Obstructive sleep apnoea: from respiratory events to coronary microvascular dysfunction

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Current opinion about the mechanisms and inter-relationships of ischaemic heart disease and obstructive sleep apnoea

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ABSTRACT

Obstructive sleep apnoea (OSA) is an emerging and independent risk factor for cardiovascular diseases; coronary artery disease (CAD) is higher in OSA patients, even in the absence of other traditional cardiovascular risk factors. There is little evidence to show abnormalities in coronary blood flow (CBF) and disorders in coronary vascular resistance (CVR), occurring during the obstructive respiratory event, suggesting coronary microvascular dysfunction (CMD) as a potential mechanism of ischaemic heart disease (IHD) OSA-as a related consequence.

Introduction

OSA is a common sleep-disordered breathing condition frequently found in the general population [1] and more frequently in cardiovascular patients [2–6]. OSA seems to be strongly related to CAD, its prevalence is very high in coronary patients [7,8] and negatively affects short- [9] and long-term [10] prognoses following the acute phase of IHD.

Nowadays, evidence supports OSA as being an independent risk factor for CAD [11], and, in this context, its presence seems to exacerbate nocturnal ischaemic events (both chest pain and ST-segment modifications), that occur mainly in the early morning (5.00–7.00 a.m.) [12]; furthermore, CBF response to the increased myocardial O_2 demand seems to be impaired, probably due to an increase in CVR following the obstructive respiratory event [13]. Accordingly, the AHI has been demonstrated as being an independent, strong predictive factor of impaired CFR [14]. In this paper, we wish to suggest the hypothesis that OSA-related underlying mechanisms of IHD may be associated with coronary microvascular disease, focussing the attention on the role of coronary microvascular function and its disorder found in OSA condition.

Basic concepts

Inflammation

The inflammatory state seems to play a key role in the setting of vascular abnormalities, associated with systemic dependent and independent endothelial dysfunction [15].

Where myocardial perfusion is concerned, chronic low-grades of CRP are negatively associated with an impaired CFR, supporting the role of inflammation in the pathophysiology of CMD [16].

Serum levels of CRP [17], TNFα, IL-6, IL-8 [18] are elevated in patients with OSA, and evidence supports chronic inflammation as a cardiovascular risk factor [19], resulting in CMD that is, in turn, an early marker of coronary atherosclerosis [20].

Myogenic response of cardiac smooth muscle cells (SMCs) to transmural pressure variations

Coronary vascular tone is regulated by a number of pathways, as largely explained in a recent review: endothelial mechanisms, metabolic regulation, autonomic nerves circulating hormones and myogenic
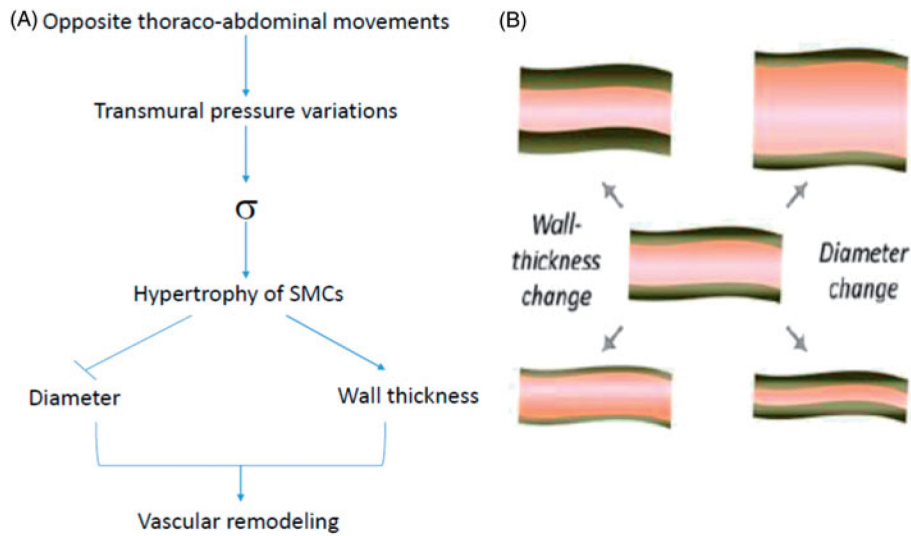
Figure 1. Possible mechanisms of vascular adaptation of coronary arterioles to obstructive respiratory events. (A) Transmural pressure variations are responsible for increase in circumferential wall stress (σ) that could lead to hypertrophy of smooth muscle cells (SMCs) and thus, changes in wall thickness and vascular remodelling. (B) Schematic illustration of changing of wall thickness and diameter leading to vascular remodelling. Modified from [21].

response [21]. The latter is the behaviour of blood vessels reacting to pressure elevations with vasoconstriction and to pressure reductions with vasodilatation, in order to establish vascular basal tone, to keep the blood flow constant and to regulate the capillary hydrostatic pressure [22].

