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

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Blasi, Anna, Javier Jo, Edwin Valladares, Barbara J. Morgan, James B. Skatrud, and Michael C. K. Khoo. Cardiovascular variability after arousal from sleep: time-varying spectral analysis. J Appl Physiol 95: 1394–1404, 2003. First published June 20, 2003; 10.1152/japplphysiol.01095.2002.—We performed time-varying spectral analyses of heart rate variability (HRV) and blood pressure variability (BPV) recorded from 16 normal humans during acoustically induced arousals from sleep. Time-varying autoregressive modeling was employed to estimate the time courses of high-frequency HRV power, low-frequency HRV power, the ratio between low-frequency and high-frequency HRV power, and low-frequency power of systolic BPV. To delineate the influence of respiration on HRV, we also computed respiratory airflow high-frequency power, the modified ratio of low-frequency to high-frequency HRV power, and low-frequency power of systolic BPV displayed increases that remained above baseline up to 40 s after arousal. High-frequency HRV power and airflow high-frequency power showed concomitant decreases to levels below baseline, whereas the average transfer gain between respiration and heart rate remained unchanged. These findings suggest that 1) arousal-induced changes in parasympathetic activity are strongly coupled to respiratory pattern and 2) the sympathoexcitatory cardiovascular effects of arousal are relatively long lasting and may accumulate if repetitive arousals occur in close succession.

autonomic nervous system; heart rate variability; blood pressure variability; sleep-disordered breathing; mathematical modeling; physiological oscillations

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

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apneas (5, 37). It is widely believed that the elevated levels of sympathetic activity constitute an important factor that could promote the development of systemic hypertension in a significant fraction of the obstructive sleep apnea syndrome population (13, 44). The effect of arousal alone on autonomic activity has been investigated in a number of studies. In human non-rapid eye movement (NREM) sleep, acoustically induced arousals were found to transiently increase muscle sympathetic nerve activity (MSNA) (28, 42), systolic and diastolic blood pressure (7, 11, 28, 34), heart rate (7, 11, 28, 34), and respiratory tidal volume (2, 18). However, these studies focused primarily on the peak autonomic and respiratory changes that occurred within the first several seconds of the arousal; little attention was paid to the subsequent time courses of these changes. Closer examination of autonomic activity in the postarousal period could provide some indication as to whether a cumulative effect might exist.

The present study was based on the premise that the application of time-varying spectral analysis to the cardiovascular and respiratory measurements obtained during arousal can provide useful insights into the autonomic processes at work during transient changes in sleep state. The availability of concurrent measurements of MSNA enabled us to compare our inferences about sympathetic activity derived from the spectral characteristics of HRV and BPV against an external reference. During arousal, large changes in respiration occur alongside cardiovascular fluctuations. Thus it is unclear whether this surge in cardiovascular activity is secondary to primary changes in respiration. To computationally delineate the respiratory-correlated component from the remaining components of HRV before, during, and after arousal, we employed a previously published method (17) and extended the algorithm for application to time-varying conditions. Our initial expectation was that the changes in the spectral characteristics of HRV and BPV during arousal would closely parallel the transient responses exhibited by heart rate and MSNA. However, contrary to this notion, we found that time course of the spectral markers indicated a surge in sympathoexcitation that remained substantially elevated above baseline, even after heart rate and MSNA had reverted back to control levels.

METHODS

Experimental Protocol

The analysis presented here was based initially on previously reported data 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’s head, which was located ~25 cm from each speaker. The subject was 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, Murraysville, 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 (Caldwell 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 airflow) every 0.5 s.

