Leukotrienes as a molecular link between obstructive sleep apnoea and atherosclerosis

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Abstract

Leukotrienes are biologically active lipid mediators of inflammation involved in atherogenesis. Obstructive sleep apnoea (OSA) patients exhibit early atherosclerosis and activation of the leukotriene pathway. In OSA patients, the production of leukotrienes is increased in relation to OSA severity and in vitro exposure of immune cells to intermittent hypoxia increases leukotriene pathway transcription. Moreover, the leukotriene transcriptional pathway is associated with early vascular remodelling. Lastly, obesity is a major confounding factor for leukotriene activation in OSA. The aim of this review was to focus on the intricate network of leukotrienes, chronic intermittent hypoxia, and atherosclerosis, with an emphasis on the role of leukotrienes in the early atherosclerosis observed in OSA patients.

Keywords

Leukotrienes • Intermittent hypoxia • Obesity • Atherosclerosis

1. Introduction

Obstructive sleep apnoea (OSA) is a worldwide public health problem with a prevalence estimated between 5 and 20% of the general population. OSA is characterized by recurrent episodes of partial or complete upper airway obstruction occurring during the sleep, leading to chronic intermittent hypoxia which harms the cardiovascular system. OSA is associated with an increased prevalence of fatal and non-fatal cardiovascular events and is an independent risk factor for death from any cause. Among the intermediary mechanisms that could explain the link between OSA and cardiovascular morbidity, the role of early atherosclerosis has been proposed since 1990 after adjustment for confounding factors, OSA per se is associated with atherosclerosis. In addition, the intensity of the vascular remodelling is more specifically related to the amount of nocturnal oxygen desaturation. Lastly, 4 months of continuous positive airway pressure (CPAP) application seems sufficient to partly reverse early atherosclerosis, confirming the link between OSA-related chronic intermittent hypoxia and atherosclerosis.

It is well established that atherosclerosis is an inflammatory disease, thus the mechanistic links between OSA and atherosclerosis could likely be mediated by inflammatory processes induced by chronic intermittent hypoxia. Among several potential inflammatory mediators involved, leukotrienes (LTs) have been described to play a major role in the onset and the progression of atherosclerosis. LTs are lipid mediators derived from arachidonic acid liberated from cell membrane phospholipids by cytosolic phospholipase A2. On activation of the enzyme 5-lipoxygenase (5-LO), which interacts with nuclear membrane-bound 5-LO-activating protein (FLAP), arachidonic acid is converted to leukotriene A4 (LTA4) in inflammatory cells (Figure 1). In polymorphonuclear neutrophil granulocytes (PMNs) and in monocytes/macrophages, LTA4 is converted by LTA4 hydrolase (LTA4H) into LTB4 which modulates transcription, or is secreted to partly reverse early atherosclerosis, confirming the link between OSA-associated inflammation. Based on an increased urinary excretion of LTE4 and increased LT concentration in exhaled breath condensate from OSA provide evidence for the contribution of the LT pathway in OSA-associated inflammation. Based on an understanding of the role of leukotrienes in OSA-related inflammation, this review was to focus on the intricate network of leukotrienes, chronic intermittent hypoxia, and atherosclerosis, with an emphasis on the role of leukotrienes in the early atherosclerosis observed in OSA patients.

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2. LT pathway activation in relation to intermittent hypoxia

