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Title	Cardiovascular sequelae of the sleep apnoea syndrome: sex, stress and therapeutic strategies.
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Publication date	2018-08-01
Original Citation	O'Halloran, K. D. (2019) 'Cardiovascular sequelae of the sleep apnoea syndrome: Sex, stress and therapeutic strategies', Acta Physiologica, 225(2), e13170 (3 pp). doi: 10.1111/apha.13170
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://onlinelibrary.wiley.com/doi/full/10.1111/apha.13170?af=R - 10.1111/apha.13170
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Download date	2026-11-15 17:28:26
Item downloaded from	https://hdl.handle.net/10468/9660



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Accepted Article

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Article type : Editorial

Cardiovascular sequelae of the sleep apnoea syndrome: sex, stress and therapeutic strategies

In this issue of *Acta Physiologica*, Ribon-Demars et al.[1] report that exogenous oestradiol administration mitigates vascular oxidative stress and elevated blood pressure in an ovariectomized rat model of sleep-disordered breathing. Sleep apnoea is a major public health issue. If untreated, it leads to premature death. Obstructive sleep apnoea, the most prevalent form of sleep-disordered breathing, is very common, but remains under-diagnosed. The underlying causes of disordered breathing during sleep[2] relate to aberrant airway anatomy as a primary driver, and additional physiological traits such as inadequate function and control of the upper airway muscles; increased likelihood of awakening during airway obstruction (low arousal threshold); and respiratory control instability (increased loop gain). Narrowing or occlusion of the upper airway arises from sleep-related reductions in the motor drive to the pharyngeal muscles, which are pivotal in the control of upper airway calibre and collapsibility. This natural state-dependent reduction in cranial nerve activity is problematic for a majority of sleep apnoea patients with at-risk i.e. narrow/collapsible airways. The Wisconsin Sleep Cohort Study[3] established prevalence estimates of moderate-to-severe sleep-disordered breathing at 10% (30-49-year-old men); 17% (50-70-year-old men); 3% (30-49-year-old women); and 9% (50-70 year-old women). Rather worryingly, the estimated prevalence rates have increased substantially over the last two decades, most likely a reflection of the growing obesity epidemic. Strikingly, the prevalence of sleep apnoea is much greater in men compared with women. However, progression through menopause is associated with greater severity of sleep-disordered breathing, independent of aging and changes in body habitus,[4] such that prevalence estimates are generally equivalent between post-menopausal women and age-matched males, revealing the critical influence of sex hormones in the propensity for the development of sleep apnoea.

The disruptive and harmful sequelae of the sleep apnoea syndrome can include excessive daytime sleepiness, neurocognitive impairments, metabolic dysregulation, and overt cardiovascular morbidity. Evidence points to a strong link between sleep apnoea and cardiac dysrhythmia, coronary artery disease, heart failure, vascular endothelial dysfunction, increased risk of stroke and vascular dementia, and most compellingly, hypertension[5], albeit with some reservations. Repeated occlusions of the upper airways evoke pressor responses and nocturnal hypertension. Strikingly, in many persons with sleep apnoea blood pressure is elevated during the daytime associated with persistent diurnal sympathetic nervous system over-activity. The reductions or cessations in pulmonary airflow

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apha.13170
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associated with periodic occlusions of the upper airways during sleep in apnoeic patients result in arterial blood gas derangements, seen clinically as episodic arterial blood deoxygenation followed by reoxygenation resulting from restoration of airflow. Thus, long-term exposure to chronic intermittent hypoxia (CIH) is a cardinal feature of the sleep apnoea syndrome, and is sufficient to cause symaptho-excitation and elevated blood pressure in human subjects and various animal models.

In the comprehensive and carefully-conducted studies by Ribon-Demars et al.,[1] adult female rats were exposed to normoxia or CIH, modelling mild sleep apnoea; subsets of rats within these two groups underwent sham surgery or were ovariectomized with subsequent chronic vehicle or chronic 17β oestradiol administration. Exposures to IH lasted 7 or 35 days allowing the comparison of responses in the period of the development of cardiovascular morbidity (days) and its relatively prolonged maintenance (weeks); outcomes which may depend on different driving mechanisms. Blood pressure, heart rate and plasma endothelin-1 levels (a potent vasoconstrictor) were determined, accompanied by assessments of thoracic aorta reactivity and oxidant status. The study design allowed for the consideration of important questions: What are the cardiovascular consequences of exposure to CIH over varying time domains in the presence and absence of ovarian steroid hormones? Does 17β oestradiol treatment ameliorate hypertension and vascular oxidative stress and dysfunction in ovariectomized rats during normoxia and CIH? This broad vista is a notable strength of the study---an important area of investigation in the context of cardiovascular risk in perimenopausal women with and without sleep-disordered breathing.

