Diurnal changes and levels of fibrin generation are not altered by continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA)

A randomised, placebo-controlled crossover study

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Summary
Obstructive sleep apnoea (OSA) is associated with increased cardiovascular disease (CVD) risk. In the general population, CVD events peak at 9:00–10:00 AM, associated with diurnal changes in thrombotic potential. However in OSA, these CVD events occur frequently at night. Measuring thrombotic potential across the sleep-wake cycle may provide insight into the temporal association of OSA with CVD. This study aimed to determine diurnal changes in fibrin generation in OSA and whether treatment of OSA with continuous positive airway pressure (CPAP) alters fibrin generation across the sleep-wake cycle. In a randomised placebo-controlled crossover trial, patients with OSA were assigned to two months each of therapeutic CPAP and placebo. After each treatment period, fibrin generation was determined by overall haemostasis potential (OHP), maximum optical density, and maximum slope (all p≤0.001). CPAP produced no change in fibrin generation parameters compared to placebo. In severe OSA patients, fibrin generation peaked at 6:00 AM and 9:00 AM rather than during the sleep period (midnight and 3:00 AM). These findings suggest a prothrombotic shift in the morning similar to individuals without OSA. There was no difference between CPAP and placebo on fibrin generation.

Keywords
Fibrin generation, fibrinolysis, obstructive sleep apnoea, continuous positive airway pressure, cardiovascular risk

Introduction
Obstructive sleep apnoea (OSA) is characterised by repetitive episodes of decreased or total cessation of airflow despite respiratory efforts during sleep, leading to a fall in oxygen saturation and sleep fragmentation (1). Although OSA is associated with an increased risk of cardiovascular disease (CVD) (2–6), the mechanisms are incompletely understood. In the general population, there is an increase in the morning period between 6:00 AM to midday in cardiovascular events, such as myocardial infarction (MI) and sudden cardiac death, with a morning peak of cardiac events around 9:00 AM (7, 8) which is associated with diurnal changes in thrombotic potential. Heart rate (9) and blood pressure (9, 10) also display diurnal variation with an increase in the morning just before and after waking. The activation and subsequent aggregation of platelets are seen as possible factors associated with the increased cardiovascular mortality observed in patients with OSA (5, 11–13).

However in OSA, studies suggest that the peak time for cardiovascular events such as acute myocardial infarction (14) and sudden death (15) occur earlier during the midnight to 6:00 AM...
period. Episodes of OSA produce intermittent arterial oxygen desaturation (16) and this is considered to be associated with the activation of a number of thrombotic, metabolic and inflammatory disease pathways which promote CVD including congestive cardiac failure, ischaemic heart disease, pulmonary hypertension, atherosclerosis, arrhythmias, insulin resistance, dyslipidaemia and hypertension (1, 5, 6). OSA is also strongly linked to obesity (6, 17), furthermore patients with obesity and type 2 diabetes have been found to have impaired fibrinolysis (18). Poor sleep quality has been recognised as a trigger of acute cardiovascular events (19).

The fibrin network structure plays a role in CVD, particularly in atherosclerosis (20). Fibrin polymerises to form clots with diverse structural and biological properties (21). The fibrin clot forms a haemostatic plug to stop bleeding and the fibrin structure must be strong enough to withstand arterial pressure (21). When there is an imbalance between coagulation and fibrinolysis a pathological clot occurs (22). Fibrin structure directly affects the rate of fibrinolysis, the process of clot breakdown (21). A relationship between myocardial infarction (MI) and reduced permeability and increased stiffness of fibrin, especially in young post-MI patients, has been found (23). Global coagulation assays, such as the overall haemostatic potential (OHP) assay, measure fibrin aggregation and fibrinolysis over time in citrated plasma samples (24) and provides information of changes in the balance of the fibrinolytic system (25). The OHP assay has been used to detect hypercoagulable changes in several disease states, including coronary heart disease, diabetes, stroke (26, 27), and in pregnancy (25, 27) and pre-eclampsia (27) but not in OSA.

