Sleep-dependent changes in the coupling between heart period and blood pressure in human subjects

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Silvani A, Grimaldi D, Vandi S, Barletta G, Vetrugno R, Provini F, Pierangeli G, Berteotti C, Montagna P, Zoccoli G, Cortelli P. Sleep-dependent changes in the coupling between heart period and blood pressure in human subjects. Am J Physiol Regul Integr Comp Physiol 294: R1686–R1692, 2008. First published February 13, 2008; doi:10.1152/ajpregu.00756.2007.—We investigated whether in human subjects, the pattern of coupling between the spontaneous fluctuations of heart period (HP) and those of systolic blood pressure (SBP) differs among wake-sleep states. Polysomnographic recordings and finger blood pressure measurements were performed for 48 h in 15 nonobese adults without sleep-disordered breathing. The cross-correlation function (CCF) between the fluctuations of HP and SBP at frequencies <0.15 Hz was computed during quiet wakefulness (QW), light (stages 1 and 2) and deep (stages 3 and 4) nonrapid-eye-movement sleep (NREMS), and rapid-eye-movement sleep (REMS). A positive correlation between HP and the previous SBP values, which is the expected result of baroreflex feedback control, was observed in the sleep states but not in QW. In deep NREMS, the maximum CCF value was significantly higher than in any other state, suggesting the greatest baroreflex contribution to the coupling between HP and SBP. A negative correlation between HP and the subsequent SBP values was also observed in each state, consistent with the mechanical feed-forward action of HP on SBP and with central autonomic commands. The contribution of these mechanisms to the coupling between HP and SBP, estimated from the minimum CCF value, was significantly lower in deep NREMS than either in light NREMS or QW. These results indicate that the pattern of coupling between HP and SBP at low frequencies differs among wake-sleep states in human subjects, with deep NREMS entailing the highest feedback contribution of the baroreflex and a low effectiveness of feed-forward mechanisms.

feedback and feed-forward mechanisms; baroreflex; central autonomic commands; cross-correlation analysis; sequence technique

THE PATTERN OF COUPLING BETWEEN THE spontaneous fluctuations of heart period (HP) and those of blood pressure indicates the contribution of different mechanisms to cardiovascular control during real-life behavior. In particular, a positive correlation between HP and the previous pressure values is the expected result of the arterial baroreflex, which acts as a delayed negative-feedback control (37). In turn, the fluctuations of HP may alter cardiac output, eliciting pressure fluctuations that are negatively correlated with them. Central autonomic commands (15) cause opposite changes in HP and vascular resistance (13), thereby apparently enhancing this feed-forward interaction.

In animal models, the pattern of coupling between HP and blood pressure suggests a variable contribution of central and baroreflex mechanisms to cardiovascular control in different wake-sleep states (33, 34, 39). The baroreflex contribution appears most prominent during quiet sleep in lambs (33) and during nonrapid-eye-movement sleep (NREMS) in rats (34, 39). On the other hand, in rapid-eye-movement sleep (REMS), the contribution of feed-forward mechanisms prevails in rats due to central autonomic commands (6, 34, 39), which manifest as phasic hypertensive events (7). In spontaneously hypertensive rats, these sleep-dependent cardiovascular changes are so substantial that regulatory derangements with respect to Wistar-Kyoto normotensive rats are masked or enhanced in specific wake-sleep states (6). This suggests that the sleep-dependent changes in the coupling between HP and blood pressure may provide useful information also in human patients, in whom the pathophysiological (28) and prognostic (4) implications of cardiovascular control during sleep are an active area of research. Therefore, we investigated whether in human subjects, the coupling between HP and systolic blood pressure (SBP) physiologically differs among wake-sleep states.

On the basis of findings in animal models (6, 33), we computed the cross-correlation function (CCF) between HP and SBP. We tested the hypotheses that deep (stages 3 and 4) NREMS entails the strongest positive correlation between HP and previous SBP values, as well as the weakest negative correlation between HP and subsequent SBP values. The CCF analysis was repeated after low-pass filtering HP and SBP data below 0.15 Hz to evaluate whether its results depended on the respiratory entrainment of cardiovascular fluctuations. Finally, to complement the results of the CCF analysis, the coupling between HP and SBP was investigated with a different temporal approach, which quantified the contribution of baroreflex and nonbaroreflex mechanisms to the changes of HP associated with spontaneous SBP ramps (12, 19).