Exposure to IH raised blood pressure after 7 and 35 days in sham and ovariectomized rats; tachycardia and increased plasma endothelin-1 levels were evident during early hypoxic stress, but values were equivalent to respective control levels after several weeks' exposure. 17β oestradiol treatment ameliorated hypertension in IH exposed rats, but blood pressure remained elevated, a result of ovariectomy per se, which was not amenable to 17β oestradiol treatment. In rats exposed to 7 days of IH, replacement hormone treatment restored heart rate and peripheral endothelin-1 levels. In thoracic aorta samples, the activity of reactive oxygen species generating cytosolic oxidases (NADPH oxidase and xanthine oxidase) was elevated in ovariectomized rats after 7 days, both in normoxia and IH, with attendant increased protein oxidation indicative of oxidative stress. Interestingly, 17β oestradiol treatment reversed aortic oxidative stress in ovariectomized rats, but by mechanisms that differed in normoxic (normal pro-oxidant enzyme activities) and IH exposed animals (abrogated increased glutathione peroxidase activity together with increased catalase but not superoxide dismutase activity). Surprisingly, all measures of oxidant status were equivalent between all groups at 35 days. Contractile responses of aortic rings to phenylephrine were blunted in short-term IH exposed sham but not ovariectomized rats; 17β oestradiol treatment led to potentiated contractile responses to alpha-adrenergic stimulation with phenylephrine. Assessment of vascular relaxation revealed slightly blunted responses to acetylcholine (endothelium-dependent), but not sodium nitroprusside (endothelium-independent), in ovariectomized rats exposed to short-term IH, which was amenable to 17β oestradiol treatment. Vascular reactivity was similar in all groups at 35 days, mirroring the consistency in aortic oxidant:antioxidant status parameters at this time point.

The study by Ribon-Demars et al.[1] illustrates that modest IH evokes hypertension in female rats, with no sex advantage or protection as is commonly observed in other forms of experimentally-induced hypertension. 17β oestradiol treatment ameliorates IH-induced hypertension, which most likely relates to recovery of IH-induced enhanced chemoreflex activation of sympathetic outflow as shown previously by this group[6]. Of note, blood pressure was elevated by ovariectomy per se, and

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unresponsive to 17β oestradiol treatment suggesting an alternative underlying mechanism of action. Of interest, short-term IH evoked only modest vascular oxidative stress and aortic dysfunction, which was fully resolved following long-term IH exposure, which differs from observations of aortic and arteriolar stress and dysfunction in male rats, revealing sex differences that are independent of the prevailing hormonal status. It appears that female vascular tissue is relatively tolerant of IH, which may relate to oestrogen-oestrogen receptor axis signalling and intrinsic resilience in female peripheral vascular tissues, similar to observations in skeletal muscle[7]. Nevertheless, ovariectomy provokes oxidative stress in the acute phase in normoxia revealing the antioxidant properties of ovarian hormones in vascular tissues. Altogether, fascinating stuff but not for the faint-hearted!

The authors acknowledge several limitations of the study, principally the biochemical and physiological assessment of a major conduit artery and not skeletal muscle resistance arterioles that predominantly contribute to arterial blood pressure regulation. Indeed, the observations of Ribon-Demars et al.[1] may have greater relevance to sleep-disordered breathing in the perimenopausal period and risk for aortic disease and/or aortic stiffness. Further work is required to confirm or otherwise in various vascular beds whether there are differences in female resistance arteriole reactivity following exposures to IH in the presence and absence of ovarian hormones compared with males. The potential influence of age and other morbid burdens is worthy of pursuit. Whilst we eagerly await the outcomes of those and other potential avenues of exploration, the elegant work of Ribon-Demars et al.[1] should provoke further debate of the potential therapeutic benefit of hormone replacement therapy (or perhaps other antioxidant strategies) in mitigating cardiovascular risk in menopausal women.

CONFLICT OF INTEREST

None.

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References

1. Ribon-Demars A, Pialoux V, Boreau A, et al. Protective roles of estradiol against vascular oxidative stress in ovariectomized female rats exposed to normoxia or intermittent hypoxia. *Acta Physiol (Oxf.)*. 2018; DOI: 10.1111/apha.13159.

2. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. *Sleep Med Rev*. 2018;37:45-59.

3. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177:1006-1014.

This article is protected by copyright. All rights reserved.

4. Mirer AG, Young T, Palta M, Benca RM, Rasmuson A, Peppard PE. Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study. *Menopause*. 2017;24:157-162.

5. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: Types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;69(7):841-858.

6. Laouafa S, Ribon-Demars A, Marcouiller F, et al. Estradiol protects against cardiorespiratory dysfunctions and oxidative stress in intermittent hypoxia. *Sleep*. 2017;40(8).

7. O'Halloran KD, Lewis P, McDonald F. Sex, stress and sleep apnoea: Decreased susceptibility to upper airway muscle dysfunction following intermittent hypoxia in females. *Respir Physiol Neurobiol*. 2017;245:76-82.

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