Contribution of Arousal from Sleep to Postevent Tachycardia in Patients with Obstructive Sleep Apnea

Ali Azarbarzin, PhD; Michele Ostrowski, RPSGT; Zahra Moussavi, PhD; Patrick Hanly, MD; Magdy Younes, MD

1Sleep Disorders Centre, Misericordia Health Centre, Winnipeg, Manitoba, Canada; 2Department of Electrical and Computer Engineering, University of Manitoba, Winnipeg, Manitoba, Canada; 3Sleep Center, Foothills Medical Centre, University of Calgary, Calgary, Canada.

Study Objectives: Heart rate increases after obstructive events in patients with obstructive sleep apnea (OSA). This response is generally attributed to arousal from sleep. However, postevent tachycardia is observed in the absence of arousal at the time of airway opening.4,7,8,16 It is not clear whether the tachycardia in such cases is, as suggested by some authors,4,7,8,16 related to subcortical arousal, which has a lower stimulus threshold than EEG arousal, or is due to innate subcortical reflex responses to changes occurring at the time of airway opening.

Repetitive postevent tachycardia is one of the main cardiovascular consequences of obstructive events and may theoretically contribute to cardiovascular morbidity in OSA. Determining its mechanism is potentially important. Furthermore, demonstrating that reflex subcortical responses can produce postevent tachycardia in the absence of arousal is of importance in understanding the mechanism of airway opening in OSA.17,18 The upper airway opens spontaneously without or before a cortical arousal in more than 30% of events,5,9 and such events are also followed by tachycardia.4,7,8,16 If reflex subcortical responses can independently produce postevent tachycardia, postevent tachycardia without cortical arousal need not signify that a subcortical arousal has occurred.

In this study we measured the heart rate response following obstructive events that were deliberately terminated before spontaneous opening. This was done, in OSA patients, by reducing continuous positive airway pressure (CPAP) to induce obstructive events of different severity and terminating the events after three obstructed breaths (brief dial-downs) by increasing CPAP. The rationale behind this approach is that, as with other innate physiologic responses (e.g., carbon dioxide response), involvement of innate (automatic) responses in

INTRODUCTION

Heart rate increases at the end of obstructive events in patients with obstructive sleep apnea (OSA).1,4 In most cases, there is an associated cortical arousal.5-9 Spontaneous arousals (i.e., without OSA) are also associated with an increase in heart rate10-14 Given these observations, the notion that postevent tachycardia is due to arousal from sleep was easy to accept and little research was undertaken to determine the true mechanism of this type of tachycardia.

Opening of an airway that has been obstructed for some time is associated with many cardiovascular and respiratory changes that can reflexively alter heart rate, including changes in ventilation; intrathoracic, intravascular, and intracardiac pressures; cardiac output; and blood gas tensions.15 It is therefore possible that postevent tachycardia is mediated in part or in total by reflexes that are unrelated to arousal. Furthermore, postevent tachycardia is observed in the absence of cortical arousal at the time of airway opening.4,7,8,16 It is not clear whether the tachycardia in such cases is, as suggested by some authors,4,7,8,16 related to subcortical arousal, which has a lower stimulus threshold than EEG arousal, or is due to innate subcortical reflex responses to the changes occurring at the time of airway opening.

Repetitive postevent tachycardia is one of the main cardiovascular consequences of obstructive events and may theoretically contribute to cardiovascular morbidity in OSA. Determining its mechanism is potentially important. Furthermore, demonstrating that reflex subcortical responses can produce postevent tachycardia in the absence of arousal is of importance in understanding the mechanism of airway opening in OSA.17,18 The upper airway opens spontaneously without or before a cortical arousal in more than 30% of events,5,9 and such events are also followed by tachycardia.4,7,8,16 If reflex subcortical responses can independently produce postevent tachycardia, postevent tachycardia without cortical arousal need not signify that a subcortical arousal has occurred.

