Cardiovascular variability after arousal from sleep: time-varying spectral analysis


Submitted 2 December 2002; accepted in final form 13 June 2003

IN RECENT YEARS, the spectral analyses of heart rate variability (HRV) and blood pressure variability (BPV) have been used frequently as noninvasive tools for the assessment of autonomic cardiovascular control (22, 31). There is a general consensus that the high-frequency (HF; 0.15–0.4 Hz) component of HRV (HFPRR), which reflects what is commonly termed “respiratory sinus arrhythmia,” represents a reasonably good index of parasympathetic activity. On the other hand, there remains a considerable amount of controversy as to whether the low-frequency (LF) HRV component (LFPRR; 0.04–0.15 Hz) represents only sympathetic activity or a combination of both sympathetic and parasympathetic modulation of heart rate (12, 30, 38). An alternative index is the ratio between LFPRR and HFPRR (LF/HF; equal to LFPRR/HFPRR). LF/HF is frequently used as a measure of “sympathovagal balance” and is based on the premise that, under most physiological conditions, cardiac sympathetic and parasympathetic influences are reciprocally regulated (24).

There is greater agreement over the notion that the LF component of arterial pressure offers a useful marker of sympathetic vasomotor modulation (25). Thus, although this principle cannot be generalized to encompass all situations (16), the application of spectral analysis to measurements of both heart rate and blood pressure constitutes a valuable noninvasive approach for studying autonomic control in humans under some conditions.

Conventional spectral analysis assumes stationarity in the signal being analyzed and thus cannot be applied to processes in which there is significant transient activity, such as during arousal from sleep. However, there exists a number of techniques, such as wavelet analysis (10), Wigner-Ville distributions (32), and time-varying autoregressive modeling (14), that can circumvent this limitation. Application of these “adaptive filtering” algorithms enables the tracking of time-varying spectral features. The time-varying autoregressive modeling approach has been used recently to estimate the transient changes in HRV and BPV accompanying orthostatic tilt and acute ischemic episodes (8). To date, we do not know of any study that has applied this approach to quantify the dynamic changes in cardiovascular variability that are likely to accompany transient arousal from sleep.

Patients suffering from obstructive sleep apnea syndrome have abnormally high levels of sympathetic activity, a result presumably of chronic exposure to the periodic episodes of hypoxia, hypercapnia, and arousals from sleep that usually accompany the recurring
Experimental Protocol

Methods

Experimental Protocol

The analysis presented here was based initially on previous reports from eight normal healthy volunteers who each participated in an overnight sleep study (28). The short duration of the recordings made during each experimental trial did not allow us to examine the complete time course of the more subtle cardiorespiratory changes that occurred after transient arousal. As such, we applied our analysis procedures to the recordings obtained from another eight healthy individuals in a second study. The results of this second study have not been previously published. We will refer to these studies as study 1 and study 2, respectively.

Study 1. Complete details of the subjects and the experimental protocol employed in this study have been described previously by Morgan et al. (28). All eight subjects were normotensive and free from cardiovascular, pulmonary, and cerebrovascular disease. Measurements included electroencephalogram (EEG; central and occipital channels), chin electromyogram, electrooculogram, ECG, respiratory airflow (by calibrated inductance plethysmograph), and arterial blood pressure (by finger plethysmography, Finapres, Ohmeda; positioned on the third finger of one hand; the hand was at heart level). Raw MSNA was recorded from the peroneal nerve and subsequently amplified and integrated; the integrated neurogram time courses were used for comparison with corresponding HRV and BPV spectral measures. All signals were digitized at 128 Hz/channel.

Throughout the night, the following experimental procedure was conducted repeatedly. After the subject had attained a stable period of NREM sleep for at least 1 min, as determined from the EEG, a brief acoustic stimulus (frequency of 1 kHz and duration of 0.5 s) was delivered, causing a transient arousal. The amplitude of the stimulus ranged from 45 to 80 dB, as subject comfort allowed to return to a stable sleep state before another arousal was induced.