METHODS

Subjects. The analysis was performed on 15 subjects (7 males and 8 females, age 44 ± 3 yr, BMI 23.9 ± 0.8), who were consecutively enrolled by the Autonomic Unit of the Neurological Department, University of Bologna, as part of an ongoing study on circadian autonomic rhythms. All subjects provided informed consent to the research protocol, which conformed to the principles of the Declara-
tion of Helsinki and was approved by the Bologna University ethical committee on human experimentation. All subjects were nonsmokers and were free of drugs and medications. Cardiac, endocrine, metabolic, and renal diseases were excluded by history, physical examination, and routine laboratory tests. Obstructive sleep apnea syndrome was excluded by a dynamic polysomnographic study (apnea-hypopnea index <10).

Experimental protocol. Before the beginning of the study, the subjects were instructed to abstain from heavy physical activity for 24 h and from alcohol and caffeine beverages for 12 h. During the study, the subjects lived in a room with controlled temperature (24 ± 1°C), humidity (40–50%), and light-dark schedule (light off from 11 PM to 7 AM), where they were required to lie in bed except for eating (1,800 kcal/day divided into three meals and three snacks with a fixed time schedule) and were allowed to read, watch television, and sleep ad libitum. After a habituation period of 24 h, continuous noninvasive recordings of physiological variables were performed for 48 h. Finger blood pressure was measured with the volume-clamp method (Portapres Model II, FMS). The electrocardiogram, electroencephalogram (C3-A2 and C4-A1 leads), electrooculogram, electromyogram (myohyoideus muscle), and ventilation were measured with a Colleague recorder (Grass). All signals were digitized at 1 kHz.

Sleep scoring. The sleep states were visually scored on 30-s epochs, according to the standard Rechtschaffen and Kales criteria (31), as light (stages 1 and 2) NREMS, deep (stages 3 and 4) NREMS, and REMS. The sleep efficiency was calculated as the percentage of the time that was spent asleep when the light was off. The REMS latency was computed as the time between the first epoch of NREMS stage 1 and the first REMS epoch.

Time series of cardiovascular signals. The data analysis was performed with MATLAB and its signal processing toolbox (The MathWorks) on all of the episodes of light NREMS, deep NREMS, or REMS with duration ≥5 min. The analysis was also performed on episodes of quiet wakefulness (QW, with subjects lying in bed), which were selected in the hour before the onset of the sleep period and the hour after its termination. HP values were computed as the intervals between adjacent QRS complexes that were due to sinus node depolarizations. Beat-to-beat values of SBP and diastolic blood pressure (DBP) were computed. Portapres calibration and occasionally subject movement in QW caused artifacts in the raw blood pressure signal, which were identified as disruptions of pulse wave morphology. When such artifacts affected the pressure signal for a time interval <4 s, beat-to-beat SBP data in that interval were reconstructed by piecewise cubic spline interpolation to allow the analysis of the CCF between HP and SBP, whereas they were excluded from the analyses performed with the sequence techniques. The time intervals longer than 4 s with artifacts in the pressure signal were excluded from all of the analyses.

Cross-correlation analysis. For each subject and wake-sleep state, the CCF between HP and SBP, HP variance, and SBP variance were averaged over consecutive data subsets of 5-min duration overlapped for 4 min (6, 33). Data subsets were included in the analysis if they were free of ectopic beats and if artifacts in the pressure signal had individual duration <4 s and cumulative duration <30 s. The time series of HP and SBP were resampled at 4 Hz by linear interpolation. The CCF was computed at time shifts between −25 s and 25 s and normalized so that the autocorrelations at 0 time shift were identically 1. The CCF analysis yielded the linear correlation coefficient between HP and SBP as a function of the time shift between these variables (3), whose sign indicates whether HP fluctuations precede (positive sign) or are preceded by (negative sign) those of SBP. For each subject and wake-sleep state, the maximum positive and the minimum negative correlation coefficients of the average CCF were retained for analysis together with the corresponding time shifts.