Continuous positive airway pressure (CPAP) is very effective at reversing sleep-related disordered breathing events (17) and is the first-line treatment of choice in OSA. Treatment of OSA has led to improvement in cardiac function (28, 29), increased quality of life (28) and reductions in fatal (2, 30) and non-fatal cardiovascular events (2). We have recently shown that CPAP treatment reduces established markers of cardiovascular risk, particularly von Willebrand factor (vWF) and coagulation factors V (FV) and VIII (FVIII) (31). In addition, previous studies have shown reductions in fibrinogen (32) and plasminogen activator inhibitor-1 (PAI-1) (33) with CPAP treatment, however it is not known what effect CPAP has on diurnal changes in thrombotic potential.

The aims of the present study were to firstly determine whether the diurnal pattern of fibrin generation in patients with severe OSA was different from the expected peak prothrombotic period at 9:00 AM, and secondly to determine whether two months of treatment with CPAP would alter any diurnal pattern or levels of fibrin generation. This study reports new data on fibrin generation for a group of patients in whom we have previously observed changes in other markers of coagulability after CPAP treatment (31).

**Methods**

**Subjects**

This study was designed as a randomised, placebo-controlled cross-over trial. The protocol was previously reported in studies which assessed the effect of CPAP treatment on postprandial lipidaemia and coagulability in OSA (31, 34). All subjects gave informed consent to the protocol. Briefly, patients aged ≥21 years with an Apnoea Hypopnea Index (AHI) ≥25 and an Oxygen Desaturation Index (ODI) ≥20 were recruited from sleep apnoea clinics. Patients were excluded if they had a body mass index (BMI) >35kg/m², if they had uncontrolled type 2 diabetes or if they had previously used CPAP. Other eligibility criteria are available on the Australian and New Zealand Clinical Trials Registry (ACTRN 1260500066684 available at http://www.anzctr.org.au). The diagnosis of sleep apnoea was based on full polysomnography, conducted in a clinical sleep laboratory prior to recruitment and apnoeas and hypopnoeas were scored using standard scoring techniques (35).

**Study protocol**

Eligible patients who met the inclusion criteria were randomised to receive either therapeutic CPAP or placebo CPAP (Remstar

![Figure 1: Study protocol.](image-url)
Auto; Philips Respironics, Murrysville, PA, USA) for a two-month treatment period, then after an intervening one month washout period patients crossed over treatments for a further two-month period (Fig. 1). The therapeutic CPAP device was set to a pressure which prevented most sleep disordered breathing whereas the pressure delivered by the placebo mask remained at 0.5 cm H2O, having no effect on sleep disordered breathing. Before commencing treatment each patient was fitted with a CPAP mask and instructed on device operation as previously described (34).

Blood sampling protocol

Blood samples (4.5 ml) were drawn from an antecubital vein and collected into citrated tubes containing 0.129 M trisodium citrate (3.2%) for fibrin generation assay at seven time points over a 24-hour (h) period at the end of each two-month treatment period encompassing both wake and sleep phases (Fig. 1). The collection times during the day were within the 30 minutes (min) prior to meal consumption which took place at 9:00 AM (breakfast), 3:00 PM (lunch), 9:00 PM (dinner), and 9:00 AM (breakfast on day 2). Patients were briefly woken during the sleep period for the blood collections performed at midnight, 3:00 AM, and 6:00 AM. After collection, samples were centrifuged at 3,080 g for 5 min to produce a clear separation of platelet-poor plasma which was then dispensed into aliquots and stored at −80°C. During sleep, each patient used their treatment device according to their habitual use at home. A priori we determined that the 9:00 AM measurement on day 2 would be the primary time point of interest, because it was obtained following 24 h of controlled meals, activity and sleep-wake cycle. Whereas the initial 9:00 AM measurement was performed immediately upon arrival at the research facility with the preceding meal and physical activity levels not being controlled. Meals were identical during each study period and were based on a Western style diet, as previously described (34).