In this study we measured the heart rate response following obstructive events that were deliberately terminated before spontaneous opening. This was done, in OSA patients, by reducing continuous positive airway pressure (CPAP) to induce obstructive events of different severity and terminating the events after three obstructed breaths (brief dial-downs) by increasing CPAP. The rationale behind this approach is that, as with other innate physiologic responses (e.g., carbon dioxide response), involvement of innate (automatic) responses in

A commentary on this article appears in this issue on page 819.
postevent tachycardia would manifest as a graded response that increases with event severity, with a temporal pattern that is linked to the time of opening, regardless of severity or duration of the preceding obstruction. However, a low threshold subcortical “arousal” would manifest as tachycardia that occurs only when the obstruction is above a certain severity and its timing would not be linked to the time of airflow opening but, rather, to the time arousal stimulus reached threshold. The latter time would vary with hypopnea severity and time elapsed since dial-down. Thus, arousal-related tachycardia should appear later, or not at all, following relief of mild obstructions than following more severe events. Our results indicate that physiologic responses unrelated to arousal contribute importantly to postevent tachycardia.

METHODS

The current results were obtained by additional analysis of data obtained during previous investigations on the pathogenesis of OSA.19-21 The methods have been described in detail elsewhere.19 Briefly, patients who had a respiratory disturbance index greater than 15 hr
-1 during a level 3 diagnostic sleep study were invited to participate. Exclusion criteria included significant comorbidities (dialysis-dependent renal failure, congestive heart failure, severe chronic obstructive pulmonary disease, previous stroke) or use of sedatives or antidepressant medication. The Conjoint Health Research Ethics Board at the University of Calgary approved the study protocol and all patients gave written informed consent to participate. For the purpose of this analysis, 72 files available from previous studies were sorted alphabetically and the first 20 patients with an apnea-hypopnea index > 40/hr were selected.

Patients underwent two studies on separate nights—a diagnostic polysomnography study followed by the dial-down sleep study.

Diagnostic Polysomnography

The diagnosis and severity of OSA was confirmed by standard overnight, attended polysomnography.19 Certified polysomnographic technologists scored sleep, arousals, and the presence and type of obstructive events using standard criteria.22-24 Apnea-hypopnea index, average and minimum oxygen saturation, and number of respiratory events with arousal were calculated for the supine and lateral positions in nonrapid eye movement (NREM) sleep.

Dial-down Sleep Study

This study was done 9.4 ± 13.3 days after diagnostic polysomnography, before treatment with CPAP. CPAP was applied via a mask connected to a multipurpose ventilator research prototype, described previously,9,25 that allowed reduction of CPAP to 1.0 cm H2O. The variables recorded were the same as during diagnostic polysomnography except for respiratory flow, which was recorded from a pneumotachograph inserted in the hose of the ventilator. Mask pressure was recorded from a side port in the mask. All signals were sampled at 120 Hz and recorded using a WinDaq data acquisition system (DATAQ Instruments, Akron, Ohio).

Studies were performed in the supine position except in four patients who could not sleep on their back. CPAP pressure was adjusted to eliminate snoring and flow limitation (holding pressure). During stable NREM sleep and while breathing room air, CPAP was reduced in steps each lasting three breaths (brief dial-downs). Three to four levels of dial-down pressure were selected that spanned the range between holding pressure and the pressure associated with complete obstruction, or 1 cm H2O, if airflow obstruction did not progress beyond hypopnea during the dial-down. Different dial-down pressure levels resulted in different degrees of flow limitation (hypopneas). Each level was administered two to four times during NREM sleep. The original purpose of this study design was to determine the dial-down pressure at which the airway closes (PCRIT). With these brief dial-downs (9-12 sec) the upper airway opened as soon as CPAP was returned to the holding pressure after the third obstructed breath.

Three to 10 long dial-downs were also performed in each patient at the pressure associated with the most severe obstruction. Here, the dial-down was maintained until the airway opened spontaneously. Figure 1 contrasts the brief and long dial-downs in the same patient.

Dial-downs were always started early in the inspiratory phase of respiration and reached the target pressure level in less than 2 sec (Figure 1). Thus, the first obstructed inspiratory effort always started after the new, reduced pressure had been reached.

Analyses

Analysis was limited to periods of NREM sleep because the large spontaneous variability in heart rate typical of rapid eye movement (REM) sleep precluded confident estimates of the effect of obstruction on heart rate. Several measurements were already on file as they were made in relation to previous analyses concerning unrelated issues.19-21 These included for each dial-down the time of onset, sleep stage, dial-down pressure, holding pressure, peak flow during the dial-down (% baseline on holding pressure), number of breaths during the dial-down, oxyhemoglobin saturation (SpO2) before and the lowest value after dial-down, and whether a cortical arousal occurred. For arousal detection, the electroencephalogram (two central EEG leads and one occipital EEG lead) was examined by an experienced polysomnographic technologist (MO) to determine if and when a cortical arousal occurred during the obstruction or after upper airway opening. A cortical arousal was identified if there was a visible shift to higher frequencies in any of the three EEG leads.22 However, such shifts were considered as arousal even if their duration was 1.5-3 sec (i.e., less than the 3-sec conventional definition), provided they were clearly not spindles.

