Reduced Nocturnal Cardiac Output Associated with Preeclampsia is Minimized with the Use of Nocturnal Nasal CPAP

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Study Objectives: Recent studies suggest a specific association between intrauterine growth restriction that commonly occurs in preeclampsia and decreased maternal cardiac output. Sleep is associated with marked hypertension in preeclampsia. We therefore aimed to determine how sleep influences other hemodynamic parameters in preeclampsia, specifically to determine if sleep-induced exacerbation of hypertension was associated with reductions in cardiac output.

Study Design: Randomized controlled trial of nasal continuous positive airway pressure.

Setting: King George V, Royal Prince Alfred Hospital.

Patients: Twenty-four women with severe preeclampsia and 15 control nulliparous subjects.

Intervention: Full polysomnography including beat-to-beat blood-pressure recording. Stroke volume, heart rate, cardiac output, total peripheral resistance, and ejection duration were derived from the blood pressure waveform. Half of the 24 preeclamptic subjects were randomly assigned to receive treatment with nasal continuous positive airway pressure and the other half to receive no treatment.

Measurements and Results: Heart rate, stroke volume, and cardiac output were similar in controls and patients with preeclampsia during wakefulness, while total peripheral resistance was significantly elevated. Sleep induced marked decrements in heart rate, stroke volume, and cardiac output in preeclamptic subjects and resulted in further increments in total peripheral resistance. Cardiac output during sleep was correlated with fetal birth weight ($r^2 = 0.64$, $P < .001$). When preeclamptic subjects were treated with continuous positive airway pressure, reductions in cardiac output were minimized, while increments in total peripheral resistance were also reduced.

Conclusions: These data indicate that sleep is associated with adverse hemodynamic changes in women with preeclampsia. These changes are minimized with the use of continuous positive airway pressure. Reduced cardiac output during sleep may have an adverse effect on fetal development.

Key Words: Preeclampsia, cardiac output, fetal, hemodynamics, nasal CPAP.

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INTRODUCTION

As normal pregnancy advances, there is a progressive increase in maternal cardiac output (CO), which provides for the increasing metabolic demands of the growing fetus. In the first trimester of pregnancy, the increase in CO is in the order of 15% to 20% above nonpregnant values and increases to an average of 50% above prepregnant levels in the third trimester. There is also an increase in plasma volume and a decrease in total peripheral resistance (TPR).

Preeclampsia is currently one of the leading causes of both maternal and fetal morbidity and mortality, affecting an estimated 7% of all pregnancies. While systemic arterial hypertension is a hallmark of preeclampsia, this is a marker of an extensive multisystem disorder in which there is generalized endothelial-cell dysfunction. The disease is associated with many other adverse hemodynamic events. While an increase in systemic vascular resistance (SVR) is the dominant mechanism of the hypertension associated with preeclampsia, this hypertension is often associated with a decrease in CO. Importantly, reduced CO has been shown to be particularly associated with intrauterine growth restriction resulting from preeclampsia.

Recent investigations from our laboratory have shown sleep to be a time particularly associated with marked episodes of hypertension in patients with preeclampsia. Furthermore, we have demonstrated a reversal of sleep-associated blood pressure increments in preeclampsia with the use of nocturnal nasal continuous positive airway pressure (CPAP) treatment, supporting our hypothesis that partial upper-airway obstruction is the proximate cause.

The current study was therefore designed to assess the impact that sleep may have on other hemodynamic parameters in subjects with preeclampsia.

METHODS

Subjects

We studied 15 normal pregnant women (control) at 34 ± 2 weeks (mean ± SD) gestation (range, 30-39 weeks). Mean maternal age was 31 ± 5 years (range, 21-36 years), maternal weight was 79 ± 11 kg (range, 62-98 kg) and maternal body mass index was 29.8 ± 4.5 kg/m² (range, 30-39 kg/m²). All women were nulliparous and healthy, had no cardiovascular or respiratory disease, and had no clinical evidence of a sleep disorder.