The circumferential wall stress on left ventricle due to intermittent but chronic transmural pressure variations as a consequence of obstructive events could be responsible for hypertrophy of smooth muscles cells (SMCs), wall thickness and diameter changes and, at least, for structural remodelling of vessels [21,22] (Figure 1).

The persistent changes in circumferential wall stress drive to long-term vascular adaptation, mainly of the small arteries, and thus, to alterations in flow resistance and perfusion.

Vascular adaptation as a consequence of the inflammatory state, SMCs and endothelial dysfunction could explain alterations in myocardial perfusion observed in OSA patients by affecting coronary microvascular functions.

Coronary microvascular dysfunction

The term coronary microcirculation identifies two of the three compartments of coronary arterial system, including pre-arterioles (100–500 μm) and arterioles (<100 μm), the role of which is to maintain an adequate myocardial perfusion in order to assure a correct contractility function [23]. Functional and/or structural abnormalities of this compartment are referred to as CMD, in order to describe abnormalities in the regulation of myocardial blood flow and perfusion.

Nonetheless, CMD plays a key role in the pathogenesis of myocardial ischaemic disease, as an additional mechanism to the obstructive disease of epicardial coronary arteries [24,25]. Clinical and pathogenetic classifications of CMD were originally proposed by Camici and Crea in a recent review [25] (Table 1).

Vascular remodelling and endothelial dysfunction are the final common pathway of traditional cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidaemia), in which condition a reduction of CFR can be found [23]. CMD derived from different mechanisms, as illustrated in Table 2.

Structural (vascular remodelling), functional (endothelial dysfunction, dysfunction of smooth muscle cells) and extravascular (extramural compressions) changes are found in OSA condition, and could possibly explain its role as an independent cardiovascular risk factor.

Clinical implications

Abnormalities of coronary blood flow (CBF) and coronary flow reserve (CFR) occurring during obstructive respiratory events

During an obstructive apnoeic event, several haemodynamic changes in myocardial flow occur. During an apnoeic event, a transient mismatch between CBF and myocardial work, it is suggested, may occur [13]: in particular, an abnormal delay in CBF rise compared to the rise in RPP and thus, myocardial energy demand,

Table 1. Classification of coronary microvascular dysfunction.

Type 1: In the absence of myocardial disease and obstructive CAD	Risk factors	Endothelial dysfunction
	Microvascular angina	SMC dysfunction
		Vascular remodelling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy	Vascular remodelling
	Dilated cardiomyopathy	SMC dysfunction
	Anderson-Fabry's disease	Extramural compression
	Amyloidosis	Luminal obstruction
	Myocarditis	
	Aortic stenosis	
Type 3: in obstructive CAD	Stable angina	Endothelial dysfunction
	Acute coronary syndrome	SMC dysfunction
		Luminal obstruction
Type 4: iatrogenic	PCI	Luminal obstruction
	Coronary artery grafting	Autonomic dysfunction

CAD: coronary artery diseases; SMC: smooth muscle cells; PCI: percutaneous coronary intervention. Modified from [25].

Table 2. Pathogenetic mechanisms of coronary microvascular dysfunction.

Alterations	Causes
Structural	
Luminal obstruction	Microembolisation in acute coronary syndrome or after recanalisation
Vascular-wall infiltration	Infiltrative heart disease (e.g. Anderson-Fabry's cardiomyopathy)
Vascular remodelling	Hypertrophic cardiomyopathy, arterial hypertension, OSA
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidaemia, diabetes, OSA
Dysfunction of smooth muscle cells	Hypertrophic cardiomyopathy, arterial hypertension, OSA
Autonomic dysfunction	Coronary recanalisation
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension, OSA
Reduction in diastolic perfusion time	Aortic stenosis

Modified from [23].

has been observed (Figure 2). This inadequate response of CBF to myocardial work is more enhanced in case of obstructive rather than central apnoea: in OSA condition, the subsequent rise of CBF slope does not increase at the same rate as RPP one, contrary to CSA events. This difference between the two type of SDB could be explained by the increase in CVR following the obstructive event as seen in panel B of Figure 2, which is not significant in case of central events (Figure 2(D)).

This abnormal response of CVR could be the consequences of transient but repetitive vascular tone changes following the apnoeic event, secondary to the LV wall stress due to the increased intrathoracic pressures.

The main factors regulating CBF are the gradient pressure (ΔP) originating within the coronary arteries and the left ventricle at the end of the diastolic phase (ΔP = diastolic pressure in aorta – LV end diastolic pressure) and CVR.