Study 2. This study was performed on a second set of eight healthy individuals at the General Clinical Research Center of the Los Angeles County/University of Southern California Medical Center. Written, informed consent was obtained from each subject before participation in the study. The experimental protocol employed was identical to the one used for the study 1, except for the standardization of the duration of each experimental trial: each recording was 4 min long and began 1 min before application of the binaural acoustic stimulus. However, in this case, MSNA was not recorded. Average age and body mass index were 41.80 ± 5.98 yr and 26.32 ± 1.74 kg/m² (means ± SE), respectively. Each subject was connected via nasal mask to a ventilator (model S/T-D 30, Respironics, Murrayville, PA) that delivered a minimal continuous positive airway pressure level of 2–3 cmH₂O. The low level of continuous positive airway pressure was applied to minimize the effects of changes in upper airway resistance on respiratory airflow during sleep and arousal. A chin strap was applied to prevent leakage of airflow through the mouth. Pressure within the mask and inspiratory and expiratory airflow were acquired by recording the patient output signals obtained from the detachable control panel (DCP 30, Respironics) available for use with the ventilator system. Continuous arterial blood pressure was monitored (model 7000, Colin Medical Instruments, San Antonio, TX), along with a single-lead electrocardiogram (BMA-831 bioamplifier, CWE, Ardmore, PA). The other standard polysomnographic variables were monitored by using the Easy II Sleep System (Cadmell Laboratories, Kennewick, WA). These variables included oxygen saturation, three electroencephalogram derivations (C4/A1, C3/A2, and O1/A2), chin electromyogram, left and right electrooculograms, and leg movements. The acoustic stimulus intensity employed in each experimental trial ranged from 55 to 90 dB. The frequency of the applied tone was 1 kHz and lasted for a duration of 0.5 s. The recorded data were digitized at 200 Hz/channel.

Data Analysis

R-wave-R-wave intervals (RRI) were extracted from the ECG by using a derivative threshold-based algorithm that also allowed manual editing of the results to verify the
absence of detection errors and then were resampled to 2 Hz by using the Berger algorithm (4). Beat-to-beat systolic blood pressure (SBP) was also deduced automatically from the arterial blood pressure signal. The RRI, SBP, and respiration time series were subsequently resampled at 2 Hz for autoregressive modeling. Spectral analysis was conducted on the cardiovascular time series at a 2-Hz sampling rate. However, spectral analysis of respiratory airflow was performed at sampling rates of 12.8 Hz (study 1) and 20 Hz (study 2). A sample of these data before and after the occurrence of the acoustic stimulus is shown in Fig. 1.

Arousals were visually scored from the EEG by using American Sleep Disorders Association standardized criteria (36). These events were divided into two categories. Type N arousals represented those responses with no change in EEG or chin electromyogram. Type A arousals included all responses in which increased EEG frequency was observed for at least 3 s. These responses were all measured during NREM sleep. Fifty-one trials from 16 subjects were found to be type A, whereas 66 trials from 14 subjects were found to be type N. The number of data sets per subject that could be analyzed was limited by a number of factors. In study 1, the difficulty of maintaining a stable MSNA recording limited the total study duration to only a few hours. Data sets in which the acoustic stimulus was delivered too close to the start of the record were rejected, since our adaptive spectral estimation algorithm required some lead time (15–20 s) for stabilization. In study 2, several individuals had difficulty returning to stable states of sleep after arousal. In addition, some arousals were accompanied by body movement that reduced signal quality; the continuous blood pressure monitor was especially prone to this problem.

**Autoregressive Modeling and Spectral Estimation**

The time-varying spectra of the RRI, SBP, and respiration time series were computed in the following way. An autoregressive model was assumed for each time series. The portion of the signal before tone onset was considered to be stationary. Time-invariant (constant coefficient) autoregressive models of orders ranging from 8 to 20 were fitted to this section of data. A first estimate of the “optimal” model order was determined by selecting the autoregressive model that minimized the Akaike Information Criterion (22) and also produced residual errors that were uncorrelated. Because the Akaike Information Criterion tends to result in overestimation of model order, we also examined the magnitude of the estimated autoregressive coefficients. If there were any coefficients that were statistically indistinguishable from zero, the present model order was discarded and the preceding (lower) model order was tested, provided that the residuals remained uncorrelated. Thus the optimal model was selected to be the one in which 1) Akaike Information Criterion was at or close to its global minimum value, 2) the model residuals

---

**Fig. 1.** An example of the effects of acoustically induced arousal from sleep on central EEG (C4/A1, used for sleep and arousal scoring together with C3/A2 and O1/A2 derivations), muscle sympathetic nerve activity (MSNA), R-wave-R-wave interval (RRI), systolic blood pressure (SBP), and respiratory (Resp.) air flow. The stimulus was delivered at time \( t = 0 \).
remained uncorrelated, and 3) all model coefficients were significantly different from zero.