We recruited 24 women with severe preeclampsia documented according to International Society for the Study of Hypertension in Pregnancy criteria. These criteria include hypertension with a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg on at least 2 occasions and significant proteinuria of at least 300 mg over a 24-hour collection period or 2+ on dipstick. Mean gestation (33 ± 4 weeks; range, 24-38 weeks; $P = .5$ compared with control), maternal age (33 ± 6 years; range, 24-49 years; $P = .4$ compared with control), maternal weight (84 ± 16 kg; range, 59-112 kg; $P = .4$ compared with control) and maternal body mass index (30.5 ± 4.7 kg/m²; range, 23-40 kg/m²; $P = .7$ compared with control) were similar to those of control subjects. All of the women were nulliparous with no previous history of hypertension prior to pregnancy and no evidence of hypertension before the 20th week of gestation. There was no history of
any pre-pregnancy cardiac abnormalities in any of the subjects; however, this was not confirmed by echocardiography.

Medications

Twenty of the preeclamptic subjects were taking clonidine; the average daily dose was 840 ± 77 µg (range, 300-1200 µg). Nine of the 20 subjects were also taking hydralazine; the average daily dose was 100 ± 25 mg (range 50-100 mg). Two subjects were taking a combination of methyldopa (750 mg), clonidine, and hydralazine. The remaining 4 subjects were not medicated at the time of the study.

Antenatal Sleep Studies

We performed full overnight polysomnography on all 36 subjects, utilizing a portable recording system (Compumedics, Melbourne, Australia). We recorded standard electrophysiologic signals including electroencephalography, electrooculography, electromyography, and electrocardiography, and standard respiratory signals, including chest and abdominal wall excursion, nasal pressure flow, and arterial oxyhemoglobin saturation (SaO₂). We also measured beat-to-beat blood pressure utilizing finger arterial photoplethysmography (Portapres, TNO BMI, Amsterdam, The Netherlands). The subjects were all inpatients on the antenatal ward of Royal Prince Alfred Hospital, Sydney, and were studied in a standard hospital bed.

Nasal CPAP Treatment

The 24 preeclamptic subjects were then randomly assigned to receive either treatment with nasal CPAP (CPAP; n =12) or no treatment (no-CPAP; n = 12) on a subsequent night of full polysomnography. The method of randomization involved the application of CPAP to every second patient. We treated subjects with nocturnal nasal CPAP utilizing autoset nasal CPAP (Autoset T, ResMed, Nth Ryde, NSW, Australia). During this subsequent study, we again measured hemodynamic parameters utilizing the Portapres system.

Portapres Measurements

The finger arterial blood-pressure measurements were recorded continuously and noninvasively for the entirety of the study. The cuffs were placed on the third and fourth fingers on the left hand and alternated every 30 minutes. The Portapres device measures finger arterial blood pressure by means of volume clamp method. The Portapres is provided with a height-correcting mechanism and corrects the blood-pressure signal according to the position of the finger relative to the level of the heart.

Data Analysis

Sleep staging and respiratory-event scoring were performed according to standard American Sleep Disorders Association (ASDA) criteria. In all subjects, we utilized the Beetscope software developed in The Netherlands (TNO-BMI, Amsterdam, The Netherlands) to derive beat-by-beat parameters including pulse pressure, heart rate, stroke volume, CO, and TPR. These calculations are based on the waveform data from each pulse-pressure wave using a pulse-contour algorithm. Left ventricular stroke volume was computed using the Modelflow method, which computes aortic flow using the 3-element model of aortic input impedance.