During the apnoeic event, both LV compliance and LV end-diastolic volume decrease as consequence of increased venous return due to the enhanced negative intrathoracic pressure; this could lead to an increase in the LV end-diastolic pressure, in a reduction in the coronary ΔP and thus CBF, partially explaining its inappropriateness to the increased myocardial work occurring throughout the obstructive apnoea. If we carefully focus our attention on CSA, the generation of negative intrathoracic pressure is less exaggerated than that observed in OSA [26], may be resulting in a more adequate response of CBF to myocardial energy demand (Figure 2(C)).

Nevertheless, this impairment of CBF could also be the consequence of an increase in CVR, as explained above (Figure 2(B)). The abnormal rise of CVR is responsible for a reduction in CBF at maximal vasodilation, resulting in a dysfunction of coronary flow reserve (CFR = CBF at maximal vasodilation/CBF at rest). Accordingly, Wang et al. showed an inverse relationship between CFR and the severity of OSA in patients affected with cardiac syndrome X (CSX) and an increased chance of having low CFR as the AHI rises [14].

In the same study, AHI emerges as a strong, independent predictor of impaired CFR and, in turn, correlates to coronary microvascular dysfunction.
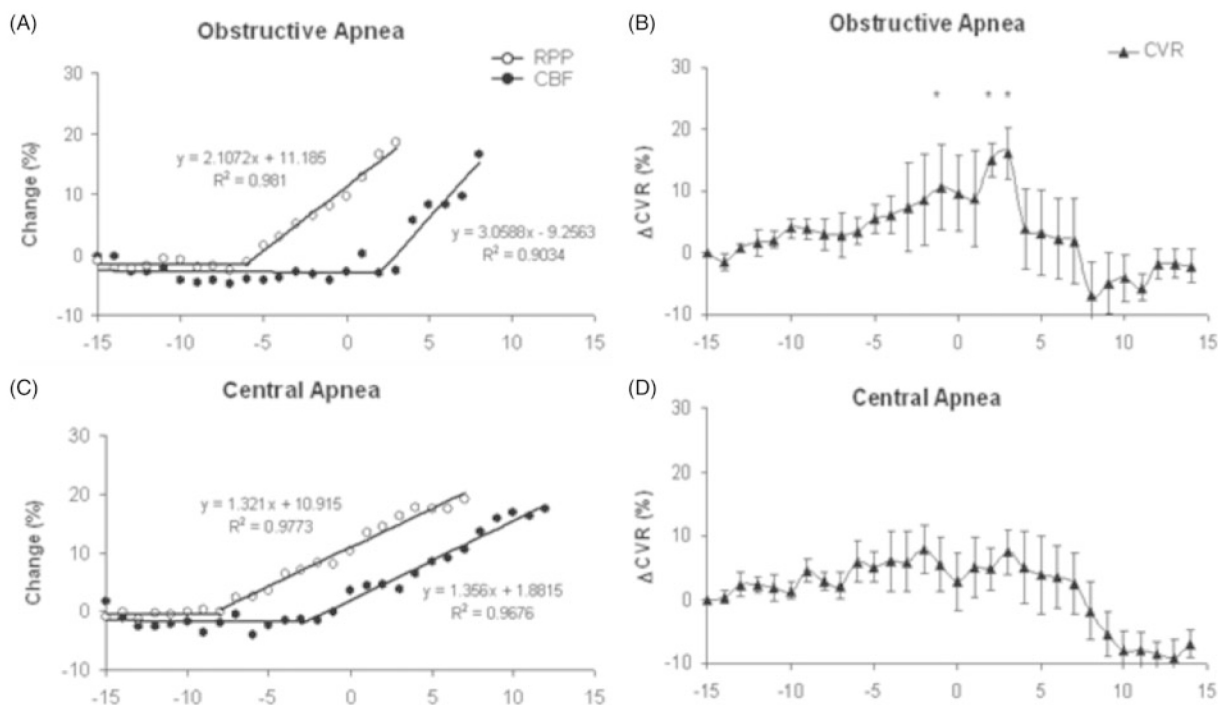
Figure 2. (A) Coronary blood flow (CBF) rise is delayed compared with in myocardial work energy demand, expressed by rate-pressure product (RPP). (B) Coronary vascular resistance (CVR) increases at the end of obstructive apnoea and this could explain the impairment of CBF response to myocardial work. On the other hand, during the central apnoeic event, the belated rise of CBF is less enhanced (C) as well as the increase in CVR (D). Modified from [13]. CBF: coronary blood flow; CVR: coronary vascular resistance; RPP: rate-pressure product.
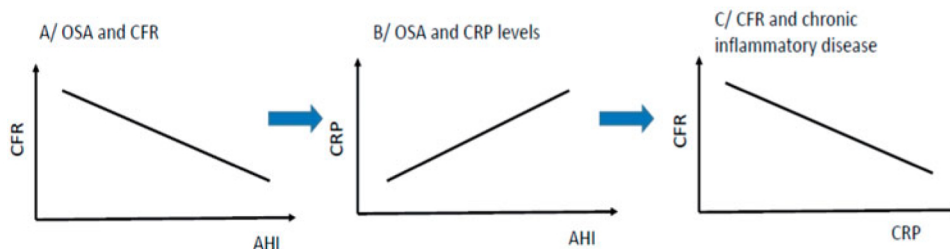

