

Pathophysiological determinants of pulse wave amplitude variations in sleep apnea patients: a crossover interventional study

Project summary:

Obstructive sleep apnea (OSA) is a highly prevalent condition causing repetitive arousals from sleep and oxygen desaturations. Although OSA has been shown to be associated with increased cardiovascular risk, recent secondary prevention interventional studies failed to demonstrate that treatment of OSA reduced the risk of recurrent cardiovascular events, probably due to the heterogeneity of cardiovascular risk in patients with OSA. **Therefore, there is a need to find new markers of OSA-associated cardiovascular risk to assign treatment resources to OSA patients who are likely to respond in terms of cardiovascular risk reduction.**

Our group investigated the value of the nocturnal signal of oximetry-based digital photoplethysmography (PPG). This is a non-invasive and easily accessible technique that detects variations in the pulsatile blood flow of the finger and provides a signal in the form of a pulse wave. The amplitude of this pulse wave (pulse wave amplitude; PWA) typically drops when the sympathetic nervous system is activated at the end of apneas or after arousals.

In a recent analysis of three prospective epidemiological cohort (HypnoLaus, Pays de la Loire (PLSC) and ISAACC), a *low* rate of PWA drops per hour (low PWAD index) was independently associated with an increased incidence of cardiovascular events in OSA. Moreover, in a subanalysis of PLSC, treatment of OSA by CPAP was able reduce incident cardiovascular events only in OSA patients with a *higher* PWAD index suggesting that a *lower* PWAD index may reflect irreversible cardiovascular damage. **However, the pathophysiological mechanisms underlying this strong association between the PWAD index and cardiovascular risk remain to be determined.**

Aim n°1: To determine the pathophysiological mechanisms underlying the variation of PWAD index in patients with sleep apnea. Given that blood flow changes in the microcirculation of the finger are primarily dependent on sympathetic activity and endothelial cell function, we hypothesize that the loss of this physiological variability may reflect a poorly reactive autonomic nervous system (ANS) and/or impaired endothelial function.

We first plan to conduct an observational study to assess endothelial and ANS function in untreated patients with OSA who have different baseline PWAD (high/low) profiles. All subjects will undergo ANS evaluation (baroreflex sensitivity assessment, reaction to cold pressure, and sleep heart rate variability), and vascular function assessment (flow-mediated dilatation test, nitric oxide [NO] test and arterial stiffness assessment).

Aim n°2: To determine the impact of sleep apnea treatment with CPAP on the nocturnal PWAD index and its pathophysiological determinants. We expect that CPAP therapy would improve ANS and/or endothelial function and restore a higher PWAD index. We also hypothesize that OSA patients with a *higher* PWAD index at baseline may show a greater benefit of CPAP in terms of vascular and ANS function compared to those with lower baseline PWAD index who may have irreversible cardiovascular damage. Using the same participants and experimental techniques as the first study, we will conduct a prospective, randomized, single-blind, crossover trial to evaluate the impact of 2 weeks of CPAP therapy versus placebo on vascular and autonomic function.

This research will highlight the value and pathophysiological mechanisms underlying the association between PWAD index and cardiovascular disease in OSA patients. **The widespread availability of pulse oximetry-derived PPG means that this marker could easily be used in all clinical settings and may help develop a precision medicine approach to the treatment of OSA.**