Critical closing pressure (PCRIT) was also on record and was determined, according to standard techniques,25-27 by plotting the relationship between dial-down pressure and flow during the second breath of the dial-down and establishing the pressure intercept at zero flow.

A technologist who is naive to this field extracted the new data required for the current study. He was asked to open the WinDaq file at the previously listed times of dial-downs, when sleep stage was N2 or N3, and to determine the time of opening of the upper airway. For brief dial-downs the time of opening was the onset of inspiratory flow in the first breath after CPAP was returned to holding pressure (arrow, Figure 1, top). Because of the fast response time of the ventilator used and...
the fact that dial-up was initiated at the beginning of the third expiratory phase in the dial-down, pressure returned to holding level prior to the onset of the next inspiration (Figure 1, top). For long dial-downs, time of opening was the onset of inspiratory flow in the first breath associated with a large step increase in flow. Because long dial-downs were always associated with severe hypopnea or apnea, the first open breath was unambiguous (Figure 1, bottom). Heart rate data were not available in the file during the process of identifying upper airway opening. Once the times of opening were identified, they were entered in a Matlab program that scanned the electrocardiogram (EKG) and pressure channels and determined the R-R interval and beat-by-beat heart rate (HR) for a period extending from 20 sec preceding the dial-down to 20 sec after upper airway opening. An Excel sheet was then generated that contained a listing of time, airway pressure, and HR at each R wave over this period for each dial-down. All subsequent analysis of HR was performed on these Excel sheets.

The R-R interval containing the time of opening was considered as time 0. For each dial-down the change in HR after airway opening was calculated as the difference between HR at 1-sec intervals postopening and average HR in the last 3 to 6 sec before dial-up, with the exact averaging duration being the respiratory cycle duration ($T_{TOT}$) of the patient (reference HR). This approach was to filter out the effect of sinus arrhythmia, if any, in the calculation of reference HR. When the reference is calculated in this manner, any difference between a postopening HR and the reference value incorporates any independent effect the increase in airway pressure may have had on HR during and after dial-up.

**Figure 1**—Top panel: Tracings showing a mild, brief (10 sec) hypopnea produced by decreasing continuous positive airway pressure (CPAP) from 13 cm H$_2$O to 10 cm H$_2$O for three breaths (dial-down). C3/A2 and C4/O1 are two electroencephalogram leads; SpO$_2$, oxyhemoglobin saturation; EKG, electrocardiogram. Time 0 is the time of upper airway opening. Note the increase in flow and in heart rate (numerals above EKG) following the increase in CPAP in the absence of cortical arousal. Bottom panel: Tracings from the same patient showing a long dial-down at 2 cm H$_2$O, producing severe obstruction, which was maintained until the airway opened spontaneously, with intense arousal, at 20 sec. Note that in the brief obstruction (top), peak tachycardia occurred about 10 sec after opening and 18 sec after the onset of the hypopnea (vertical dotted line). At 18 sec following the onset of apnea in the long dial-down (dotted line) there was still no appreciable increase in HR even though the obstruction was much more severe and had lasted longer at this point. Thus, the timing of tachycardia is linked to the end of obstruction and not to the severity of arousal stimuli.
Brief dial-downs were divided into four categories depending on the severity of obstruction. Severity was defined as the lowest peak inspiratory flow observed during the dial-down, expressed as % of baseline peak flow on holding CPAP prior to dial-down.

1. No Hypopnea: Peak inspiratory flow during the dial-down > 90% baseline with no evidence of flow limitation (flattening). HR responses in this category define the independent effect of increasing CPAP at the end of dial-down.

2. Minimal obstruction: Peak inspiratory flow 60-90% baseline.

3. Mild/moderate obstruction: Peak flow during dial-down was 20-60% baseline.

4. Severe obstruction: Peak inspiratory flow during dial-down was < 20% baseline. Most of these events were complete obstructions.