Figure 3. Obstructive sleep apnoea (OSA) could be considered a chronic inflammatory disease. High levels of C-reactive protein (CRP), as well as high apnoea-hypopnoea index (AHI) values, are inversely associated to low coronary flow reserve (CFR) (panels A and C). Nonetheless, greater AHI values are associated with high CRP levels (panel B). Panel A: modified from [14]; Panel B: modified from [17]; Panel C: modified from [16]. AHI: apnoea-hypopnoea index; CFR: coronary flow reserve; CRP: C-reactive protein; OSA: obstructive sleep apnoea.

Possible mechanisms linking OSA to CMD, expressed as an impaired CFR, could be the inflammatory state and the mechanical stress on LV wall, secondary to exaggerated negative intrathoracic pressure with both phenomena paving the way to vascular remodelling.

High levels of CRP are linked to lower CFR as well [16]: in OSA condition, there are high plasma levels of CRP [17] so that inflammation may be responsible for the impairment of CFR observed in OSA state. This could also apply to other chronic inflammatory diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [20] (Figure 3).

To summarise, CMD can reasonably be proposed as an underlying mechanism linking OSA to ischaemic heart disease. This disorder in coronary resistance vessels could be the consequence of vascular remodelling of pre-arterioles and arterioles of coronary arterial system, resulting from the interaction of different mechanisms, as set out in Figure 4.

Conclusions

Increasingly, OSA is considered as an emerging risk factor for coronary artery diseases; the underlying mechanism remains unclear. Even though the frequent
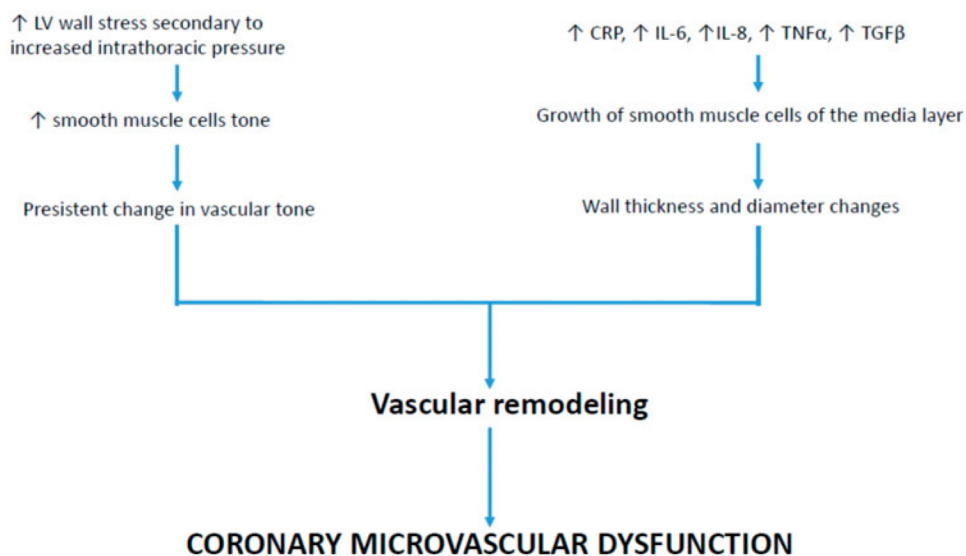
Figure 4. Possible multiple mechanisms explaining vascular remodelling of small artery vessels in myocardial muscle, leading to microvascular dysfunction. The increased LV wall stress due to intrathoracic negative pressure is a strong stimulus to vascular tone changing, mainly caused by the myogenic response; the persistent increased vascular tone drives long-term vascular adaptation by structural remodelling. The increased release of cytokines due to the abnormal inflammatory state, can induce local production of growth factors, such as TGFβ, that stimulates smooth muscle cells of the media layer to proliferation; all these abnormalities pave the way to vascular remodelling and thus, to coronary microvascular dysfunction.

co-existence of traditional cardiovascular risk factors, which often muddle the direct cause–effect relationships, interestingly, there is little evidence to show the emergence of ischaemic heart disease, from cardiac syndrome X to acute coronary syndrome, in apnoeaic, but otherwise healthy people. Microvascular coronary dysfunction may be suggested as a potential mechanism of OSA-related IHD; making this syndrome an independent cardiovascular risk factor.

Disclosure statement

No potential conflict of interest was reported by the authors.

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