We calculated hemodynamic parameters for stable wakefulness (ie, alpha activity in the electroencephalogram, no evidence of muscle activity, and no gross fluctuations in heart rate), for polysomnographically confirmed sleep (both non-rapid eye movement [NREM] and rapid eye movement [REM] sleep) and for sleep and wakefulness combined. These data were pooled for each of the subject groups, and mean and SD calculated for each. The difference in each of the hemodynamic parameters between sleep and wakefulness was calculated for each study, and data were pooled separately for each of the subject groups. Comparisons were made between groups utilizing analysis of variance. Comparisons were made between all 3 groups (control, preeclamptic no-CPAP, and preeclamptic CPAP) for the first study night. For data obtained on the second study night, comparisons were made between the untreated and treated preeclamptic groups and also between the first and second study nights in both the untreated and treated preeclamptic subject groups.

We performed regression analysis between each of the hemodynamic parameters measured on the first study night in all subjects (both no-CPAP and CPAP) and fetal outcome in terms of fetal weight as a percentage of the normal for gestational age. The level at which P values were considered to indicate a significant difference between measures was .05; however, all P values are reported.

RESULTS

Sleep

All subjects had at least 5.5 hours of sleep (5.9 ± 0.2 hours, 5.6 ± 0.2 hours, and 5.8 ± 0.2 hours in control subjects, no-CPAP, and CPAP subjects during night 1, respectively; P = .44 comparing all 3 groups). However, the amount of REM sleep was significantly reduced in both the no-CPAP and CPAP subjects on the first study night when compared with the control subjects (23% ± 3%, 12% ± 6%, and 12% ± 7% of total sleep time in control, no-CPAP, and CPAP subjects, respectively, P < .001), and was not significantly increased in either the no-CPAP or the CPAP subject group on the subsequent study night (12% ± 6% and 16% ± 5% of total sleep time, respectively, P = .14).

The respiratory disturbance index, while marginally increased in both no-CPAP and CPAP subjects during the first study night when compared with control subjects, was not significantly so (9 ± 4 events per hour, 19 ± 10 events per hour, and 22 ± 23 events per hour in control, non-CPAP, and CPAP subjects, respectively, P = .10). However, all preeclamptic subjects had upper-airway flow limitation as previously described. As expected, the respiratory disturbance index was reduced when preeclamptic subjects were treated with nocturnal nasal CPAP, although this did not reach statistical significance because of the wide variability of sleep-disordered breathing on the first study night (reduced to 3 ± 1 events per hour, P = .13). The mean maximum pressure required to reverse partial upper-airway obstruction in these subjects was 8 ± 2 cm H2O, which is similar to that previously reported.

Cardiac Output

The mean CO during wakefulness was similar between control, no-CPAP, and CPAP subject groups (8.0 ± 0.7 L/min, 7.9 ± 1.7 L/min, and 7.7 ± 1.9 L/min, in control, no-CPAP, and CPAP subject groups, respectively, P = .89) (Figure 1). However, there was a large scatter of values in both the no-CPAP and CPAP subject groups, ranging from 5.6 to 11.2 L/min and 5.4 L/min to 11.4 L/min, respectively, whereas in the control group the range was within normal limits (7.2-9.4 L/min). The CO during wakefulness was not significantly altered during the subsequent study night in either the no-CPAP (7.9 ± 1.7 L/min, P = .48 compared with study night 1) or CPAP groups (7.8 ± 1.2 L/min, P = .85 compared with study night 1).

The major finding of this study was that CO during sleep was significantly reduced in the preeclamptic subjects (both no-CPAP and CPAP) when compared with control subjects (7.7 ± 1.0 L/min, 5.5 ± 0.9 L/min, and 5.7 ± 1.3 L/min, in control, no-CPAP, and CPAP subjects, respectively, P < .001). Thus, in no-CPAP and CPAP subjects, CO decreased by a mean of 2.4 ± 1.5 L/min and 2.0 ± 1.1 L/min, while in control subjects, the decrease was only 0.3 ± 0.6 L/min (P < .001). The magnitude of the reduction in CO during sleep in all preeclamptic subjects was highly correlated with the CO during wakefulness (R² = 0.65, P < .001).