The activation of the LT pathway by intermittent hypoxia has been suggested by both experimental and clinical studies. In OSA patients, the mean SaO2 and the percentage of time spent with SaO2 < 90% are important determinants of increased neutrophil LTB4 production. These data suggested that intermittent hypoxia, leading to oxygen desaturation, may play a major role to increase LTB4. The desaturation-re-oxygenation sequence, that is a typical for the majority of respiratory events in OSA patients, leads to an oxidative/nitrosative stress with production of reactive oxygen species and reactive nitrogen species. The increased levels of reactive oxygen species contribute to generate adhesion molecules, to activate leukocytes, and to produce systemic inflammation. Since 5-LO activity is regulated by the cellular redox status and reactive oxygen species, the increased production of reactive species in leukocytes from OSA patients could contribute to the activation of the LT pathway in OSA. Moreover, in vitro exposure of either PMNs or monocyte THP-1 cells to intermittent hypoxia leads to an increase in LTB4 production. These observations suggest that the intermittent hypoxia associated with OSA may induce a systemic activation of immune cells, which potentially could participate in an accelerated atherosclerosis. These observations are supported by studies in animal models for other diseases, such as second organ ischaemia-reperfusion injury of the lung, which enhances the production of LTB4 in vivo. Enhancement of arachidonic acid release through increased phospholipase activity has also been implicated in other pathological conditions related to hypoxia, such as hypoxic pulmonary vasoconstriction. In addition, an up-regulation of the mRNA levels of the LT pathway components has been reported in leucocytes and endothelial cells exposed to hypoxia. Indeed, in vitro exposure of PMNs to intermittent hypoxia (four cycles of 35 min hypoxia followed by 25 min re-oxygenation) induces increased FLAP and LTA4H mRNA compared with normoxic conditions. Similar results were obtained in a study on monocyte THP-1 cells, in which longer intermittent hypoxia in vitro also increased expression levels of LTB4 synthesizing enzymes. Lastly, a recent study in apolipoprotein E (ApoE-/-) mice demonstrated that acute bouts of hypoxia increased LTC4S and CysLT1 receptor mRNA levels in the myocardium. Although the pathways involved in the up-regulation of LT synthesizing enzyme mRNA levels by intermittent hypoxia remain to be established, severe hypoxic conditions in vitro enhance FLAP mRNA as well as a number of other proteins regulated by HIF-1α.

Figure 1: The biosynthesis of LTs and LT receptors. LT synthesizing enzymes are depicted in shaded rectangles, whereas open rectangles indicate the LT receptor subclasses. FLAP, 5-lipoxygenase activating protein; GT, glutamyl transferase; LO, lipoxygenase; LT, leukotriene; LTC4S, leukotriene C4 synthase; LTA4H, leukotriene A4 hydrolase.
Leukotrienes and atherosclerosis in sleep apnoea

expression is regulated by HIF-1α and NF-κB which activate transcription of FLAP after binding to hypoxia-response elements and NF-κB-binding motif in the FLAP promoter.34

Although these observations suggest that intermittent hypoxia directly participates to LT pathway activation in OSA, in vitro experiments may not completely mimic the repetitive desaturation-re-oxygenation sequences in OSA. However, the proof of concept for this suggestion has been obtained through studies of cells isolated from subjects with OSA. In summary, PMNs derived from OSA patients exhibit increased production of LTB₄ compared with those derived from controls when challenged by the calcium ionophore A23187 ex vivo.20,21 In the initial study including only cardiovascular disease-free OSA patients, LTB₄ production by stimulated PMNs was significantly correlated to the main parameters evaluating hypoxia severity, including mean nocturnal SaO₂, minimal nocturnal SaO₂, percentage of total sleep time spent with SaO₂ < 90% and apnoea–hypopnoea index (AHI).20,21 These findings have subsequently been extended to a larger cohort of OSA patients presenting cardiovascular comorbidities as seen in clinical practice.21

In the latter study, A23187-induced LTB₄ production was enhanced in PMNs derived from severe OSA patients (AHI > 30) and correlated with AHI and percentage of total sleep time with SaO₂ < 90%.21 Interestingly, the enhanced production of LTB₄ in PMNs derived from OSA patients was associated with a significant increase in FLAP mRNA and protein levels, with a major contributing role of chronic intermittent hypoxia as suggested by the significant association of FLAP expression with an AHI.21 Taken together, these studies suggest that intermittent hypoxia, leading to oxygen desaturation, may play a major role in the increased LT production evidenced in OSA patients, and that transcriptional activation in leucocytes may be a determinative mechanism in the up-regulation induced by chronic intermittent hypoxia.