After the optimal model order was determined, the next step was to allow the autoregressive model to have time-varying coefficients. The recursive least squares (RLS) algorithm (8, 14) was used to estimate the autoregressive model coefficients at each time step. This adaptive estimation procedure was applied to the entire length of the dataset (i.e., before and after tone onset). The estimated time-varying autoregressive model coefficients were subsequently transformed into the frequency domain to produce estimates of the corresponding power spectra (14). This approach allowed us to obtain an estimate of the spectrum of the time series in question (RRI, SBP, or respiratory air flow) every 0.5 s.

An important parameter that had to be determined was the value of the “forgetting factor” (λ) used in the RLS algorithm. The λ basically reflects the memory of the adaptive filter: a value equal to unity represents the case in which all data before the present time is used in computing the model estimates, whereas a value substantially smaller than unity implies that only the most recent data points are utilized. A λ that is too large results in a filter that does not adapt quickly enough to the changes in the data, whereas a λ that is too small can lead to unstable estimates. Thus, to obtain the optimal λ, the following procedure was carried out. The RLS algorithm was applied to each data set multiple times, with λ set equal to a different value each time. Subsequently, we selected the value of λ that minimized the mean square error between the model prediction and the data. The average value of λ across all subjects and signals was 0.954. The range of values over which λ was varied ranged from 0.9 to 0.99.

The algorithm was initially tested on simulated signals with the same primary spectral components as the SBP and RRI data sets. These simulated signals generally consisted of two sinusoidal functions with different degrees of added white noise and with amplitudes that changed abruptly. Figure 2 displays an example of such a signal in which there is an abrupt step increase in HF power and concomitant decrease in LF power. Depending on the dynamic content of the signal, the RLS algorithm required 15–20 s (from the start of the time series) to stabilize; thus trials in which the acoustic stimulus was delivered <20 s after the start of the recording were not eligible for analysis. In Fig. 2, the algorithm was able to detect the abrupt decrease in LF power in ~1 s. On the other hand, it took almost 20 s to track the step increase in HF power.

From each successive spectral estimate, we computed the powers of the LF and HF spectral components of RRI (LFPRR and HFPRR), the LF/HF (equal to LFPRR/HFPRR), and LF power of SBP (LFPBP). We also computed the spectral power of respiratory airflow in the HF band (HFPAP), since this represented the component of breathing waveform most likely to influence HFPRR. As well, to delineate the respiratory-related components of the RRI spectrum from the non-respiratory components, we computed the following modified spectral indexes from the RRI and respiration spectra, as proposed by Khoo et al. (18): 1) the modified ratio of LF to HF power (MLHR) and 2) the transfer gain between respiration and RRI (G_{RSA}) computed in the HF band. MLHR is analogous to LF/HF, except that the numerator and denominator in the former ratio both represent the power of HRV in the respective frequency bands after all influences from respiration were decorrelated. G_{RSA} provides an index for quantifying the extent to which HFPRR is influenced by respiration. Computation of MLHR and G_{RSA} at successive time steps of 0.5 s required the application of the RLS algorithm to estimate the time-varying coefficients of an autoregressive with exogenous input model that related respiration as input to RRI as output (22) and subsequently converted these coeffi-

![Fig. 2. Time-varying spectral analysis of a simulated signal that consisted of 2 sinusoidal components. A: the simulated (noiseless) signal, which contains a strong 0.1-Hz component and a weak 0.3-Hz component, changes abruptly at f = 0 into a signal that contains a weak 0.1-Hz component and a strong 0.3-Hz component. B: the time-varying power spectral density (PSD) function estimated from the above signal with the use of the recursive least squares algorithm.](image-url)
coefficients into the frequency domain to obtain the corresponding time-varying transfer function.

The effects of arousal on respiration were also quantified by computing tidal volume, inspiratory duration, expiratory duration, and minute ventilation on a breath-by-breath basis before and after presentation of the acoustic stimulus.