Measurement of fibrin generation and fibrinolysis

After storage, frozen samples were thawed to 37°C and measured using the overall haemostatic potential (OHP) assay, which we have adapted from a method described by Blombäck et al. (24, 36). Fibrin generation time curves were measured in microtiter plate wells (Becton Dickinson Labware, Franklin Lakes, NJ, USA) and plasmas were tested in duplicate. Kinetic absorbance was measured using a Powerwave XS Biotek microplate reader (Biotek, Bethel, VT, USA). The turbidimetry caused by fibrin polymerisation was generated from automated spectrophotometric measurements at 390 nm taken every minute for 60 min to construct the two fibrin-aggregation curves, the overall coagulation potential (OCP) and overall haemostasis potential (OHP). The OCP microtiter wells contained 75 μl plasma and 75 μl of Tris buffer (Tris 66 mM, NaCl 130 mM, CaCl2 33 mM; pH 7.0) containing thrombin 0.05 IU/ml (Dade-Behring, Lane Cove, NSW, Australia). For the OHP microtiter wells, recombinant tissue plasminogen activator (rt-PA; Boehringer-Ingelheim, North Ryde, NSW, Australia) was added to the buffer to give a final concentration of 300 ng/ml. Values for OCP and OHP represent the area under the relevant fibrin time curve calculated by summation of absorption values (24, 36). The overall fibrinolytic potential (OFP) represent the area under the fibrinolytic portion of the curve as a percentage of the total OCP value and is calculated by the formula OFP (%) = [(OCP-OHP)/OCP] x 100. Additional data derived from the fibrin time curve include maximum optical density (Max OD), maximum slope (Max slope) and delay in the onset of fibrin generation (Delay). As all assays were performed in duplicate, Max OD is the mean of the maximum OD reached in the two OCP curves. Maximum slope was calculated progressively for each OD reading on the OCP curve, using a minimum of three time points. The greatest increase in OD for these points represents the maximum slope. Delay is defined as the time taken to reach the line of maximum slope on the OCP curve from baseline absorbance at time zero. To reduce inter-assay variation, all CPAP and placebo samples from a single patient were run in batches and analysed simultaneously.

Table 1: Polysomnography data: baseline and end of treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Mean ± SEM</th>
<th>CPAP Mean ± SEM</th>
<th>Placebo Mean ± SEM</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep apnoea</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>AHI (events/h)</td>
<td>37.9 ± 23.9</td>
<td>6.9 ± 2.1</td>
<td>40.0 ± 5.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ODI (events/h)</td>
<td>31.3 ± 22.4</td>
<td>5.2 ± 1.9</td>
<td>38.7 ± 4.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SaO2-T90 (%TST)</td>
<td>6.90 ± 11.3</td>
<td>1.0 ± 0.4</td>
<td>9.7 ± 2.2</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Min SaO2 (%)</td>
<td>78.3 ± 11.0</td>
<td>89.0 ± 1.4</td>
<td>78.0 ± 1.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Treatment compliance (h/night)</td>
<td>-</td>
<td>4.4 ± 2.2</td>
<td>3.4 ± 2.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

AHI = Apnoea-hypopnoea index; ESS = Epworth Sleepiness Score (maximum sleepiness score = 20); Min SaO2,% = minimum arterial oxygen saturation; ODI = oxygen desaturation index; SaO2-T90, %TST, percentage of total sleep time spent with arterial oxygen saturation less than 90%; SEM = Standard Error of Mean. CPAP and placebo measurements were determined during the 24 hour studies at the end of each treatment arm. * CPAP vs. Placebo. Significance is reached when p≤0.05.
Statistical analysis

All fibrin generation parameters were analysed across 24 h using linear mixed models. We examined treatment, order, time-point and treatment by time-point interaction as fixed effects and the patient as a random effect in all models. Our primary area of interest was the final time-point of 9:00 AM versus the other time-points of the previous day (9:00 AM, 3:00 PM, 9:00 PM), during CPAP or placebo use (midnight, 3:00 AM) and at 6:00 AM. Correlation analyses were also performed to determine associations between the fibrin generation parameters OHP and OFP and fibrinogen, FVIII and plasminogen activator inhibitor type-1 (PAI-1) determined from our previous study (31). The final analyses included 28 patients (25 male and 3 female) who had completed the crossover trial and who had usable samples. Data were analysed, without adjustments for compliance with either therapeutic CPAP or placebo. PASW statistics version 17 (SPSS, Chicago, IL, USA) was used for all analyses.