The average time course of HR for all observations in a given category was obtained in each patient. These patient/category specific averages were then averaged for all patients to obtain the overall average ± standard deviation change in HR at 1-sec intervals following opening at the end of each category of dial-downs and after spontaneous opening in the long dial-downs. A change in average HR at any instant following opening was considered significant if the average change, relative to the reference HR, was significantly different from zero (t-test, n = 19). Significant difference among responses in different brief dial-down categories was evaluated by repeated-measures analysis of variance (ANOVA) and, if a significant difference (P < 0.05) was found at a specific time, Tukey post hoc test for multiple comparisons was used to identify which categories differ from each other. P < 0.05 was considered significant.

**RESULTS**

One of the 20 files was not analyzed because the cardiac rhythm was atrial fibrillation. Table 1 shows the anthropometric and polysomnographic findings in the other 19 patients. With one exception (P_{CRIT} = 0.0) P_{CRIT} was ≥ 0 in all patients.

Figure 1 shows tracings of a brief and a long dial-down in one patient. The two panels are aligned at the onset of dial-down. In the brief dial-down (top panel), dial-down was terminated by increasing CPAP to the holding pressure and the airway opened well before it opened spontaneously in the sustained dial-down (bottom panel). HR increased following relief of the obstruction with CPAP even though the obstruction was briefer and much less severe than in the long dial-down, and in the absence of cortical arousal. The vertical dashed line in this figure shows that at 18 sec from the onset of dial-down, postevent tachycardia was at its highest following the brief dial-down. At 18 seconds following the onset of the sustained dial-down (vertical line), there was still no increase in HR even though arousal stimuli would have been more pronounced than at the same time following the brief dial-down.

Table 2 shows some characteristics of the different dial-downs. Long dial-downs were invariably associated with severe hypopnea or apnea with an average flow (standard deviation) of 11.9 ± 6.9% baseline during the event. The airway opened spontaneously after an average 21.9 ± 8.4 sec from the onset of obstruction (Figure 1, bottom panel). SpO₂ decreased on average 6.5 ± 2.5%. In one patient, opening was not associated with

<table>
<thead>
<tr>
<th>Table 1—Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>M/F</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Apnea-hypopnea index (hr⁻¹)†</td>
</tr>
<tr>
<td>Average SpO₂ (%)²</td>
</tr>
<tr>
<td>% time SpO₂ &lt; 90%³</td>
</tr>
<tr>
<td>P_{CRIT} (cm H₂O)</td>
</tr>
</tbody>
</table>

*Polysomnography data are those observed during nonrapid eye movement sleep (stages 1-3) in the body position used in the dial-down study (15 supine, four lateral). F, female; M, male; P_{CRIT}, closing pressure; SpO₂, oxyhemoglobin saturation. Values are mean ± standard deviation.

<table>
<thead>
<tr>
<th>Table 2—Characteristics of different dial-downs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of obstruction</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Arousal</td>
</tr>
<tr>
<td>CPAP pressure (cm H₂O)</td>
</tr>
<tr>
<td>DD pressure (cm H₂O)</td>
</tr>
<tr>
<td>Baseline flow on CPAP (L/s)</td>
</tr>
<tr>
<td>Min flow during DD (% baseline)</td>
</tr>
<tr>
<td>Time to opening (sec)</td>
</tr>
<tr>
<td>Baseline SpO₂ (%)</td>
</tr>
<tr>
<td>Min SpO₂ (%)</td>
</tr>
<tr>
<td>Delta SpO₂ (%)</td>
</tr>
<tr>
<td>Observations per patient</td>
</tr>
<tr>
<td>Baseline heart rate (min⁻¹)</td>
</tr>
</tbody>
</table>

CPAP, continuous positive airway pressure; DD, dial-down; H, hypopnea; Min, minimum; Mod, moderate; SpO₂, oxyhemoglobin saturation. Values in parenthesis are standard deviations.
cortical arousal in any of the long dial-downs. In the other 18 patients, cortical arousals occurred near the time of opening in all long dial-downs. Consistent with an earlier report, onset of cortical arousal was coincident with spontaneous airway opening (± 0.5 sec) in 44% of (45 of 102) of long dial-downs, while occurring 0.5-5.0 sec after airway opening in 43% and 0.5-2.8 sec before airway opening in 13% of such observations. The average difference between arousal onset and time of airway opening for all long dial-downs associated with arousal was 0.5 ± 0.7 sec.