These computations were repeated after low-pass filtering the resampled time series of HP and SBP below the breathing rate (<0.15 Hz, 10 pole Butterworth filter) to evaluate whether the results depended on the respiratory entrainment of cardiovascular fluctuations. This approach was followed in previous applications of the CCF analysis in animal models (6, 33) and is based on evidence that a major cause of respiratory sinus arrhythmia is a central link between respiratory and cardiac vagal motor neurons rather than the arterial baroreflex (25). The relative magnitude of the respiratory fluctuations of HP and SBP was also quantified by computing the ratio of the spectral power of each variable in the high- and low-frequency bands, which were defined between 0.15 and 0.40 Hz and between 0.07 and 0.14 Hz, respectively (38).

Analyses with the sequence technique. The sequence technique was implemented with criteria that have been validated in animal models and applied in human subjects (8, 12, 19, 20). SBP ramps were identified as sequences of ≥3 consecutive beats with monotonic changes of SBP ≥ 1 mmHg/beat. The baroreflex sequences were identified as SBP ramps that were linearly correlated (squared correlation coefficient >0.85) with monotonic changes of HP, which had amplitude ≥ 5 ms/beat, the same direction as the SBP changes (e.g., hypertension-bradycardia), and a delay of 0, 1, or 2 heart beats (8, 12). The occurrence of these sequences reflects a physiological rather than a chance coupling in human subjects (8) and is dramatically reduced by sinoaortic denervation in cats (12). The definition of nonbaroreflex sequences differed in that monotonic changes of HP with direction opposite to that of SBP changes (e.g., hypertension-tachycardia) and delayed by 1 heart beat were required (19, 20). These sequences reflect positive-feedback mechanisms of cardiovascular regulation, and their occurrence is not significantly affected by sinoaortic denervation in rabbits (19).

The baroreflex effectiveness index (BEI) was computed as the ratio between the number of baroreflex sequences and the total number of SBP ramps, while cardiac baroreflex sensitivity (BRS) was computed as the average slope of the regression lines between HP and SBP values in each baroreflex sequence (12). The corresponding indexes computed on nonbaroreflex sequences were defined as NBEI and NB-slope, respectively.

Table 1. Mean values and variance of blood pressure and heart period

<table>
<thead>
<tr>
<th>Subj</th>
<th>QW</th>
<th>NREMS 1 and 2</th>
<th>NREMS 3 and 4</th>
<th>REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>130±4‡</td>
<td>117±4*</td>
<td>113±4</td>
<td>122±4†</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71±2‡</td>
<td>63±2*</td>
<td>60±2</td>
<td>64±2†</td>
</tr>
<tr>
<td>HP, ms</td>
<td>9520±47‡</td>
<td>1057±50*</td>
<td>1042±49</td>
<td>1008±46†</td>
</tr>
<tr>
<td>SBPV, mmHg²</td>
<td>74±7‡</td>
<td>55±5‡</td>
<td>34±4</td>
<td>73±6‡</td>
</tr>
<tr>
<td>HPV, ms²</td>
<td>5664±1203‡</td>
<td>2769±597‡</td>
<td>1334±260</td>
<td>4002±804‡</td>
</tr>
<tr>
<td>LF-SBPV, mmHg²</td>
<td>71±7‡</td>
<td>53±5‡</td>
<td>31±4</td>
<td>71±6‡</td>
</tr>
<tr>
<td>LF-HPV, ms²</td>
<td>5187±1075‡</td>
<td>2127±403‡</td>
<td>853±131</td>
<td>3442±638‡</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. QW, quiet wakefulness; NREMS 1 and 2, 3 and 4, stages 1–4 of nonrapid-eye-movement sleep, respectively; REMS, rapid-eye-movement sleep; SBP and DBP, systolic and diastolic blood pressure, respectively; HP, heart period; SBPV and HPV, variance of SBP and HP time series, respectively. LF-SBPV and LF-HPV, variance of the low-pass filtered (<0.15 Hz) time series of SBP and HP, respectively. Friedman test: *P < 0.001 for all variables. Differences vs. NREMS 3–4: *P < 0.05, †P < 0.01, ‡P < 0.001.
Statistical analysis. Statistical tests were performed with the SPSS software (SPSS) and were significant at $P < 0.05$. Differences among states were tested with Friedman ANOVA by ranks test. For each subject, 97, 319, 155, and 154 min of raw recordings were considered for the analyses in QW, light NREMS, deep NREMS, and REMS, respectively. Of this recording time, 81%, 77%, 80%, and 79% met the criteria for inclusion in the data subsets subjected to the CCF analysis, respectively.