3. LTB₄ in OSA in relation to measures of atherosclerosis

Importantly, calcium ionophore-induced LTB₄ production in PMNs correlates with systolic and diastolic carotid diameters in severe hypoxic OSA patients without a medical history of cardiovascular disease, suggesting a link between LTB₄ and subclinical atherosclerosis in the form of vascular remodelling.20 Also in this respect, the transcriptional regulation of the LTB₄ pathway may be directly involved, as suggested by the significant correlations between PMN mRNA and protein levels for FLAP with the mean carotid luminal diameter and mean intima-media thickness of common carotid arteries.21 Similarly, PMN 5-LO mRNA was associated with carotid luminal diameter and intima-media thickness.21 Furthermore, 5-LO mRNA levels are greater in PMNs derived from subjects with atherosclerotic plaques vs. those without plaque and higher in patients with carotid wall hypertrophy.21 Finally, LTA₄H protein in PMNs is associated with right carotid luminal diameter and left intima-media thickness.21

4. Mechanisms of LT signalling in OSA-associated atherosclerosis

The increased LTB₄ production in OSA20,21 in combination with the potent effects of LTB₄ as an activating and chemoattractant factor for leucocytes, and vascular smooth muscle cells implicate LTB₄ as a potential mediator of aggravated atherosclerosis in OSA. The potential mechanisms may include LTB₄-induced effects on monocytes/macrophages, PMNs, and structural cells of the vascular wall. Mice lacking ApoE⁻/⁻ exhibit hyperlipidaemia and develop spontaneous atherosclerosis. Exposure of these mice to chronic intermittent hypoxia induces an accelerated atherosclerosis.28 In addition, either pharmacological or genetic targeting of the BLT₁ receptor for LTB₄ reduces the atherosclerosis burden in ApoE⁻/⁻ knock-out mice.37 Indeed, deletion of the gene encoding the BLT₁ receptor prevents the acceleration of atherosclerosis induced by chronic intermittent hypoxia exposure in ApoE⁻/⁻ mice,31 suggesting an important role of the LTB₄-BLT₁ pathway in intermittent hypoxia-induced atherosclerosis. A recent study suggested that the blockage of the BLT₂ receptor could improve endothelial function and reduce the release of reactive oxygen species in the aorta from ApoE⁻/⁻ mice fed with a high-cholesterol diet.38 However, this pharmacological treatment failed to reduce the development of atherosclerosis. Since this notion has not been evaluated in chronic intermittent hypoxia, the involvement of the BLT₂ receptor in intermittent hypoxia-induced atherogenesis remains to be established.

LTB₄-induced activation of human monocytes derived from patients with OSA has been associated with the release of pro-inflammatory cytokines [IL-6 and monocyte chemotactant protein 1 (MCP-1)]19 and reactive oxygen species. In line with these findings, lipopolysaccharide-stimulated monocytes derived from patients with severe OSA exhibit elevated production of MCP-1 and matrix metalloproteinases (MMP)-9 after sleep when compared with before sleep.39 An increased LTB₄ production induced by chronic intermittent hypoxia in OSA could hence promote LTB₄-induced leucocyte recruitment and activation in the context of atherosclerosis. A major role of the LTB₄ pathway in intermittent hypoxia-induced monocyte recruitment and differentiation has also been supported by the observation that pre-treatment of THP-1 cells with the BLT₁ receptor antagonist U75302 reduces the intermittent hypoxia exposure-mediated monocyte recruitment, whereas pre-treatment with either U75302 or a BLT₂ receptor antagonist reduces intermittent hypoxia exposure-mediated monocyte differentiation to macrophages.31 PMN-derived production of LTB₄ may also act as a source of LTB₄ acting on lymphocytes, leading to a subsequent release of pro-inflammatory cytokines, i.e. interferon-γ or interleukin 17.13 However, autocrine effects on PMNs may also participate in LTB₄-induced pro-atherosclerotic signalling. In addition to being a major PMN chemotactic agent, LTB₄ stimulates neutrophil release of proteolytic enzymes, such as lysozyme, myeloperoxidase, and MMPs, which may participate in the atherosclerosis process.40 Interestingly, also other pathological processes associated with PMNs have been reported in OSA patients. For example, patients with moderate-to-severe OSA exhibit delayed PMN apoptosis and an increased expression of the CD16 subgroup of the adhesion molecule β3-selectin.41 In this context, it is interesting to note that LTB₄ induces delayed neutrophil apoptosis,42 suggesting that the increased LTB₄ production in OSA could contribute to the increased PMN survival in OSA patients. The latter suggestion opens up for additional potential beneficial effects of targeting the LTB₄ pathway in OSA patients.

