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Ayers, Lisa ; Turnbull, Chris ; Petousi, Nayia ; Ferry, Berne ; Kohler, Malcolm ; Stradling, John

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Withdrawal of Continuous Positive Airway Pressure Therapy for 2 Weeks in Obstructive Sleep Apnoea Patients Results in Increased Circulating Platelet and Leucocyte-Derived Microvesicles

Lisa Ayers^a Chris Turnbull^b Nayia Petousi^b Berne Ferry^a Malcolm Kohler^{d,e} John Stradling^c

^aDepartment of Clinical and Laboratory Immunology, Oxford University Hospitals NHS Foundation Trust, ^bOxford Centre for Respiratory Medicine and NIHR Oxford Biomedical Research Centre, Churchill Hospital Campus, Oxford University, and ^cSleep Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK; ^dCentre for Interdisciplinary Sleep Research, University of Zurich, and ^eSleep Disorders Centre and Pulmonary Division, University Hospital Zurich, Zurich, Switzerland

In 2013 we reported that in patients with obstructive sleep apnoea (OSA), withdrawing their continuous positive airway pressure (CPAP) therapy for 2 weeks led to a significant increase in endothelial cell-derived microvesicles (MVs) [1]. Several other studies have found that the initiation of CPAP therapy in patients with OSA leads to a fall in endothelial [2, 3] and platelet [4, 5] MVs, but there have been no further studies investigating the impact of CPAP withdrawal in patients established on therapy, which provides a more robust experimental protocol. Therefore, in this further exploratory study we have examined the impact of CPAP withdrawal on other subtypes of MVs.

Fourteen of the patients in this study were included in a previously published study, where the primary outcome measure was a marker of oxidative stress (PMID 26022961) and this publication includes the full protocol. A total of 23 OSA patients established

on CPAP therapy were recruited. Eleven were randomised to continue on CPAP for 2 weeks as the control, and 12 were randomised to receive sham CPAP for 2 weeks, i.e. CPAP withdrawal, in a double-blinded manner [6]. Participants were well matched for age [CPAP mean 59 (SD 7.8) years old, sham CPAP 61.1 (8.9) years old], original OSA severity (established by having withdrawn CPAP for 4 nights prior to the actual trial to prove that their OSA did indeed return), oxygen desaturation index (ODI) [CPAP 53.1 (14.5), sham CPAP 54.6 (22.0)] and BMI [CPAP 36.8 (7.4), sham CPAP 36.9 (7.5)]. CPAP withdrawal led to a rise in ODI of >4% from 3.1 (3.2)/h to 43.0 (24.2)/h, whereas the ODI in the control group remained unchanged as expected.

MVs were measured by flow cytometry, as described previously [7]. Procoagulant MVs were determined using annexin V binding, platelet MVs were identified by CD31 and CD41 dual positivity or CD61 expression, and leucocyte MVs were stained with CD45. The analyses were carried out blind of the group allocation.

There was no significant difference between the baseline levels of MVs in the CPAP versus sham CPAP groups. We found significant elevations in procoagulant MVs ($p = 0.043$) and platelet-derived MVs (CD31+CD41+ $p = 0.033$, CD61+ $p = 0.032$) in the CPAP withdrawal group, which were not seen in the participants that continued on CPAP therapy. For procoagulant and platelet-derived MVs there was a significant difference in the treatment effect between the patient groups. For leucocyte-derived MVs there was a trend towards a greater increase in the CPAP withdrawal group; however, the change was not significantly different between the two groups (table 1).

In contrast to our previous study we found significant elevations in procoagulant and platelet-derived MVs in individuals withdrawn from effective CPAP therapy for 2 weeks, when compared to matched patients continuing on CPAP therapy. This difference may be due to the cohort of participants in the current study having higher BMIs and a greater increase in ODI during CPAP withdrawal, when compared to the previous study. Untreated OSA patients are known to have elevated levels of platelet MVs and levels correlate with OSA severity [4, 8, 9]. Elevated levels of platelet MVs may play a role in the development of the coagula-

Table 1. Baseline and 2-week levels of circulating MVs by mean (SD)

	CPAP (n = 11)			Sham CPAP (n = 12)			Treatment effect (delta change)	
	baseline	2 weeks	p value	baseline	2 weeks	p value	mean (95% CI)	p value
Annexin V+ procoagulant MVs	2,576 (412)	2,410 (377)	0.724	2,001 (658)	3,264 (963)	0.043*	+1,489 (239 to 2,739)	0.019*
CD31+CD41+ platelet MVs	2,331 (416)	2,191 (362)	0.760	1,808 (678)	3,030 (934)	0.033*	+1,439 (344 to 2,555)	0.020*
CD61+ platelet MVs	2,373 (426)	2,208 (353)	0.699	1,847 (681)	3,093 (945)	0.032*	+1,480 (363 to 2,597)	0.019*
CD45+ leucocyte MVs	15 (2)	18 (3)	0.186	13 (2)	21 (4)	0.018*	+10.5 (-1.1 to 16.1)	0.241

Treatment effect shows the difference between groups in delta change of microvesicle (MV) levels. * $p < 0.05$.

tion, inflammatory and atherogenic processes potentially providing a link between OSA and cardiovascular disease. The findings that successful CPAP therapy reduces platelet MV levels, and the withdrawal of this CPAP leads to an elevation, as shown in the current study, suggests that platelet MVs are a potential biomarker of an OSA-induced effect on atherogenic processes, and that therapy can reduce them.

Leucocyte MVs have also been shown to be elevated in untreated OSA patients [8] and a correlation was noted with the apnoea-hypopnoea index in children with OSA [9]. Leucocyte MVs are present at high levels in patients with atherosclerosis and diabetes, and they are thought to be involved in the processes of inflammation, thrombosis and endothelial dysfunction [10].

Although there is a paucity of robust randomised and controlled studies and conflicting data, CPAP therapy and the consequent reduction in intermittent hypoxia and catecholamine levels may reduce platelet activation [11] and inflammation [12], processes thought to trigger MV release, thus potentially explaining the changes in circulating MVs found with the commencing or withdrawal of CPAP. Thus, CPAP therapy may reduce the risk of patients developing co-morbidities such as cardiovascular disease [13], and if this link is firmly established, then lowered circulating MVs may be a part of the explanation. However, the true causal nature of MVs in the pathogenesis of vascular co-morbidities linked to OSA requires further investigation.

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