To the Editor:

Return of sleep apnoea and sleep fragmentation following CPAP withdrawal in patients with obstructive sleep apnoea.

We recently published data in this journal describing the return of obstructive sleep apnoea (OSA) following the withdrawal of CPAP [1]. In this study about one third of patients did not experience a significant return of OSA by the fourth night without CPAP, as measured using the oxygen desaturation index (ODI). This suggested that CPAP need not be an every night therapy in some patients with OSA, although there was no clear way of identifying such patients in advance of the trial of CPAP withdrawal. Limitations to this study were discussed in the paper and correctly highlighted by van Zeller and Drummond [2]. In particular, it was possible that the ODI might not be sufficiently sensitive to sleep fragmentation occurring during the first nights of CPAP withdrawal. Although ODI derivatives and respiratory indices (with or without markers of arousal) have generally been found to be strongly correlated [3], and the ODI as good at predicting sleepiness as the apnoea-hypopnoea index (AHI) [4], it is possible that, in the early stages of OSA return, an arousal might tend to occur in advance of a significant desaturation event, perhaps due to a normalisation of the arousal threshold following a period on successful CPAP [5] [6].This would mean that using ODI values alone might underestimate the degree of sleep fragmentation and thus potentially the return of symptoms. This explanation has also been used to explain excessive daytime sleepiness occurring in the so-called upper airway resistance syndrome where there are respiratory events but oxygen desaturations are much smaller [7].

In order to explore this issue further we have looked at complete data from 184 patients having oximetry performed at home on each of the first four nights of CPAP withdrawal, from two centres (Oxford, n=109, and Zurich, n=75) which were screening potential patients for inclusion in subsequent CPAP withdrawal trials. The criteria for study entry included an initial diagnosis of moderate-to-severe OSA, >1 year on CPAP, average CPAP use >4 hours/night, and an AHI (from machine download) on CPAP of <10. In the Oxford trials, the patients recruited had on average more severe OSA than the Zurich patients, which thus provided a wide range of OSA severity to study. We used the number of transient rises in heart rate per hour of study as a surrogate of arousal frequency [8] [9], to explore if there was indeed evidence of a return of sleep fragmentation prior to the development of a significant ODI. This index is derived from a manually supervised automated analysis of the heart rate (Visi-Lab, Stowood Scientific, Oxford, UK) which itself is derived from the oximeter's plethysmogram. Given the concerns over interscorer reliability when identifying EEG arousals [10], autonomic arousals could potentially be a more reliable marker of the increasing sleep fragmentation following CPAP withdrawal than EEG-defined events, and may also capture the more subtle events that presumably are less deleterious to sleep than those that incur full cortical arousal. [11] [12] [13]. Heart rate responses to arousal have been shown to be reproducible within individuals, but there is considerable inter-individual variation in the relationship between EEG arousals and heart rate rises [14].

The mean ($\pm$ standard deviation) ODI (>3%) on the fourth night of CPAP withdrawal was 28.8 $\pm$ 19.8, (Oxford 34.3 $\pm$ 21.2, Zurich 21.7 $\pm$ 15.3). The mean heart rate arousal index (HRAI) on the fourth night was 34.4 $\pm$ 20.4, (Oxford 39.9 $\pm$ 21.6, Zurich 27.7 $\pm$ 17.0). If the $ODI_{3\%}$ and HRAI on the first, second and third nights of CPAP withdrawal are quoted as a percentage of the 4th night value, then

the return was 99 ± 43%, 106 ± 53%, 115 ± 96%, and 108 ± 45%, 108 ± 52%, 108 ± 54% respectively. Thus, from the overall data, on the first night of withdrawal, the $ODI_{3\%}$ and HRAI were already as high as that of night four (Table).

In order to explore this further we analysed the subgroup from both centres (n=37) who only experienced a less than 70% return of their $ODI_{3\%}$ on night one of CPAP withdrawal compared to night four; individuals in whom the $ODI_{3\%}$ alone might have particularly underestimated the return of OSA. In this subgroup, by night four of CPAP withdrawal, there was no difference in severity compared to the whole group ($ODI_{3\%}$ 33.9 ± 20.6 and 28.8 ± 19.8, HRAI 34.9 ± 16.8 and 34.2 ± 20.1 respectively). In these 37 subjects, although the $ODI_{3\%}$ was only 51 ± 14% on the first night of CPAP withdrawal, compared to that of night four, the HRAI was already 85 ± 43% that of night four (Table). An ANOVA with trend analysis showed no statistically significant trend across the four nights for HRAI ($p=0.12$), but there was a highly significant trend across the four nights for the ODI ($p<0.001$).

Whilst the majority of patients following CPAP withdrawal show a rapid rise in their ODI, we have shown that there are a minority of individuals who, despite a slower return of OSA as evidenced by the $ODI_{3\%}$, do in fact have evidence of a faster return of sleep fragmentation when this is measured by an autonomic marker of arousal. Thus the $ODI_{3\%}$ should perhaps not be used alone to assess whether patients can safely stop CPAP for short periods of time; an additional assessment of an arousal index, such as the HRAI, could perhaps be usefully included. These data would also support the idea that OSA and its associated sleep fragmentation blunt the arousal threshold, leading to longer respiratory events and thus larger hypoxic dips [6]. However, it should be noted that because autonomic markers of arousal, such as heart rate rises, are more sensitive to disturbing influences (for example they do not habituate to repetitive stimuli, as do EEG arousals [15]), it is not clear whether they are as important in leading to daytime symptoms, particularly if not propagated to the cortex [12]. Conversely, because there are some individuals in whom heart rate rises during an arousal are less pronounced, this may lead to an underestimation of the degree of sleep fragmentation in this situation. Just as there is a clear disconnect between respiratory events and the degree of EEG arousal [13], there can also be a disconnect between autonomic arousals and respiratory events characterised from oximetric indices.

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Table

Oximetry and heart rate data from the 1st, 2nd, 3rd and 4th nights following CPAP withdrawal, displayed for all patients (n=184), and for those in whom there was a gradual return of OSA (n=37), defined as an ODI on the 1st night of CPAP withdrawal that was less than 70% of the ODI on the 4th night of CPAP withdrawal. Data are displayed as means ± standard deviation.

All patients following CPAP withdrawal (n=184)				
	Night 1	**Night 2**	**Night 3**	**Night 4**
ODI>3%	26.0 ± 17.4	27.0 ± 18.1	28.6 ± 19.1	28.8 ± 19.8
ODI>3% as % of Night 4	99 ± 43	106 ± 53	115±96	100
BPM>6	34.4 ± 20.4	33.4 ± 19.0	34.2 ± 19.2	34.2 ± 20.1
BPM>6 as % of Night 4	108 ± 45	108 ± 52	108 ± 54	100
Patients with a gradual return of oxygen desaturations following CPAP withdrawal (n=37)				
	Night 1	**Night 2**	**Night 3**	**Night 4**
ODI>3%	17.5 ± 13.3	25.8 ± 18.9	28.3 ± 20.4	33.9 ± 20.6
ODI>3% as % of Night 4	51 ± 14	83 ± 42	83 ± 22	100
BPM>6	28.8 ± 16.9	30.8 ± 16.8	32.2 ± 17.5	34.9 ± 16.8
BPM>6 as % of Night 4	85 ± 43	92 ± 39	94 ± 35	100

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