Finally, the correlation of expression levels of LTB₄ synthesizing enzymes in PMNs with vascular wall hypertrophy, measured as intima-media thickness, is consistent with the direct chemotactic and proliferative effects of LTB₄ on vascular smooth muscle cells.43 In animal models, BLT receptor antagonism has been shown to reduce the intimal hyperplasia associated with thickening of the arterial wall after vascular injury.44 Furthermore, inhibition of LT biosynthesis decreases neutrophil deposition at the sites of arterial injury,44 hence reinforcing the notion that increased PMN production of LTB₄ may have implications
for vascular wall hypertrophy and smooth muscle cell proliferation. Interestingly, OSA has been shown to be an independent predictor for clinical and angiographic outcomes after percutaneous coronary interventions, with restenosis rates being significantly higher in OSA patients compared with coronary patients without OSA.45

Whereas most mechanistic studies of the LT pathway in OSA focused on LTB₄, OSA is also associated with increased CysLTs concentration,18 and several CysLT-induced effects could potentially also be involved in the link between OSA and atherosclerosis. For example, CysLTs induce a pro-inflammatory gene expression in monocytes13 and vascular smooth muscle cells,16 as well as, for example, an increased expression of endothelial P-selectin or macrophage inflammatory protein 2, a chemokine that attracts neutrophils. In addition, CysLT signalling induce smooth muscle cell proliferation and constrict atherosclerotic coronary arteries.46 Similarly, CysLTs have been shown to activate the release of RANTES, a potent leukoattractant chemokine, by platelets through CysLT₁ receptor activation in healthy subjects.47 Since both RANTES18 and CysLTs concentration18 are increased in OSA, the role of CysLTs in platelet activation and atherothrombosis in OSA could be hypothesized.

Overall, data suggest a role of the LT pathway in the early stages of intermittent hypoxia-related atherosclerosis and vascular remodelling, with monocytes, PMNs, and probably platelets as sources, and several cell types as potential targets both in terms of immunological reactions and direct effects on structural cells within the vascular wall, as depicted in Figure 2.

5. Obesity as a significant contributor to LT pathway activation in OSA

A classical issue in clinical research addressing cardiovascular consequences associated with OSA is confounding factors. Including obese OSA with severe desaturation is generally criticized owing to the prominent role of a body mass index (BMI). This confounding factor may also interfere with studies of the LT pathway, as suggested by studies in both children17,22 and adults with OSA.18 In the latter studies, urinary LTE₄ levels, an established analytical parameter for monitoring endogenous synthesis of CysLTs, were significantly enhanced in obese subjects with OSA, and the BMI remains an independent predictor of urinary LTE₄ concentration in obese (BMI ≥30 kg/m²) or overweight (25 < BMI < 30 kg/m²) OSA patients, even after adjustment for OSA severity. Interestingly, overweight and obesity were gradually associated with a significant increase of FLAP mRNA levels in peripheral mononuclear cells derived from patients with OSA.18 Such an activation of the LT pathway transcriptional profile in relation to the obesity pathway was also reported in PMNs from OSA patients, where FLAP and LTA₄H protein expression were significantly associated with BMI.21 In addition to monocytes and PMNs, also adipocytes have the capability to synthetize LTB₄ and CysLTs.49,50 Levels of FLAP and 5-LO mRNA are about eight- and two-fold up-regulated, respectively,

![Figure 2](biochemical_mechanisms.png)