An important parameter that had to be determined was the value of the “forgetting factor” (\( \lambda \)) used in the RLS algorithm. The \( \lambda \) 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 \( \lambda \) that is too large results in a filter that does not adapt quickly enough to the changes in the data, whereas a \( \lambda \) that is too small can lead to unstable estimates. Thus, to obtain the optimal \( \lambda \), the following procedure was carried out. The RLS algorithm was applied to each data set multiple times, with \( \lambda \) set equal to a different value each time. Subsequently, we selected the value of \( \lambda \) that minimized the mean square error between the model prediction and the data. The average value of \( \lambda \) across all subjects and signals was 0.954. The range of values over which \( \lambda \) 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 (LFP_RRI and HFP_RRI), the LF/HF (equal to LFP_RRI/HFP_RRI), and LF power of SBP (LFP_SBP). We also computed the spectral power of respiratory airflow in the HF band (HFP_AIR), since this represented the component of breathing waveform most likely to influence HFP_RRI. As well, to delineate the respiratory-related components of the RRI spectrum from the nonrespiratory 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_RRI) 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_RRI provides an index for quantifying the extent to which HFP_RRI is influenced by respiration. Computation of MLHR and G_RRI 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.](image-url)
occurs at time \((t)\) shown before and after the acoustic stimulus, which power spectrum of the RRI time series of a subject is displayed in Fig. 3. In that during acoustically induced arousal from NREM sleep 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 \(\pm SE\). 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 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 airflow 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 \(\pm\) 0.45 l/min. During arousal, ventilation increased to 9.20 \(\pm\) 1.02 and 7.85 \(\pm\) 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, HFPAf, HFPrr, and Grsa, 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 HFPrr 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 HFPrr 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 HFPrr time course exhibited behavior similar to that of HFPaf (Fig. 4B, top) by displaying an initial increase followed by a sustained decrease to levels below baseline. The average correlation between HFPaf and HFPrr was modest \((r = 0.45)\) but significant \((P < 0.005)\). In contrast, there were no significant arousal-induced changes in Grsa. Type N arousals produced no changes in breath-by-breath ventilation, HFPaf, HFPrr, or Grsa.

Averaged Time Courses: Markers of Sympathetic Activity

The averaged time-courses for the responses in SBP, MSNA, LFPsbp, LF/HF, LFPpr, 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 LFP_{SBP} 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, LFP_{RR}, and MLHR) displayed little change until \( >4 \) s after the stimulus. The blood pressure indexes (SBP and LFP_{SBP}) 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 \((8.1 \pm 1.1 \text{ vs. } 22.1 \pm 3.3\%)\), but it is important to note that the type N peak SBP increase was significant \((P < 0.05)\). SBP

**Fig. 3.** A: time course of the PSD of RRI (PSDRR) 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.
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 index 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 RR, MLHR, and LFP SBP. 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 arousal 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 RR started to show increases only at ~5 s poststimulus, followed by increases in SBP and LFP SBP 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 RR) and blood pressure (represented by LFP SBP) 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.
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 esti-
mated 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 algo-

rithm is relatively slow in its ability to track abrupt
amplitude changes in HF oscillations. After $t > 10$ s,
HFPRR hovered at levels not different from baseline. The si-
multaneous decrease in HFPAAF over the same duration
suggests that the sustained reduction in HFPRR was
secondary to changes in respiration. Overall, these
findings lead us to conclude that the parasympathetic
heart rate response to arousal was mediated predomi-
nantly by the coupling between respiratory drive and
heart rate. This conclusion is at variance with a previ-
ous study (15) using a canine preparation made apneic
with mechanical hyperventilation; in that study, phar-
macological blockade demonstrated the presence of a
strong vagal withdrawal that accompanied arousal in-
dependent 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, mea-
sures of respiratory effort (diaphragmatic electromyo-
gram and mask pressure) exhibited an increase at
arousal, implying that one could not dismiss the pos-
sibility that the increase in ventilatory drive, in the
form of the “wakefulness stimulus” was indirectly re-

sponsible for the heart rate change.

An initially puzzling finding was the inconsistency in
pattern between the average time courses of HFPAAF
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
HFPAAF showed some tendency to increase between
breaths 3 and 4 ($t = -9–10$ s). Second, ventilation
became not significantly different from baseline when $t$
was $>9$ s, whereas HFPAAF remained at a level $\sim 20–$
30% below baseline during this phase of the arousal
response. To elucidate the reason for these discrep-
ancies, 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 du-

ration for $t > 10$ s after stimulus presentation (Fig. 6B).
The average ventilation for the two segments are sim-
ilar (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 wave-
form, 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 be-
lieve the substantial reduction in HFPAAF to be primar-
ily responsible for the late postarousal depression in
HFPRR, even though ventilation was not different from
baseline during this period.

Could our observations of arousal-induced changes
in LFPRR and HFPRR 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 identi-

fied 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 < 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.

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DISCLOSURES

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