Brief dial-downs were terminated after approximately 12 sec, an average of 10 sec before severe events terminated spontaneously in the sustained dial-downs (Table 2, Figure 1, top). The severity of the obstruction and the decrease in SpO2 varied with the pressure level during the dial-down (Table 2). In dial-downs associated with no obstruction (No H, Table 2) the pressure decrease during the dial-down (10.8 to 7.2 cm H2O) was approximately half the decrease in dial-downs associated with severe hypopneas or apneas (10.6 to 2.9 cm H2O, Table 2). Cortical arousals were observed at some point during or after the dial-downs in only five of 220 dial-downs associated with minimal to moderate obstructions. These were considered incidental and were omitted from further analysis. In five patients no arousals were observed at any time during or following any dial-downs associated with severe obstruction. In the other 14 patients some of the brief, severe obstructive events were followed by brief cortical arousals (Table 2, last column). Most of these arousals (63 of 83, 76%) began after airway opening. The average difference between arousal onset and time of airway opening for all severe brief events associated with arousal was 2.4 ± 1.7 sec.

Figure 2 shows the average sec-by-sec change in HR following upper airway opening for the four levels of brief dial-downs that are not associated with arousal and for the severe, long dial-downs. Data from severe, brief obstructions associated with arousal are not shown here because not all patients are included in this group (Figure 3).

HR at the time of opening (time 0) was significantly lower (P < 0.005) than reference HR (at the end of dial-down) in all brief dial-downs except the most severe. In dial-downs with no associated hypopnea (diamonds, Figure 2), HR showed evidence of sinus arrhythmia during the first breath and was still significantly lower than reference HR (P < 0.05) at 3 sec after opening. Thereafter, it was not significantly different from reference HR.

The response following minimal hypopneas (open squares) was systematically higher than the response with no hypopnea, and showed a similar decrease at 3-4 sec. The increase in HR, relative to reference HR, following these minimal brief hypopneas was significant at 7, 8, and 9 sec. As the severity of preceding hypopneas increased the HR response also systematically increased, but with still evidence of flattening or dip at 3-4 sec. Significant increases from reference HR were found between 6-12 sec for mild/moderate hypopneas and from 1-12 seconds following the brief severe obstructions. Repeated-measures ANOVA revealed significant differences among the brief obstructions (P < 0.01) at all time points between 1 and 11 sec, inclusive. Tukey post hoc test showed significant differences among
es between severe and mild/moderate hypopneas from 2 to 10 sec, and between mild/moderate hypopneas and no hypopneas at 3 and 6 sec to 10 sec. No significant differences were found between minimal and mild/moderate hypopneas.

The change in HR following the severe, long obstructions (with arousals) showed a similar pattern, peaking at 7 sec following airway opening, but was substantially larger than with the brief severe obstructions without arousals. Nonetheless, the increase in HR following brief, severe obstructions (3.8 ± 3.0 min\(^{-1}\)) was approximately half the change following the long, severe dial-downs (7.8 ± 4.0 min\(^{-1}\)), despite the fact that the brief dial-downs were not associated with arousal, were of shorter duration (12.6 ± 2.5 versus 21.9 ± 8.4 sec), and were associated with milder reductions in \(\text{SpO}_2\) (6.5 ± 2.5 versus 4.4 ± 1.9%, Table 2).

To isolate the independent effect of arousal, we compared the change in HR following severe, brief obstruction (i.e. similar duration of obstruction) with and without arousal in the 14 patients who had responses with and without arousals. Furthermore, to isolate the effect of duration of obstruction on ∆HR, we compared the response following brief severe obstruction with arousals with the response following long obstructions with arousal in the same 14 patients. Figure 3 shows the results. Repeated-measures ANOVA showed significant differences (\(P < 0.0005\)) at all times following upper airway opening. The response after long obstructions with spontaneous arousals was significantly higher than after brief obstruction without arousal at all time points and higher than brief obstructions associated with arousals at all time points except at 2 and 3 sec. ∆HR after brief obstructions with arousals was significantly higher than after brief obstruction without arousals only at 7 sec after upper airway opening. There was no significant difference between brief obstructions with and without arousal in severity of obstruction (minimum flow 7.8 ± 3.9 versus 11.6 ± 5.2% baseline; \(P = 0.06\), duration of obstruction (12.8 ± 2.6 versus 12.6 ± 2.9 sec) or extent of desaturation (\(\Delta\text{SpO}_2\) 4.7 ± 2.0 versus 4.5 ± 1.8).