**Figure 2** Biochemical mechanisms linking OSA to LT pathway activation, inflammation, and vascular remodelling. The illustration depicts the role of intermittent hypoxia and obesity in the activation of the LT pathway in polymorphonuclear neutrophil granulocytes and monocytes/macrophages. Transcellular LT biosynthesis is exemplified by dotted arrow. Red arrows indicate increased expression by intermittent hypoxia and/or obesity, grey arrows indicate link to vascular remodelling and atherosclerosis. Open rectangles represent LT receptor expression, and yellow boxes indicate examples of the cellular responses induced by LT receptor activation. FLAP, 5-lipoxygenase activating protein; LO, lipoxygenase; LT, leukotriene; LTC₄S, leukotriene C₄ synthase; LTA₄H, leukotriene A₄ hydrolase; SMC, smooth muscle cell; PAI, plasminogen activator inhibitor.
in an obese mice model [mice lacking the obesity gene product leptin (ob/ob)] compared with C57BL/6 mice and immuno-histochemical studies revealed adipose tissue FLAP protein localization to infiltrating macrophages. With respect to a major role of adipose tissue in the underlying inflammation associated with the pathogenesis of metabolic abnormalities and cardiovascular risk in OSA patients, all these data suggested that adipose tissue-derived LTs could also contribute to the increased cardiovascular risk in OSA patients.

6. LT activation in childhood sleep apnoea

Paediatric OSA has both distinct and similar characteristics to adult OSA. The activation of the LT pathway has been reported in separated independent studies performed in children with obstructive sleep disorder breathing (SDB) in whom hypertrophy of adenotonsilar tissues is the predominant aetiological factor involved in paediatric OSA. Nevertheless, the pattern of intermittent hypoxia and the effects of hypoxia/re-oxygenation are similar to adult OSA, and in exhaled breath condensate from snoring children, the concentrations of LTD4 and CysLTs are increased in children with AHI >5 compared with children with AHI <5. However, it should be mentioned that BMI was also higher in the SBD group in this study. Furthermore, upper airway lymphoid tissues of paediatric patients with SDB displayed enhanced expression of CysLT1 and CysLT2 receptors and elevated concentration of CysLTs and LTD4 compared with children with recurrent tonsillitis that may contribute to the proliferation of adenotonsilar cells. Indeed, the addition of LTD4 to tonsillar cell culture induces a dose-dependent proliferative response that was partly blocked by either the CysLT1 receptor antagonist montelukast or the dual CysLT1 and CysLT2 receptor antagonist BAYu9773. Compared with subjects with recurrent tonsillitis, children with OSA had significantly higher expression of the CysLT1 receptor in small-size CD19+B-lymphocytes and CD3+T-lymphocytes. All these data suggested that LT pathway activation may contribute to the local proliferative and inflammatory pathway within the tonsils and adenoids in SBD at least in part through the release of pro-inflammatory cytokines. The active inflammation of the lower airways in OSA children is reflected by enhanced urinary levels of LTE4 being gradually increased with respect to OSA severity. Urinary LTE4 levels were also slightly correlated to adenotonsilar size and multiple linear regression analysis revealed that LogLTE4 and adenotonsilar size were significant predictors of AHI. The increased concentration of CysLTs in urine, exhaled breath condensate, and adenotonsilar tissues of children with OSA suggested that CysLT receptor antagonists could be useful in treating OSA. An open-label intervention study in children showed that 16-week treatment with the CysLT1 receptor antagonist montelukast improved the underlying respiratory disturbances during the sleep and therefore could be of benefit in the management of children with mild SDB. These findings were subsequently confirmed by a randomized double-blind study.

7. Effects of CPAP on LT pathway activation

Studies showing that CPAP treatment could decrease LT production provide supportive evidence of the role of intermittent hypoxia severity in LT pathway activation. In non-obese OSA patients and in those with a normal BMI (BMI ≤25 kg/m²), both the production of LTD4 by stimulated PMNs and the urinary excretion of LTE4 were respectively reduced after a 3-month period of CPAP in compliant patients while, during the same time, LTD4 production remained unchanged in control subjects or non-observant OSA patients. These data suggested that, in the absence of confounding factors, LT pathway activation could be reversed by CPAP treatment. However, CPAP treatment failed to reduce LTE4 urinary concentration in overweight and obese OSA patients, further underlining the role of obesity as a confounder in the activation of LTs with chronic intermittent hypoxia. Since LTD4 increases chemokine secretion and MMPs, it is interesting to mention that the production of MCP-1 and MMP-9 by monocytes is also significantly decreased after long-term nasal CPAP treatment. Likewise, CD15 expression is attenuated, whereas apoptosis markers are increased in neutrophils derived from nasal CPAP-treated patients.