The reduction in CO associated with sleep in the CPAP group was minimized with the use of nocturnal nasal CPAP. Whereas CO during the
first study night in the CPAP group decreased from 7.7 ± 1.9 L/min during wakefulness to 5.7 ± 1.3 L/min during sleep, during the second study, it decreased from 7.8 ± 1.2 L/min during wakefulness to 7.7 ± 1.0 L/min during sleep (a reduction of only 0.13 ± 1.3 L/min, P = .03 comparing night 1 to night 2 in this group). In contrast, the decrease in CO from wakefulness to sleep on the second study night in the untreated preeclamptic group was similar (decreasing from 7.9 ± 1.7 L/min during wakefulness to 5.5 ± 0.9 L/min during sleep, a reduction of 2.4 ± 1.5 L/min, P = .91 compared with the reduction noted to occur on the first study night).

The mean CO during NREM sleep was lower than that during both REM sleep and wakefulness in all 3 groups of subjects (Table 1); however, this was much more pronounced in both of the preeclamptic subject groups. This was predominantly due to CO being at a nadir during slow-wave sleep in both these subject groups.

Blood Pressure and Heart Rate

As expected, on the first study night, blood pressure was significantly greater during wakefulness in both no-CPAP and CPAP subject groups when compared with control subjects for systolic (136 ± 18 mmHg, 135 ± 10 mmHg, and 118 ± 14 mmHg in no-CPAP, CPAP, and control groups, respectively; P = .005) and diastolic (77 ± 10 mmHg, 79 ± 8 mmHg, and 64 ± 12 mmHg in no-CPAP, CPAP, and control groups, respectively; P = .001) blood pressures. Furthermore, while there was a decrement in blood pressure during sleep in control subjects (with a drop in mean arterial pressure [MAP] of 9 ± 6 mmHg from wakefulness to sleep), this was reversed in both no-CPAP and CPAP subjects, such that there were additional increments in blood pressure during sleep (with an increase in MAP of 3 ± 5 mmHg and 6 ± 8 mmHg from wakefulness to sleep in no-CPAP and CPAP subject groups, respectively, P < .001 comparing the change in MAP from wakefulness to sleep in all 3 groups during the first study night). When preeclamptic subjects were treated with nocturnal nasal CPAP, blood pressure was reduced during sleep when compared with wakefulness (MAP decreased by 3 ± 3 mmHg from wakefulness to sleep, P = .005 compared with the change during night 1) (Figure 2). In contrast, a similar increment occurred in blood pressure from wakefulness to sleep in the no-CPAP subjects during study night 2 when compared with study night 1 (MAP increased by 3 ± 4 mmHg, P = .34 comparing the change during night 1 to that during night 2).

Heart-rate values during wakefulness and sleep in the control subject group and both preeclamptic subject groups on both study nights are displayed in Table 2. While heart rate was similar between the control subject group and both preeclamptic subject groups during wakefulness (82 ± 6 bpm, 77 ± 8 bpm, and 82 ± 10 bpm in control, no-CPAP, and CPAP subject groups, respectively, P = .18) (Table 2), heart rate was significantly lower during NREM sleep in both the no-CPAP and CPAP subject groups (64 ± 9 bpm and 68 ± 12 bpm) compared with control subjects (76 ± 6 bpm minute, P = .003). The reduction in heart rate that was associated with sleep was partially normalized with the use of nocturnal nasal CPAP treatment in preeclamptic subjects (75 ± 6 bpm, P = .06 compared with no-treatment study night), while the reduction in heart rate associated with sleep in the no-treatment group on the second study night was similar to the first study night (decreasing by 13 ± 12 bpm, P = .44 comparing study night 1 with study night 2 in the no-CPAP subject group).

![Cardiac output during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (no-continuous positive airway pressure [CPAP]), and in the CPAP-treated subject group (treated with nasal CPAP).](image1)

**Figure 1—** Cardiac output during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (no-continuous positive airway pressure [CPAP]), and in the CPAP-treated subject group (treated with nasal CPAP). Clearly, marked decrements in cardiac output occurred during sleep in preeclamptic subjects, and this was reversed with the use of nasal CPAP during sleep.