Figure 4, left panel, shows average heart rate in individual patients in the interval dial-down onset ± 10 sec for long dial-downs. These dial-downs were always associated with severe obstruction and with the largest drop in CPAP pressure (from 10.9 ± 2.0 to 3.0 ± 2.0 cm H\(_2\)O). Many patients displayed sinus arrhythmia. Because all dial-downs began in early expiration, all breaths during which dial-down was performed were more or less synchronized and the sinus arrhythmia is evident in the average data (heavy line). There was no significant difference (paired t test) between the peak averages at +5 and −5 sec (66.1 ± 8.5 versus 65.7 ± 8.5 min\(^{-1}\)). There was also no significant difference between the troughs at +2 and −2 sec (64.7 ± 8.7 versus 64.6 ± 8.7 min\(^{-1}\)), or between HR at +10 and −10 sec (65.1 ± 8.4 versus 65.2 ± 8.4 min\(^{-1}\)). The first average peak following the dial-down was prolonged by 1 sec relative to pre-dial-down peak.

The right panel of Figure 4 shows average individual data and overall average (heavy line) for the final 10 sec before spontaneous opening in the same long dial-downs shown in the left panel. Data were synchronized (time 0) at the onset of the first open breath. Sinus arrhythmia is again evident. The trend
in HR in the last 10 sec of the event varied considerably, with four patients showing an increase of more than two beats per min (2.8-6.2 min⁻¹) and four showing a decrease greater than two beats per min (3.4-8.1 min⁻¹). In the remaining 11 patients the changes were minimal (less than two beats per min in either direction). On average, there was no significant difference between HR just before spontaneous opening and HR 10 sec earlier (64.6 ± 7.4 versus 64.6 ± 7.9 min⁻¹), or HR at time 0 (64.8 ± 7.8 min⁻¹) or 1 sec (63.9 ± 8.1 min⁻¹) after dial-down.

**DISCUSSION**

The main findings from the current study are: (1) Deliberate opening of the obstructed airway well before spontaneous opening occurred in sustained dial-downs, and in the absence of cortical arousal, is followed by an increase in HR. (2) The response begins within 1 sec of the onset of the first open inspiration. (3) The timing of peak HR response relative to upper airway opening (approximately 7 sec) is similar for brief, deliberately terminated obstructions without arousal and long, spontaneously terminated obstructions associated with arousal. The timing of peak HR response is also unaffected by severity of the preceding obstruction. (4) The magnitude of the response is graded, increasing with severity of preceding obstruction and with no apparent threshold. (5) The response after brief, severe obstructions is approximately half the response observed after spontaneously terminated obstructions, even though their duration was much less and there was no cortical arousal. Collectively, these findings indicate that postevent tachycardia is to a large extent mediated by physiologic subcortical responses linked to upper airway opening.

**Subcortical or Brainstem “Responses” Versus Subcortical or Brainstem “Arousals”**

Since the inception of sleep monitoring, arousal from sleep has been defined as an abrupt, brief increase in EEG frequency.22,28-31 As defined, excessive EEG arousals have been found to impair sleep quality and result in daytime sleepiness and impaired cognitive function (see Bonnet et al.31 for review). Regardless of their causation, EEG arousals are associated with an increase in HR.1,2,5,10-14 EEG arousals occur only when a threshold stimulus intensity (sound, respiratory effort, etc.) has been exceeded.7,19,32-35

When stimuli that result in EEG arousals above a certain threshold are introduced in graded subthreshold levels during sleep, they elicit graded responses even though there are no obvious EEG changes. For example, in the course of obstructive apneas, inspiratory muscle activity increases and intrathoracic pressure decreases, progressively well before EEG arousal occurs.5,36,37 When ventilation is stimulated with carbon dioxide or hypoxia during sleep, ventilation increases progressively until a finite level is reached at which EEG arousal occurs.10 Genioglossus activity increases progressively during apneic episodes prior to or without EEG arousal.7 Subthreshold auditory stimuli also result in an increase in HR.35 These observations, when added to the extensive literature documenting similar responses in deeply anesthetized animals and, particularly as they relate to HR in sleep, the ubiquitous short-term (e.g., sinus arrhythmia), medium-term (e.g., HR changes during REM sleep), and long-term (overnight) changes in HR that normally occur during sleep leave no doubt that there is an active subcortical system that is capable of changing HR in response to a variety of stimuli without the need to awaken the individual.