Figure 2: Changes in overall coagulation potential (OCP), overall haemostasis potential (OHP) and overall fibrinolysis potential (OFP) across the wake and sleep periods during CPAP and placebo. Changes in OCP, OHP and OFP across the wake and sleep periods during CPAP and placebo end-of-treatment studies. The shaded area represents the sleep period during which patients were treated with a CPAP or placebo device. Note sample 1 (9:00 AM) occurred soon after arrival at the laboratory whereas sample 7 (9:00 AM) occurred after restricted activity. Data are means with their standard errors represented by vertical bars. P_{TREAT} = main p-values are for the treatment effects of CPAP versus placebo. Individual p-values are for comparisons of each individual time point to the 9:00 AM time point of the second day. *Significance is reached when p≤0.05.
Results

Overall, the patients (25 males and 3 females) were middle-aged (49 ± 14 years), obese (31.7 ± 4.1 kg/m²) and had severe OSA (AHI = 37.9 ± 23.9/h and ODI = 31.3 ± 22.4/h) (Table 1). Females tended to be older than males, and all were aged over 60 years. The numbers of patients with co-morbidities included two patients with controlled type 2 diabetes, nine with hypertension and ten with hypercholesterolaemia. Nine patients were taking anti-hypertensives, seven were taking statins and one patient was taking aspirin. None of the patients were receiving anti-coagulant treatment (e.g. heparins or warfarin) or had a history of prior cardiovascular disease, deep vein thrombosis or peripheral vascular disease. During the study, body weight did not change and no patients commenced any medication or altered the dose of existing medication. The details of patient flow through the study have been previously described (34). Twenty-nine patients completed the study; however, blood samples from one patient could not be analysed due to haemolysis leading to a total number of 28 patients with viable samples. Table 1 shows polysomnography data at baseline and from the endpoint of each treatment arm comparing the effects of CPAP and placebo on sleep apnoea. Compared to placebo, therapeutic CPAP markedly reduced OSA severity (AHI and ODI, both p<0.00001). Compliance was higher with CPAP than with placebo (p<0.05) (Table 1).

Diurnal variation was found for all fibrin generation parameters except the delay in the onset to fibrin generation, both on CPAP and placebo. When analysed across the 24-h period, there was no significant effect of CPAP on the fibrin generation parameters measured (Figs. 2 and 3). Unexpectedly, a trend was found in favour of placebo for the parameter of maximum slope (p=0.053) (Table 2). Figure 2 shows the diurnal variation of the OCP, OHP and OCP time points of CPAP and placebo measured over the 24-h period of measurements while Figure 3 shows the parameters of the delay in onset of fibrin generation, MaxOD, and maximum slope of fibrin generation. Positive correlations were found between the fibrin generation parameter OHP and plasma levels of fibrinogen (r = 0.671, p≤0.001) and FVIII (r = 0.314, p≤0.001). Plasma PAI-1 was negatively correlated with fibrinolytic activity (OFP) (r = –0.294, p≤0.001).

Diurnal variation of fibrin generation parameters

Total fibrin generation parameters in the absence (OCP) or presence of tPA (OHP) were significantly increased at 9:00 AM compared to 3:00 PM the previous day, midnight and 3:00 AM (all p≤0.001) (Fig. 2). Compared to 9:00 AM there was a significant increase of OHP at 6:00 AM (p=0.016). The indicator of fibrinolytic activity (OFP) was significantly decreased at 9:00 AM compared to 3:00 PM the previous day (p<0.001) and midnight (p=0.036) (Fig. 2).

Discussion

In this randomised placebo-controlled trial, patients with OSA showed a diurnal pattern of fibrin generation with a maximum at 6:00 AM and 9:00 AM, concurrent with the time of increasing onset of myocardial infarction for the general population (7, 8). For the parameter of OHP there was a significant increase at 6:00 AM compared to 9:00 AM which shows a relationship with the early morning period of increased frequencies in the onset of MI.