8. Could LT modifiers being interesting in the treatment of OSA-associated atherosclerosis?

Pharmacological inhibition of FLAP has been shown to reduce lesion size in different atherosclerosis-prone mice (see review in Riccioni and Bak). In a randomized double-blind trial vs. placebo performed in patients with acute coronary syndrome, the 5-LO inhibitor VIA-2291 reduced urinary LTE4 concentration and reduced the non-calcified plaque volume. In a registry-based nation-wide Swedish cohort of almost 7 million subjects followed for 3.5 years, the use of the CysLT1 receptor montelukast reduced the risk of myocardial infarction in male, and reduced the risk of stroke in subjects not on angiotensin-modifying drugs. Taken together, these studies highlight the potential interest of LT pathway inhibition in the prevention of cardiovascular disease. However, the effect of pharmacological inhibition of the LT pathway in the prevention of intermittent hypoxia-induced human atherogenesis still remains to be demonstrated. An in vitro study on TNP-1 cells showed that BLT1 receptor blockade markedly attenuated chronic intermittent hypoxia-induced MCP-1 expression, suggesting that disruption of the LTD4 –BLT1 pathway could prevent intermittent hypoxia-induced monocyte recruitment. Similarly, BLT1 and BLT2 receptor blockage prevented intermittent hypoxia-induced CD14 and CD18 expression, suggesting that the blockage of the LTD4 pathway could prevent intermittent hypoxia-induced monocyte differentiation.

CPAP treatment is regarded as the cornerstone of treatment for OSA. An observational study showed that CPAP reduced the risk of fatal and non-fatal cardiovascular events in men with severe OSA. These results were in line with the findings that 4 months of effective treatment with CPAP significantly improved validated markers of atherosclerosis in relatively young patients without significant comorbidities and on no medication. However, a recent randomized, parallel, 6-month controlled trial demonstrated that the impact of CPAP in obese mild-to-moderate OSA patients presenting cardiovascular and/or metabolic morbidities was more relative. Moreover, ~ 30–40% of OSA patients refuse or are non-compliant to treatment with CPAP, highlighting the need of pharmacological strategy in association with CPAP in patients at high cardiovascular and metabolic risk.

Of course, the activation of the LT pathway itself could not be the sole mechanism of vascular remodelling in OSA patients. But in contrast to the LT pathway, the cyclooxygenase (COX)-dependent pathway of arachidonic acid metabolism has been less extensively studied in OSA patients. For example, thromboxane A2 (TXA2), which is predominantly
generated by platelets through COX type 1 isoform and thromboxane synthase, induces vasoconstriction, vascular smooth muscle cell proliferation, platelet activation and increases the expression of adhesion molecules binding on its TP receptors. 36 We recently demonstrated the involvement of the TXA2 pathway in the acceleration of atherosclerosis in ApoE−/− mice exposed to intermittent hypoxia. 37 However, the role of hypoxia in the TXA2-dependent pathway remains to be established in OSA since the urinary concentrations of 11-dehydro-thromboxane B2, a stable metabolite of TXA2, were similar in healthy subjects and OSA patients free of cardiovascular risk factor and carefully matched for age and BMI, 36 suggesting that OSA itself might not be associated with thromboxane pathway activation. Other potential mechanisms including decreased nitric oxide availability have been detailed elsewhere to explain OSA-associated atherosclerosis. 63

9. Conclusion

As discussed in this review, there is a growing body of evidence from both experimental in vitro or in vivo animal model studies and clinical studies, suggesting that the LT pathway could represent a major molecular link between OSA and atherosclerosis. To summarize (Figure 2), both intermittent hypoxia and obesity, that are characteristic features of OSA, induce a transcriptional activation of FLAP in PMNs and monocytes, respectively, leading to an increased production of LTB4 and CysLTs. This enhanced production of LTs contributes to the underlying systemic and vascular inflammation associated with OSA. With respect to their biological effects, LTs may play a major role in the early vascular remodelling, and atherosclerosis development in OSA patients. Thus, LT modifiers may provide interesting novel therapeutic drugs for OSA-associated atherosclerosis.

Conflict of interest: none declared.

References