**Table 1**—Cardiac output* in pregnant women with and without preeclampsia

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Wake</th>
<th>Sleep State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NREM</td>
</tr>
<tr>
<td>Control</td>
<td>8.0 ± 0.7</td>
<td>7.7 ± 1.4 †</td>
</tr>
<tr>
<td>No CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night 1</td>
<td>7.9 ± 1.7</td>
<td>5.4 ± 2.3</td>
</tr>
<tr>
<td>Night 2</td>
<td>7.9 ± 1.7</td>
<td>5.6 ± 1.9</td>
</tr>
<tr>
<td>CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night 1</td>
<td>7.7 ± 1.9</td>
<td>5.6 ± 1.8 ‡</td>
</tr>
<tr>
<td>Night 2</td>
<td>7.8 ± 1.2</td>
<td>7.4 ± 1.6</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†P < .001 comparing all subjects in the control group with those with preeclampsia in the no-CPAP treatment and CPAP treatment groups on study night 1.
‡P < .05 comparing preeclamptic subjects on night 1 and night 2 in the CPAP treatment group.

![Mean arterial pressure (MAP) during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (no-continuous positive airway pressure [CPAP]), and in the CPAP-treated subject group (treated with nasal CPAP).](image2)

**Figure 2—** Mean arterial pressure (MAP) during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (no-continuous positive airway pressure [CPAP]), and in the CPAP-treated subject group (treated with nasal CPAP). Sleep was associated with increased MAP in preeclamptic subjects, and this was reversed with the use of nasal CPAP during sleep.

**Table 2**—Stroke volume and heart rate* during wakefulness and sleep in pregnant women with and without preeclampsia

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Stroke Volume, mL</th>
<th>Heart Rate, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wake</td>
<td>Sleep</td>
</tr>
<tr>
<td>Control</td>
<td>98 ± 11</td>
<td>102 ± 16 †</td>
</tr>
<tr>
<td>Preeclampsia - no CPAP</td>
<td>104 ± 21</td>
<td>87 ± 17</td>
</tr>
<tr>
<td>Night 1</td>
<td>104 ± 21</td>
<td>87 ± 17</td>
</tr>
<tr>
<td>Night 2</td>
<td>103 ± 21</td>
<td>88 ± 15</td>
</tr>
<tr>
<td>Preeclampsia - CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night 1</td>
<td>90 ± 15</td>
<td>77 ± 9 ‡</td>
</tr>
<tr>
<td>Night 2</td>
<td>97 ± 13</td>
<td>103 ± 13</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†P = .005 comparing no-CPAP treatment and CPAP treatment groups on study night 1.
‡P < .001 comparing all groups on the first study night.
§P < .001 comparing study night 1 with study night 2 in CPAP-treated preeclamptic subject group.
**Stroke Volume**

Data on stroke volume during wakefulness and sleep in control subjects and both preeclamptic subject groups on both study nights are displayed in Table 2. While stroke volume was similar between control and both no-CPAP and CPAP subjects during wakefulness $(P = .20)$, a significant decrement in this parameter occurred in the first study night during sleep in both CPAP and no-CPAP subject groups (increasing by $4 \pm 10 \text{ mL}$ in control subjects, and decreasing by $17 \pm 20 \text{ mL}$ and $13 \pm 14 \text{ mL}$ in the no-CPAP and CPAP subject groups, respectively; $P = .002$ comparing the change in all 3 groups) (Table 2). Once preeclamptic subjects were treated with nocturnal nasal CPAP, the decrease in stroke volume that was associated with sleep was eliminated (with stroke volume increasing by $6 \pm 18 \text{ mL}$ during sleep; $P = .004$ compared with the no-treatment night). However, stroke volume still decreased during sleep in the no-CPAP group during the second study night (decreasing by $15 \pm 15 \text{ mL}$, $P = .35$ comparing study night 1 with study night 2 in the no-CPAP subject group).