Statistical Analysis

Because multiple trials were available for analysis in each subject, we determined at each time point the median value of the parameter in question. Median filtering, rather than ensemble averaging, was employed to minimize the effect of outliers. All values in each median time course were normalized with respect to the average baseline value (i.e., the mean of the last 10 s before the stimulus) and expressed as percent change from baseline. In each condition (type A arousal and type N arousal), we computed the group-averaged time course across subjects for each parameter.

To determine whether each of the parameters attained levels significantly different from baseline with each class of arousal, we performed one-way repeated-measures analysis of the variance on each parameter (with poststimulus time being the single factor) in each of the two conditions. The null hypothesis was that there were no changes in the time course of the parameter with respect to the baseline level. In those cases where the null hypothesis was rejected, we sought to identify the time points at which a significant change occurred relative to baseline. This was achieved by performing post hoc multiple pairwise comparisons between each poststimulus data point against the prearousal baseline by using Dunn’s test. A P value of <0.05 was assumed to indicate statistical significance. Unless otherwise stated, all results are presented as means ± SE.

In the data sets derived from study 1, the arousal responses available for analysis were limited to a poststimulus maximum duration of 28 s. As such, time-varying spectral analysis was performed up to that time point only for all 16 subjects in both studies. However, a separate statistical analysis was applied to the data sets obtained from the eight individuals in study 2; in that study, arousal responses up to 70 s poststimulus were included in the analysis.

RESULTS

Spectral Changes in HRV During Arousal

An example of the changes in HRV that occurred during acoustically induced arousal from NREM sleep is displayed in Fig. 3. In that figure, the time-varying power spectrum of the RRI time series of a subject is shown before and after the acoustic stimulus, which occurs at time (t) = 0 s. There was a rapid surge in the overall magnitude of the RRI spectrum accompanying the arousal, particularly in the LF region. It should also be noted that the increased LF power remained at an elevated level for up to 40 s after the presentation of the stimulus. HF power was also lower than baseline in the postarousal period, although the change was not as substantial as the increase displayed by LF power. The corresponding time courses for RRI and respiratory air flow are displayed below the time-varying power spectrum of the RRI time series plot for comparison. In the first few seconds after stimulus presentation, there was a large decrease in RRI (increase in heart rate) and a concomitant increase in airflow for the first three to four breaths. This was followed by an overshoot before RRI settled back to baseline.

The ventilatory response to transient arousal displayed in this example is representative of the average response to type A arousals measured in all subjects. Prearousal baseline minute ventilation averaged 6.15 ± 0.45 l/min. During arousal, ventilation increased to 9.20 ± 1.02 and 7.85 ± 0.47 l/min on the first and second breaths (P < 0.001; post hoc Dunn’s pairwise comparisons vs. baseline gave P values of <0.05 for breaths 1 and 2 poststimulus), respectively, before reverting to levels indistinguishable from baseline ~10 s after stimulus presentation (see Fig. 4A, top). These increases in ventilation were predominantly due to increases in tidal volume, with no significant changes in inspiratory or expiratory breath durations, consistent with the patterns reported in previous studies (1, 2, 18). Ventilation did not show significant changes during type N arousals.

Averaged Time Courses: Markers of Parasympathetic Activity

The time courses for changes in ventilation, RRI, HFP_{AF}, HFP_{RR}, and GR_{SA}, averaged across all subjects in each condition, are displayed in Fig. 4. Asterisks indicate the times at which each of these group-averaged time courses attained a value significantly different from baseline. With type A arousals, RRI displayed a rapid and significant decrease of 10–15% of baseline levels ~4 s after stimulus presentation (Fig. 4A, bottom). However, after ~10 s, RRI returned to levels indistinguishable from baseline. This behavior is consistent with the example displayed in Fig. 3 for one of the trials in one subject. In contrast, with the type N arousals, we found no significant changes in RRI, even in the first few seconds after stimulus presentation.

Type A arousals produced changes in HFP_{RR} that were highly variable across and within subjects (Fig. 4B, middle), particularly in the first 10 s of the arousal response. On average, there was a tendency for HFP_{RR} to display an initial dip, a transient reversion toward the baseline level, and subsequently a second and more sustained depression. The second and third phases of the average HFP_{RR} time course exhibited behavior similar to that of HFP_{AF} (Fig. 4B, top) by displaying an initial increase followed by a sustained decrease to levels below baseline. The average correlation between HFP_{AF} and HFP_{RR} was modest (r = 0.45) but significant (P < 0.005). In contrast, there were no significant arousal-induced changes in GR_{SA}. Type N arousals produced no changes in breath-by-breath ventilation, HFP_{AF}, HFP_{RR}, or GR_{SA}.

