AngII also stimulates other ROS-generating systems such as xanthine-oxidase, uncoupled nitric oxide synthase (NOS) and mitochondria (Lee & Griendling, 2008). Selective deletion of superoxide dismutase-3 further increased the AngII-induced increase in heart rate, blood pressure, inflammatory leukocyte infiltration and vascular ROS (Lob *et al.* 2010). Additionally, inducible NOS-dependent ROS production in RVLM increased SA and blood pressure (Kimura *et al.* 2005). The antioxidant tempol, which decreased ROS in hypertensive rats, also decreased arterial pressure, heart rate and sympathetic nerve activity (Shokoji *et al.* 2003). Increased ROS mediated by endothelin-1 (ET-1) was also shown in sympathetic ganglia of hypertensive rats, indicating that a redox change in the environment of sympathetic ganglia may activate sympathetic neurons resulting in vasoconstriction and hypertension (Dai *et al.* 2004). Thus, both AngIIb and ET-1 were implicated in ROS formation accompanied by vasoconstriction and hypertension in rat vasculature. Importantly, similar findings were described in clinical studies showing increased ROS, decreased antioxidant enzyme activity and a preventive effect of antioxidants in hypertension, suggesting that enhanced oxidative stress is a risk factor for hypertension in humans (Abdilla *et al.* 2007; Lee & Griendling, 2008).

Oxidative stress was also shown to promote hypertension in animal models treated by chronic IH through increased ET-1 production. Tempol treatment prevented the increase in blood pressure, lowered oxidative stress and plasma ET-1 (Troncoso Brindeiro *et al.* 2007). Exposure to chronic IH also induced hypoxic sensing in rat adrenal medulla via increased ROS. This resulted in adrenal medulla catecholamine efflux, and elevated blood pressure and plasma catecholamines that were prevented by antioxidants (Kumar *et al.* 2006). Likewise, blood pressure, plasma noradrenaline, and oxidative stress markers were increased by chronic IH in wild-type mice and could be reversed by a potent antioxidant. In partially deficient hypoxia inducible factor (HIF)-1α mice, chronic IH did not increase blood pressure, noradrenaline, or oxidative stress, thus, implicating ROS and HIF-1α activation in the development of hypertension by IH (Peng *et al.* 2006). Also, carotid body sensitivity to oxygen levels in IH-treated mice required HIF-2α redox regulation to restore autonomic functions, and prevent hypertension and elevated plasma noradrenaline (Peng *et al.* 2011). Data from patients with OSAS are mostly in agreement with the animal studies. Both AngII and ET-1 were shown to increase in OSAS and were correlated with blood pressure (Moller *et al.* 2003). These findings suggest that in OSAS, oxidative stress could be one of the mediating factors between IH, AngII, ET-1 and hypertension.

Endothelial dysfunction and early signs of atherosclerosis

Endothelial dysfunction is a documented prognostic marker of atherosclerosis. It is greatly affected by oxidative stress that alters vascular function and tone and decreases nitric oxide bioavailability (Schulz *et al.* 2011), as was also noted in OSAS patients (Lavie *et al.* 2003). Severity dependent endothelial dysfunction is prevalent in normotensive OSAS patients (Kato *et al.* 2000) and is improved by vitamin C infusion (Grebe *et al.* 2006) or allopurinol treatment (El Solh *et al.* 2006), suggesting predominant involvement of oxidative stress. Moreover, an increase in oxidative stress markers as well as decreased endothelial NOS activity was directly shown in venous endothelial cells harvested from OSAS patients (Jelic *et al.* 2008). Additionally, early signs of atherosclerosis, such as increased pulse wave velocity, carotid diameter and intima-media thickness, were reported to be severity dependent in normotensive co-morbidity free OSAS patients (Drager *et al.* 2005).

Oxidative stress in aggregating co-morbidities

A great number of conditions and co-morbidities such as hypertension, insulin resistance, diabetes mellitus, hyperlipidaemia and endothelial dysfunction which promote cardiovascular morbidities through ROS-dependent mechanisms, also aggregate with OSAS. These may further exacerbate oxidative stress in OSAS (Lavie & Lavie, 2009).

In summary, although sympathoexcitation plays a major role in the cardiovascular sequelae of OSAS, it should be recognized that it is initiated in response to increased ROS formation and oxidative stress, resulting from the nightly occurrence of IH. Thus, OSAS-related ROS formation should be considered a novel therapeutic target for preventing cardiovascular morbidities in OSAS.

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