When ejection time was analyzed, a marked prolongation was noted to occur in both no-CPAP and CPAP subject groups during sleep. While ejection time during wakefulness was $0.33 \pm 0.01 \text{ milliseconds}$, $0.34 \pm 0.03 \text{ milliseconds}$, and $0.35 \pm 0.02 \text{ milliseconds}$ in control, no-CPAP, and CPAP groups, respectively $(P = .17)$, during sleep this was unchanged in control subjects $(0.34 \pm 0.01 \text{ milliseconds})$, and increased to $0.36 \pm 0.03 \text{ milliseconds}$ and $0.36 \pm 0.03 \text{ milliseconds}$ in no-CPAP and CPAP subjects, respectively $(P = .04$ comparing all 3 groups). Furthermore, when preeclamptic subjects were treated with nocturnal nasal CPAP, the ejection time during sleep normalized to $0.33 \pm 0.02 \text{ milliseconds}$ $(P = .04$ compared with the no-treatment night). By contrast, this parameter was similar during study night 2 in the no-CPAP subject group $(0.36 \pm 0.03 \text{ milliseconds}, P = .034$ compared with study night 1).

**Peripheral Vascular Resistance**

The TPR was greater in both preeclamptic groups when compared with control subjects during wakefulness $(827 \pm 150 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5} , 1048 \pm 240 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ and $1141 \pm 199 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ in control, CPAP, and no-CPAP subjects, respectively; $P = .0001$) (Figure 3). Furthermore, while TPR decreased during sleep in control subjects (decreasing by $42 \pm 88 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$), it increased markedly during sleep on study night 1 in both no-CPAP and CPAP subject groups (by $482 \pm 268 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ and $552 \pm 236 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$, respectively, during sleep; $P < .001$ compared with the change in control subjects). The increase in TPR that occurred during sleep in CPAP subjects was markedly attenuated during treatment with nasal CPAP (decreasing from wakefulness to sleep by $17 \pm 139 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$, $P = .002$ compared with the change on study night 1). In contrast, TPR still increased markedly during sleep in the no-CPAP group on the second study night (increasing by $451 \pm 198 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ from wakefulness to sleep; $P = .44$ comparing the increase from wakefulness to sleep in the no-CPAP group on study nights 1 and 2).

The TPR in preeclamptic subjects during NREM sleep was greater than that during both REM sleep and wakefulness (Table 3) $(1612 \pm 177 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ during NREM sleep; $P = .002$ compared with REM sleep, and $P = .009$ compared with wakefulness).

**Fetal Outcome**

All control and preeclamptic subjects delivered live babies. However, 1 of the babies of the preeclamptic mothers died 2 days after delivery from intraventricular hemorrhage. When we compared fetal birth weight with CO during sleep in preeclamptic subjects, we found a significant correlation ($R^2 = 0.62, P < .001$) (Figure 4).

**DISCUSSION**

In this study, we have shown that while the average CO during wakefulness in patients with preeclampsia is similar to that seen in normal pregnancy, there is a specific sleep-linked reduction of CO in preeclamptic patients. These data are consistent with previous data linking maternal CO with fetal birth weight. The reduction in CO associated with sleep in this group of subjects occurred as a result of a combination of an exaggerated reduction in both stroke volume and heart rate that was induced by sleep. Furthermore, we have shown that the reduction in CO associated with sleep in preeclampsia is minimized with the use of nocturnal nasal CPAP treatment. We have previously demonstrated blood

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**Table 3**—Total peripheral resistance in pregnant women with and without preeclampsia