Averaged Time Courses: Markers of Sympathetic Activity

The averaged time-courses for the responses in SBP, MSNA, LF_{SBP}, LF/HF, LFP_{RR}, and MLHR before and after tone presentation are shown in Fig. 5. In type A arousals, the averaged time course for MSNA was very similar to the sample profile displayed in Fig. 1B;
MSNA increased dramatically above baseline \( \sim 2 \) s after the stimulus but returned to baseline levels before the end of 5 s. In contrast, the other five parameters displayed an initial increase with overshoot, followed by a more gradual decline toward final levels that remained significantly above baseline. Although LFPSBP became indistinguishable from baseline \( \sim 23 \) s after the tone, the indexes of LF HRV remained elevated (Fig. 5). Separate analysis of the longer data sets (up to 70 s poststimulus) from the eight subjects in study 2 revealed that the LF HRV parameters returned to baseline only after 40 s poststimulus. It should also be noted that the indexes of LF HRV (LF/HF, LFFPRR, and MLHR) displayed little change until \( \sim 4 \) s after the stimulus. The blood pressure indexes (SBP and LFPSBP) started increasing even later, at \( \sim 5 \) s after the tone.

With type N arousals, the poststimulus peak increase in MSNA was more variable and not as large as the corresponding response in the type A arousals, but the change was statistically significant (\( P < 0.01 \)). As in the case for type A arousals, MSNA rapidly returned to baseline. The results for the average peak increase in SBP were similar. The responses in type N were smaller compared with those in type A (8.1 \( \pm \) 1.1 vs. 22.1 \( \pm \) 3.3%), but it is important to note that the type N peak SBP increase was significant (\( P < 0.05 \)).

Fig. 3. A: time course of the PSD of RRI (PSD_{RRI}) from 1 arousal trial. RRI (B) and respiratory air flow (C) signals corresponding to the time-varying RRI spectrum are also displayed. The acoustic stimulus was delivered at \( t = 0 \). Positive values of airflow represent inspiration.
reverted to baseline levels after ~15 s. The time courses displayed by LFP<sub>SBP</sub>, LF/HF, LFP<sub>RR</sub>, and MLHR in type N arousals were quite different from that of SBP; none exhibited significant changes with respect to baseline after stimulus presentation.

**DISCUSSION**

A key finding in this study is that cortical (type A) arousals were accompanied by large increases in MSNA and correspondingly large increases in all spectral indexes of LF cardiovascular variability, i.e., LF/HF, LFP<sub>RR</sub>, MLHR, and LFP<sub>SBP</sub>. However, unlike the increases in MSNA, which lasted only 2–3 s, the spectral parameters remained elevated above the prearousal baseline for up to 40 s after the application of the brief acoustic stimulus. SBP also continued to remain significantly higher than baseline during this postarousal period. In noncortical (type N) arousals, the rise in SBP was small but nevertheless significant; however, SBP returned quickly to baseline. These results are consistent with the conclusion derived from a previous study that arousal responses lie on a continuous rather than discrete scale (33).