Table 2: Main effects CPAP versus placebo.

| Fibrin generation parameters | Main effects CPAP – Placebo Mean difference | Lower 95% CI | Upper 95% CI | P-value*
<table>
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<tbody>
<tr>
<td>OCP (ΣOD)</td>
<td>1.12</td>
<td>–0.31</td>
<td>2.56</td>
<td>0.124</td>
</tr>
<tr>
<td>OHP (ΣOD)</td>
<td>0.53</td>
<td>–0.46</td>
<td>1.52</td>
<td>0.296</td>
</tr>
<tr>
<td>OFP (%)</td>
<td>–0.29</td>
<td>–2.06</td>
<td>1.49</td>
<td>0.752</td>
</tr>
<tr>
<td>MaxOD</td>
<td>0.02</td>
<td>–0.01</td>
<td>0.05</td>
<td>0.137</td>
</tr>
<tr>
<td>Slope (MaxOD/min)</td>
<td>14.57</td>
<td>–0.20</td>
<td>29.33</td>
<td>0.053</td>
</tr>
<tr>
<td>Delay (s)</td>
<td>–11.30</td>
<td>–38.19</td>
<td>15.59</td>
<td>0.409</td>
</tr>
</tbody>
</table>

Cl, confidence interval; MaxOD, maximum optical density; OCP, overall coagulation potential; OFP, overall fibrinolysis potential; OHP, overall haemostasis potential. * Significance is reached when p≤0.05.
and sudden cardiac death (8). There was a trough-like effect observed around the midnight and 3:00 AM time points which was similar to that found for the lower frequency of MI onset (37). CPAP treatment did not alter the diurnal night time profile or the levels of the fibrin generation parameters measured across the 24-h period.

Diurnal variation was seen in the specific measures of OCP, OHP, OFP, MaxOD and slope of fibrin generation but not for the delay in onset of fibrin generation. Previously, Blombäck et al. (38) measured fibrin generation over 24-h periods in pregnant women with previous thromboembolism. To the best of our knowledge, this is the first study measuring fibrin generation repeatedly across a 24-h period in patients with OSA. The OCP and OFP provide details of underlying changes in coagulation and fibrinolysis, respectively (25). It has been previously shown by Blombäck et al. (24) that the OCP and OHP reflects plasma levels of multiple coagulation factors, such as FV, FVII, FVIII, FIX, and FX, providing a more global analysis of coagulation than standard laboratory tests, such as prothrombin time (PT) and activated partial thromboplastin time (APTT). The PT and APTT are screening tests for haemostasis used to investigate bleeding and measure the effect of anticoagulants (39). The PT and APTT tests indicate the endpoint of

Figure 3: Changes in delay to fibrin generation, maximum OD and slope of fibrin generation across the wake and sleep periods during CPAP and placebo. Changes in delay to fibrin generation, maximum optical density (MaxOD) and slope/velocity of fibrin generation across the wake and sleep periods during CPAP and placebo end-of-treatment studies. The shaded area represents the sleep period during which patients were treated with a CPAP or placebo device. Note sample 1 (9:00 AM) occurred soon after arrival at the laboratory whereas sample 7 (9:00 AM) occurred after restricted activity. Data are means with their standard errors represented by vertical bars. $P_{\text{TREAT}}$ = main $p$-values are for the treatment effects of CPAP versus placebo. Individual $p$-values are for comparisons of each individual time point to the 9:00 AM time point of the second day. * Significance is reached when $p<0.05$. 

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clot formation, analogous to the delay in OHP, and cannot measure fibrinolysis (40) and are not designed to investigate hypercoagulability. Only marked changes in levels of individual factors will affect PT and APTT clot-based assays (40).

The diurnal distribution of cardiovascular events strongly suggests an interaction between sleep, arousal, and acute thrombosis. Myocardial infarction and sudden death exhibit a peak occurrence between 6:00 AM and midnight (7) particularly between 9:00 AM and 10:00 AM. Platelets play an important role in the pathogenesis of cardiovascular disease and increases in platelet aggregation and activation have been demonstrated in patients with OSA (13, 41, 42). Increased plasma levels of fibrinogen are associated with increased fibrin formation and platelet aggregation (43). In our previous study (31) we found no diurnal variation in fibrinogen levels, whereas another study in patients with OSA (32) found plasma fibrinogen levels were significantly higher at 8:30 AM than on the previous afternoon at 3:30 PM (p<0.02). The results of the present study showing increased fibrin generation in the morning (9:00 AM) are in accordance with prior studies that patients with OSA had increases in morning coagulability, shown by increased fibrinogen (4, 44, 45), decreased fibrinolytic activity (PAI-1) (46, 47) and elevated platelet function (11–13, 42, 45). This is consistent with our finding of increased fibrin generation (OCP, OHP and maximum OD) at 9:00 AM compared to the early morning times of midnight and 3:00 AM and of 3:00 PM the previous day.