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Total Peripheral Resistance, dynes·s·cm⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wake</td>
</tr>
<tr>
<td>Control</td>
<td>827 ± 150</td>
</tr>
<tr>
<td>Preeclampsia - no CPAP</td>
<td></td>
</tr>
<tr>
<td>Night 1</td>
<td>1048 ± 240</td>
</tr>
<tr>
<td>Night 2</td>
<td>1052 ± 234</td>
</tr>
<tr>
<td>Preeclampsia - CPAP</td>
<td></td>
</tr>
<tr>
<td>Night 1 (no CPAP)</td>
<td>1141 ± 70</td>
</tr>
<tr>
<td>Night 2 (with CPAP)</td>
<td>981 ± 135</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD.
NREM refers to non-rapid eye movement sleep; REM, rapid eye movement sleep; CPAP, continuous positive airway pressure.
†$P < .02$ comparing baseline night 1 with night 2 in the CPAP-treated preeclamptic group.
pressure to be maximal in preeclamptic subjects during NREM sleep,\textsuperscript{12} this being a result of increased upper-airway resistance, in the absence of arousal, leading to relative hypercapnia and thus centrally mediated increases in peripheral sympathetic nervous system activity. Similarly, we found TPR to be markedly higher during slow-wave sleep, while CO was at its nadir during this stage of sleep, further corroborating the previous data demonstrating slow-wave sleep to be a time of particular cardiovascular vulnerability in preeclamptic patients.

The accurate noninvasive measurement of CO is extremely difficult, with interpatient and intrapatient inconsistencies even in the nonpregnant state.\textsuperscript{4} Because of the difficulty in measuring CO, we had no way of crosschecking the values for CO obtained in the current study. There are many inconsistencies in the literature regarding the absolute value of CO during late pregnancy. Values reported at 36 to 40 weeks range from 5.7 L/min to 8.7 L/min.\textsuperscript{1.2,12-17} The use of Portapres to measure CO has been validated in nonpregnant subjects over a range of CO values. While absolute values of CO have not necessarily correlated well with invasive measurements of CO, relative values of CO correlated very well with these measurements ($r = 0.79$).\textsuperscript{18} Thus we are not certain that the absolute values of CO obtained in the current study are accurate. However, the measurements obtained were found to be internally consistent, with a reduction in CO following delivery consistent with that expected.\textsuperscript{11} The within-patient changes (increasing CO with the duration of pregnancy and reduction of CO in the postnatal period for normal subjects) and the reversal of the sleep-induced reduction in CO provides strong support for the veracity of our results. In particular, the results for preeclamptic subjects on CPAP provide an internally consistent set of results, which gives a degree of confidence in the measurements of CO.

A limitation of the study design is that we did not perform true randomization to allocate subjects into the treatment group but, rather, allocated every second subject to receive treatment. However, there were no differences between the data obtained on the first study night between the 2 subject groups. Clearly then, any differences noted between the 2 subject groups on the subsequent night would be expected to stem directly from the intervention undertaken in the subject group who received treatment on this night.

A number of changes occur in CO during normal sleep, with a reduction during NREM sleep stages and variable changes during REM sleep.\textsuperscript{19} Other hemodynamic changes during normal sleep include a reduction in TPR from wakefulness to the onset of NREM sleep,\textsuperscript{20} with variable changes in TPR during REM sleep. Thus, the relative changes in hemodynamics during sleep in pregnancy were found to be similar to those of nonpregnant subjects. In contrast, subjects with pregnancy complicated by preeclampsia had markedly altered hemodynamic responses during sleep, with reductions in CO over the duration of the night, associated with marked increments in TPR and blood pressure.

The reason for the reduction in CO during sleep in some patients with preeclampsia is unclear. However it is clear that the proximate cause was relieved by the use of nasal CPAP to control partial upper-airway obstruction. The physiologic changes consequent to CPAP use were a reduction in SVR and systemic blood pressure and an increase in heart rate. The failure of the heart to maintain CO during the marked sleep-induced increase in SVR may have many explanations.