Although the arousal-induced surge in MSNA occurred within the first few seconds of stimulus presentation, LF/HF and LFP<sub>RR</sub> started to show increases only at ~5 s poststimulus, followed by increases in SBP and LFP<sub>SBP</sub> that began ~1 s later. Because the RLS algorithm was able to track changes in LF power rapidly, we believe that these latency differences were not merely artifacts of our methodology. Instead, the differences in latencies among central sympathetic activity (most closely reflected by MSNA), cardiac sympathetic activation, and sympathoexcitation of the peripheral vasculature were likely to be due to differences in the response times of the end-effector organs (26, 35). Thus arousal-induced sympathoexcitation of skeletal muscle vasculature may have been rapid and brief, whereas sympathetic outflow to the other peripheral vascular beds, such as the visceral or renal systems, tended to follow a more prolonged time course. The latter has been observed in a porcine model (20). Spatial and temporal nonuniformity in the distribution of sympathetic outflow to the various target organs was also likely to have played an important role in producing these disparate arousal responses (26). For instance, regional nonuniformity of sympathoexcitation has been observed in defense-like cardiovascular responses in cats (19). The role played by baroreflex feedback also could have been substantial. First, the postarousal rise in blood pressure was likely to have inhibited the early arousal-induced increase in central sympathetic activity, thus contributing to the rapid return of MSNA to baseline (40). Second, there was likely a transient decrease in baroreflex sensitivity during arousal, analogous to the reduction in baroreflex control of heart rate that is produced by mental arousal in wakefulness (9). This transient inhibition of the baroreflex, in turn, may have allowed the rise in blood pressure to be larger than it would have been without any change in baroreflex sensitivity. Finally, the baroreflex modulation of heart rate and baroreflex-mediated control of peripheral vascular resistance have been shown to be capable of generating oscillations in the LF range (25, 26). Thus resonances in these baroreflex loops may have been the mechanism through which LF oscillations in heart rate (represented by LFP<sub>RR</sub>) and blood pressure (represented by LFP<sub>SBP</sub>) remained relatively sustained in the late phase of the arousal response (t > 10 s), even after mean heart rate and blood pressure had returned to baseline levels.

The rapid surge in heart rate that accompanies the first several seconds of arousal is frequently taken to indicate a substantial parasympathetic withdrawal (15, 28). However, the use of heart rate change as an

---

*J Appl Physiol* • VOL 95 • OCTOBER 2003 • www.jap.org
index of parasympathetic activity during arousal is complicated by the simultaneous occurrence of large changes in respiration (Fig. 4A, top). For this reason, we examined jointly the time courses of RRI, HFP RR, and GRSA to delineate respiratory-related from respiratory-uncorrelated contributions to the parasympathetic response. Although RRI decreased rapidly in the first few seconds during arousal, the corresponding reduction in HFP RR was smaller in magnitude and followed a noticeably slower time course. GRSA remained indistinguishable from baseline. This suggests that the initial phase of the arousal response likely
involved some degree of vagal withdrawal correlated to the respiratory response but not detected in the estimated time-varying RRI spectra. This discrepancy in our observations may have been the consequence of a limitation in our methodology, since our tests with simulated data (Fig. 2) indicated that the RLS algorithm is relatively slow in its ability to track abrupt amplitude changes in HF oscillations. After \( t > 10 \) s, HFP\(_{RR} \) remained below control levels, whereas G\(_{RSA} \) hovered at levels not different from baseline. The simultaneous decrease in HFP\(_{AF} \) over the same duration suggests that the sustained reduction in HFP\(_{RR} \) was secondary to changes in respiration. Overall, these findings lead us to conclude that the parasympathetic heart rate response to arousal was mediated predominantly by the coupling between respiratory drive and heart rate. This conclusion is at variance with a previous study (15) using a canine preparation made apneic with mechanical hyperventilation; in that study, pharmacological blockade demonstrated the presence of a strong vagal withdrawal that accompanied arousal independent of any change in respiratory drive. In the study by Trinder et al. (39), sleeping humans were placed under assisted ventilation. During arousal, these subjects demonstrated a brisk increase in heart rate despite the fact that ventilation was maintained at a constant level by the ventilator. On the other hand, although airflow remained unchanged, measures of respiratory effort (diaphragmatic electromyogram and mask pressure) exhibited an increase at arousal, implying that one could not dismiss the possibility that the increase in ventilatory drive, in the form of the “wakeness stimulus” was indirectly responsible for the heart rate change.