We believe that the HR responses described here clearly belong in the category of subcortical responses and not of arousal-mediated responses. The responses have no apparent threshold, occurring with minimal obstructions (open square, Figure 2), and their magnitude is related to the severity of the preceding perturbation (Figure 2). Their timing and pattern are strictly linked to the time of airway opening and not to the severity or duration of the obstruction or to the presence of cortical arousal (Figure 2). Furthermore, if the stimulus that caused the increase in HR after the brief obstructions were an arousal with a lower threshold, HR would be expected to increase long before spontaneous upper airway opening in the sustained severe obstructions. This was not the case (vertical dashed line, Figure 1, and Figure 4). Given these observations, along with the short latency to the onset of postevent tachycardia (<1 sec, Figure 2), we conclude that the increase in HR observed following brief obstructions is a reflex response to changes that occur at the time of airway opening.

Some investigators have applied the term subcortical or brainstem “arousal” to postevent tachycardia when there is no apparent EEG arousal. In fact, the occurrence of postevent tachycardia has been used by some as evidence that arousal occurred at the end of spontaneous events when no EEG arousals could be seen.4,7,8,16 Given the current results, the use of the term “arousal” to characterize the HR response to upper airway opening in the absence of EEG arousal is no longer warranted and may be misleading. This, we believe, is not simply a semantic argument. A large amount of literature has accumulated concerning EEG arousals. The use of the term arousal to describe reflex responses is not only unjustified (it has no definition or means to prove), but it may lead to the false impression that, similar to their EEG namesakes, these subcortical responses are harmful. There is in fact no convincing evidence that subthreshold responses impair sleep quality or cognitive function.18,31,35 Furthermore, because postevent tachycardia is nearly universal in OSA, the use of the term arousal to describe postevent tachycardia when there is no EEG arousal may lead to the mistaken impression by many that physiologic responses are incapable of opening the airway without arousal. This may adversely affect progress in the OSA field. For these reasons, we think that the term arousal should be limited to cases where there are accepted EEG changes.

**Were Cortical Arousal Missed?**

It has been argued that using frontal electrodes or spectral analysis of the EEG may reveal cortical arousals that are not visible in the central electrodes. The findings of O’Malley et al.38 that, at times, arousals could be identified in frontal electrodes when not found in central electrodes could not be confirmed in a subsequent study.39 Furthermore, the data presented in the study by O’Malley et al. show that in such cases (arousals in F but not C electrodes) central electrodes also showed arousal-like changes that simply did not meet the 3-sec rule. In our study EEG arousals were scored even when the high frequency shift lasted less than 3 sec (see Methods section). As to the use of spectral analysis to exclude subtle EEG changes at the time of opening, we previously performed spectral analysis...
in the 3-sec epoch astride the point of upper airway opening and compared the power in different frequency ranges to the values found in 20 3-sec epochs prior to CPAP dial-down. The procedure was similar to the one used in the current study (i.e., dial-downs from CPAP). Among 206 cases of upper airway opening with no visible EEG arousal, there were no significant changes in any frequency range in 114 (55%) (Table E1, Younes et al.3). In another 30% there was an increase in delta power either alone (17%) or in combination with an increase in higher frequencies (13%). Interpretation of these changes is difficult because the increase in delta power may simply represent a K complex or even progression into deeper sleep.4 An increase in high-frequency power in association with an increased delta power is also difficult to interpret when there are no visible alpha or beta waves. Unless the delta waves are perfect sinusoids (which is never the case), spectral analysis will show an increase in higher frequencies to account for the nonsinusoidal nature of the delta wave (harmonics). Only in 15% of the observations was there an increase in theta, alpha, and/or beta power in the absence of delta waves. Some of these would be predictable statistically when using 20 measurements as the reference. Others may represent missed visible arousals. Thus, we believe that spectral analysis would not have altered our findings. Furthermore, the graded nature and absence of a threshold for eliciting the HR response argue strongly against the presence of an undetected cortical arousal at the time of opening.

Another possible argument is that the tachycardia following brief dial-downs was not a response to upper airway opening but was due to subcortical arousal or some reflex response to the increase in CPAP at the end of the dial-down. This possibility was excluded by the response to CPAP increase when there was no preceding hypopnea (diamonds, Figure 2). These responses indicate that if the CPAP increase had any effect it was in the opposite direction; a very mild bradycardic influence that lasts 3-4 sec after increasing CPAP (Figure 2). The reflex response to the rise in CPAP likely accounts for the attenuated HR response at 3-4 sec after opening when dial-downs were associated with hypopneas.