While a positive intrathoracic pressure such as that applied with the use of nasal CPAP may result in a small reduction in stroke volume under normal circumstances, clearly the hemodynamic effects of nasal CPAP during sleep in the preeclamptic subjects were sufficient to overcome this, and actually minimize the decrement in CO associated with sleep. We have previously demonstrated a high incidence of partial upper-airway obstruction during sleep in women with preeclampsia, which resulted in a marginal reduction in tidal volume on the order of 10% to 20%, and this was shown to be associated with increments in systemic arterial blood pressure during sleep.\textsuperscript{12} The resultant increments in PaCO$_2$ may be responsible for the increase by way of central chemoreceptor stimulation leading to an increase in peripheral secretion of catecholamines. One of the hallmarks of preeclampsia is endothelial dys-function and resultant increased sensitivity to vasoconstrictive agents, including catecholamines.\textsuperscript{21} Thus, we suggest that the small increments in PaCO$_2$ associated with sleep in preeclamptic subjects results in the marked increase in TPR noted to occur in these subjects. Following substantial increments in TPR and systemic arterial blood pressure, many physical and reflex changes occur in hemodynamics. An increase in TPR may lead to a decrement in stroke volume as a result, which was also noted to occur during sleep in the preeclamptic subjects. Furthermore, prolongation of the ejection time could also be accounted for by increments in TPR.

The reduction in heart rate during sleep in the preeclamptic subjects was likely due to stimulation of the baroreceptors, and this is probably the dominant component in the reduction in CO. The application of nasal CPAP eliminated upper-airway obstruction, such that there was a normalization of ventilatory tidal volume during sleep, thus reducing the increments in PaCO$_2$, allowing the subjects to become eucapnic and a consequential diminution in TPR and systemic blood pressure. This in turn may have been responsible for reducing peripheral catecholamine hyperactivity and the associated hemodynamic changes reported to occur in these subjects during sleep. The net result being reduced baroreceptor-mediated suppression of heart rate and stroke volume and, thus, effectively increasing CO.

Another mechanism for the improvement in CO in the treated preeclamptic group may be due to enhanced left ventricular function. Cardiac adaptation in normal pregnancy involves hypertrophy of the left ventricle due to an increase in circulating volume and a decrease in TPR. Although discrepancies exist regarding the extent of cardiac remodeling in preeclampsia,\textsuperscript{22,23} Borghi et al have shown an exaggerated increase in left ventricular mass and volume and a reduction in left ventricular ejection fraction and fractional shortening of the left ventricle in a group of preeclamptic subjects.\textsuperscript{24} During the transition from wakefulness to sleep, systemic arterial blood pressure, sympathetic nervous system activity, and afterload all decrease in normal pregnancy; however, an increase occurs in preeclampsia. The applications of nasal CPAP during sleep may effectively improve left ventricular function by eliminating partial upper-airway obstruction associated surges in blood pressure and also by increasing intrathoracic pressure. This mechanism would effectively reduce left ventricular afterload and thus improve CO in the preeclamptic group.

While reduced CO in preeclampsia has previously been reported to be associated with intrauterine growth restriction, this study provides further evidence that CO during sleep may be of particular importance to fetal growth, with a significant correlation found between maternal CO during sleep and fetal birth weight. The period of maternal sleep may be a particularly important time for fetal growth, as this is normally when TPR is at a nadir, and thus fetal blood delivery is at its peak. Furthermore, sleep is well known to be a time when the majority of neurohormones are manufactured, including growth hormone,\textsuperscript{20} many of which may be important for fetal growth. Thus, reduction in placental blood flow specifically during maternal sleep may be particularly detrimental to fetal growth and well-being. These findings would suggest that treatment with nasal CPAP in the longer term may be beneficial in increasing maternal CO during sleep, thereby increasing fetal growth.

In conclusion, from these data it seems clear that the hemodynamic abnormalities associated with preeclampsia are amplified during sleep when fetal growth restriction is involved and that these abnormalities can be reversed with the use of nocturnal nasal CPAP treatment. We would suggest that maternal sleep in preeclamptic subjects is an important time during which adverse maternal hemodynamic changes need to be avoided in order to optimize fetal well-being.

\textbf{REFERENCES}