An initially puzzling finding was the inconsistency in pattern between the average time courses of HFP\(_{AF} \) and breath-to-breath minute ventilation. First, the arousal-induced increases in minute ventilation were largest in the initial first and second breaths following stimulus presentation (\( P < 0.05 \)), whereas average HFP\(_{AF} \) showed some tendency to increase between breaths 3 and 4 (\( t = -9–10 \) s). Second, ventilation became not significantly different from baseline when \( t > 9 \) s, whereas HFP\(_{AF} \) remained at a level \( \sim 20–30\% \) below baseline during this phase of the arousal response. To elucidate the reason for these discrepancies, we reanalyzed in greater detail the power spectra of the respiratory airflow waveforms in the prearousal and postarousal periods. An example is shown in Fig. 6. Here, the airflow waveform corresponding to the data set presented in Fig. 3 has been segmented into two equal portions. The first corresponds to the 25 s before application of the acoustic stimulation (Fig. 6A), whereas the second corresponds to the equivalent duration for \( t > 10 \) s after stimulus presentation (Fig. 6B). The average ventilation for the two segments are similar (5.77 l/min prearousal vs. 5.93 l/min postarousal). However, the power spectra of these airflow segments display significant differences (Fig. 6C). There was a decrease of 23.9% in HF power from the prearousal to postarousal segments. At the same time, there was a corresponding increase of 38.4% in spectral power in the 0.4- to 1.0-Hz range in the postarousal segment relative to the prearousal period. Thus arousal led to a redistribution of spectral power in the airflow waveform, so that there was an increase in higher-frequency (>0.4 Hz) harmonics and a corresponding reduction of HF power. Overall power was relatively unaffected so that changes were not detectable in the breath-to-breath descriptors. As mentioned previously, we believe the substantial reduction in HFP\(_{AF} \) to be primarily responsible for the late postarousal depression in HFP\(_{RR} \), even though ventilation was not different from baseline during this period.

Could our observations of arousal-induced changes in LFP\(_{RR} \) and HFP\(_{RR} \) be explained by the possibility of an increase in total HRV not specific to either the LF or HF components? Statistical analysis of total RRI power in type A arousals detected a significant change in the poststimulus time course (\( P = 0.002 \)). However, post hoc pairwise comparisons vs. the baseline level identified only three time points (\( t = 7.5, 8, \) and \( 9.5 \) s) that were significantly higher than in control. In contrast,
the LFP_RR and HFP_RR time courses were significantly different from baseline over a much longer duration (from ~10 to 40 s poststimulus). Furthermore, the changes in LFP_RR and HFP_RR were opposite in direction to one another, whereas a generalized increase in total power would have led to increases in both LF and HF components.

A previous study in normal humans demonstrated that the application of sustained or intermittent asphyxia produces an increase in sympathetic activity that persists for several minutes after cessation of the chemical stimulus (27). A subsequent study by Xie et al. (43) has shown that it is the hypoxia component of asphyxia that results in long-lasting sympathoexcitation. These findings are consistent with the results obtained in an elegant canine model of obstructive sleep apnea, in which the animals developed nocturnal and daytime hypertension after exposure to artificially induced periodic airway obstruction for several weeks (6). The importance of the sympathetic nervous system in this reaction to hypoxia was demonstrated in a study where surgical denervation of peripheral chemoreceptors, adrenal demedullation, and chemical denervation of the peripheral nervous system prevented the increase in blood pressure that results from the hypoxia-induced sympathetic activation (21). Can exposure to intermittent sympathetic activation produced by periodic arousal lead to similar chronic elevations of blood pressure? In the canine model of Brooks et al. (6), sustained exposure to periodic acoustically induced arousals without prior upper airway obstruction led only to nocturnal hypertension with no carry-over effect in the daytime. Similar findings have been reported in arousal experiments involving rats (3). On the other hand, an epidemiological study on humans found that sleep fragmentation, in the absence of significant sleep-disordered breathing (apnea-hypopnea index of <1), was significantly associated with elevated levels of SBP during wakefulness (29). A recent study (23) found daytime baseline plasma norepinephrine levels in obstructive sleep apnea syndrome patients to be correlated with movement arousals during sleep, independent of the apnea-hypopnea index and nighttime arterial oxygen saturation. Thus it is possible that the contradiction in conclusions between these studies may derive from species differences in the cumulative autonomic response to repetitive arousal. The findings of our study suggest that it is indeed physiologically feasible for the sympathoexcitatory cardiovascular effects of arousal to accumulate in normal humans over the time course of ~1 min. We speculate that such a mechanism may act to supplement the cumulative sympathoexcitatory effect on the cardiovascular system of intermittent hypoxia during periodic apnea, especially when consecutive arousals occur in close succession to one another.

We are grateful to Dominic Puleo for technical assistance in restoring old data files from the Wisconsin database.

DISCLOSURES

This work was supported in part by National Institutes of Health Grants RR-01861, M01 RR-43, and HL-58725, and the Medical Research Service of the Department of Veterans Affairs.

REFERENCES