**Contribution of Cortical Arousal to Postevent Tachycardia**

Spontaneous or induced arousals in the absence of airway obstruction are associated with transient tachycardia.10–14 Thus, there is reason to believe that arousals contribute to postevent tachycardia when they occur near the time of airway opening. The current study provided an opportunity to determine this contribution. In 14 patients some brief, severe obstructions were followed by arousals. Most of these arousals occurred a few sec after opening. They were likely due to the fact that blood gas tensions continued to deteriorate for several sec (circulation delay) after opening or, as suggested earlier,9 were triggered by sensory inputs associated with airway opening (e.g., snoring, pharyngeal vibration). The difference in HR response between those brief obstructions with and without arousal was relatively small, accounting for approximately 30% of peak HR response in observations with arousal (Figure 3), and barely significant (Figure 3). It must be pointed out, however, that most of these arousals were brief (2-6 sec) and not associated with movement. However, because most arousals associated with OSA are also brief and not intense, it is likely that the postevent tachycardia observed in that disorder is mostly due to physiologic responses and not to arousals.

The arousals associated with spontaneous opening in long dial-downs were generally more intense (Figure 1, bottom panel) and lasted much longer, often progressing to full awakening. Sforza et al.14 observed that prolonged (> 10 sec) spontaneous arousals are associated with more protracted unimodal (i.e., no secondary bradycardia) tachycardia than briefer ones, which were associated with bimodal changes in HR. With brief, severe obstructions the time course of HR increase was similar with and without arousal, with the tachycardia being followed by bradycardia at approximately 12 sec (Figure 3). The tachycardia associated with long dial-downs was more protracted and no bradycardia was observed within the 20 sec of postevent observation (Figures 2 and 3). It is, therefore, very likely that the difference in HR beyond 12 sec between long and brief, severe obstructions (Figure 2) was mediated by the more prolonged arousals associated with the long dial-downs.

In summary, we believe that brief (< 6 sec), nonintense arousals associated with airway opening in OSA contribute little to postevent tachycardia, whereas prolonged, intense arousals and awakenings result in more protracted tachycardia, and possibly a greater increase in HR.

Jordan et al.4 measured ventilatory and HR responses after spontaneous upper airway opening in the course of sustained dial-downs. Some of these spontaneous openings were not associated with cortical arousal. They found that ventilatory responses were greater in the presence of arousal. However, when the obstructive events were matched for severity, the ventilatory responses were no longer different. This lack of difference was interpreted as indicating that subcortical arousals accounted for the postevent increase in ventilation. The main argument to support this conclusion was that HR responses were similar with and without cortical arousal, whereas both were greater than the increase in HR observed when the obstructive events were terminated by increasing CPAP, after failing to terminate spontaneously. The obstructions terminated by increasing CPAP were, however, extremely mild.4 Where our interventions were comparable to those of Jordan et al., the findings were identical. Thus, when severity of obstruction was matched, there was little difference in HR responses whether or not a cortical arousal was present (Figure 3). Also, as in the study by Jordan et al., the HR response with more severe obstructions was substantially higher than with mild obstructions (Figure 2). However, by measuring the HR response following deliberately terminated events of different severity well in advance of spontaneous opening, our study provided additional evidence that clearly points to a radically different conclusion, namely that postevent tachycardia is primarily a physiologic response, whereas the lack of difference between observations with and without cortical arousal simply reflects a minimal contribution of arousal when it occurs in this setting.

In summary, our results indicate that postevent tachycardia is mediated primarily by subcortical reflex responses, whereas arousal contributes little except when prolonged and intense.

**ACKNOWLEDGMENTS**

This study was supported by the Canadian Institutes of Health Research.
REFERENCES

6. Dingli K, Fietze I, Assimakopoulos T, Quispe-Bravo S, Witt C, Doug- 

DISCLOSURE STATEMENT

This was not an industry supported study. Ms. Ostrowski receives salary from Younes Sleep Technologies Ltd. Dr. Mous- 
savi receives research support from Philips/Respironics and has received income from Neural Diagnostics Ltd Pty; she has also received equipment from the ND Company. Dr. Younes is majority owner of YRT Ltd and YST Ltd. The other authors have indicated no financial conflicts of interest.