In the present study, there was no effect of CPAP on fibrin generation (OHP or OPF). This occurred despite there being CPAP related improvements in individual coagulation factors FV, FVIII and vWF established in our previous study (31) However, in this same study, fibrinogen and PAI-1 remained unchanged (31). This is despite uncontrolled studies showing positive effects of CPAP on reducing plasma levels of fibrinogen (32) as well as reductions in platelet activation and aggregation (13, 48). In our analysis, fibrinogen, which is the substrate for the endpoint fibrin, had the strongest correlation with OHP and OPF measures whilst PAI-1 which is an inhibitor of plasmin generation had a weaker negative correlation with fibrinolysis (OPF). It is therefore possible that overall fibrin generation remained unchanged with CPAP because neither of these markers changed. There may also be other markers which influence fibrin generation which we did not measure and which also did not change with CPAP. Although FVIII was also correlated with OHP, its influence is likely to be weaker since the variation in plasma levels is very wide and FVIII is a cofactor rather than a protease. Alternatively, the lack of change in fibrin generation with CPAP treatment suggests that the reduction in FV, FVIII and vWF work through non fibrin generation pathways, such as platelet aggregation (12) and endothelial function (49) which have both been shown to improve with CPAP. It is also important to consider that changes in fibrin generation may not be a direct effect of OSA itself but rather independently associated with the cardiovascular risk factors seen in this group, such as diabetes and obesity. In this context it also may be that in this group, who are already at increased CVD risk (hypertension, hypercholesterolaemia), two months of CPAP treatment may not be long enough to realise significant changes in the generation of fibrin and subsequent fibrinolysis. A longer treatment length, for example > 6 months, may be required to derive any overall benefit on fibrin generation in OSA patients. Although CPAP treatment did not alter fibrin generation, our data indicate that the temporal variability in coagulation is important. As seen with a prior study on platelet function (7) we observed an increase in global coagulation during the morning waking period as compared to 3:00 AM and midnight. This coincides with the 6:00AM to midday increase in the frequency of onset of myocardial infarction, sudden cardiac death, and stroke (8, 50). Although we could not establish an independent effect of OSA treatment on fibrin generation, further studies which examine the temporal variability in coagulation in other groups at high risk of cardiovascular events are required.

Strengths of this study include the placebo-controlled crossover design, length of each treatment period, and intensive blood sampling using a novel global fibrin generation assay (overall haemostatic potential) that has not been previously used in the OSA population. With reference to our analyses of the treatment effects on fibrin generation, we acknowledge that our observations were based on a relatively small sample size of 28 patients. We also acknowledge that with only three women in this trial, all of whom were aged over 60 years, we cannot adequately compare results with the men. Nevertheless, there is evidence to suggest that women with OSA have a decreased risk of developing coronary heart disease, heart failure and stroke compared to their male counterparts (51, 52). Future studies which examine markers of coagulation in OSA should confirm whether the responses to treatment are similar between men and women and to determine whether there are gender-specific differences in diurnal coagulability and fibrin generation and whether these differences remain after menopausal age. A final limitation of the present study was that there was no control group included to compare diurnal variation of fibrin generation.

Conclusion

In patients with severe OSA, there was a diurnal change in fibrin generation peaking at 6:00 AM and 9:00 AM, rather than over-
night. Although CPAP reduced the severity of OSA, it did not alter fibrin generation measures across the 24-h period. These findings suggest that changes in fibrin generation are not the explanation for altered diurnal rhythm of CVD events in OSA, nor do they explain the benefits of CPAP on CVD risk. Although this is a “real life” study, future studies with higher CPAP compliers may demonstrate more significant changes in the alteration of fibrin generation.

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Conflicts of interest
None declared.

References