RESULTS

Total duration of the wake-sleep episodes recorded and analyzed. The total sleep time averaged 375 ± 11 min/night, with a sleep efficiency of 78 ± 2% and a REMS latency of 107 ± 14 min. The subjects spent 54 ± 3%, 24 ± 3%, and 22 ± 1% of the total sleep time in light NREMS, deep NREMS, and REMS, respectively. For each subject, 97 ± 6, 319 ± 24, 155 ± 14, and 154 ± 14 min of raw recordings were considered for the analyses in QW, light NREMS, deep NREMS, and REMS, respectively. Of this recording time, 81 ± 3%, 77 ± 3%, 80 ± 3%, and 79 ± 3% met the criteria for inclusion in the data subsets subjected to the CCF analysis, respectively.

Mean values and variance of blood pressure and heart period. The mean values and the variance of blood pressure and HP are shown in Table 1. The mean value of SBP was significantly lower in deep NREMS than in any other state. The mean values of SBP and DBP were significantly lower in deep NREMS than in any other state. The mean value of HP was significantly higher in deep NREMS than either in QW or REMS and significantly lower in deep NREMS than in light NREMS. The variance of SBP and HP time series and that of their fluctuations <0.15 Hz.
were significantly lower in deep NREMS than in any other state.

The spectral power of SBP fluctuations in the frequency band 0.15–0.40 Hz relative to that in the band 0.07–0.14 Hz was 0.41 ± 0.06, 0.58 ± 0.17, 1.14 ± 0.44, and 0.32 ± 0.05 in QW, light NREMS, deep NREMS, and REMS, respectively. For HP fluctuations, the corresponding values were 0.68 ± 0.10, 1.38 ± 0.20, 2.02 ± 0.30, and 0.89 ± 0.15.

**Cross-correlation analysis.** The visual analysis of the time series (Fig. 1) revealed that the fluctuations of HP tended to be parallel with the previous SBP ones in deep NREMS, and to a lower extent, in light NREMS and REMS. On the other hand, HP and SBP mostly fluctuated in opposite directions during QW. The removal of the fast respiratory fluctuations made these patterns of coupling more readily evident on the low-pass filtered time series of HP and SBP.

In each state, the average CCF computed on the unfiltered time series of HP and SBP (Fig. 2A) and that computed on the low-pass filtered time series (Fig. 2B) were similar, except for the presence in the former of a periodic fast ripple, which was most prominent in deep NREMS. According to the visual analysis of the time series, the average CCF between HP and SBP showed a positive peak at negative time shifts in deep NREMS, which became progressively less evident in light NREMS and REMS. In QW, such a peak was reduced to a hump of the CCF, which showed a negative correlation between HP and both previous and subsequent SBP values. At positive time shifts, a negative CCF peak occurred in all wake-sleep states.

The time shifts corresponding to the CCF maxima clustered at negative values in the sleep states but not in QW, while the time shifts corresponding to the CCF minima clustered at positive values in all wake-sleep states. Similar values of the time shifts were obtained on unfiltered and low-pass-filtered data (Table 2).

The maximum and minimum CCF values are shown in Table 3. The maximum CCF value was significantly higher in deep NREMS than in any other state. The minimum CCF value computed on the low-pass-filtered time series of HP and SBP was significantly higher in deep NREMS than either in QW or light NREMS. On the other hand, the minimum CCF value computed on unfiltered data did not differ significantly among states (P = 0.065).

**Analyses with the sequence technique.** The number of SBP ramps/100 heart beats was 18 ± 1, 19 ± 1, 19 ± 1, and 18 ± 1 in QW, light NREMS, deep NREMS, and REMS, respectively. A duration of three heart beats characterized more than 84% of baroreflex and nonbaroreflex sequences in each wake-sleep state. A time delay of 0 heart beats between HP and SBP characterized the majority of baroreflex sequences, with a percentage ranging from 68 ± 3% in QW to 85 ± 3% in deep NREMS.

In deep NREMS, BEI was significantly higher than in either QW or REMS, while NBEI was significantly lower than in any other state (Table 4). BRS was significantly lower in deep NREMS than in light NREMS, while NB-slope did not differ significantly among wake-sleep states.

An example of the combined application of the sequence technique and the CCF analysis to a representative time series of data is shown in Fig. 3.

**DISCUSSION**

We observed substantial sleep-dependent differences in the pattern of coupling between HP and SBP in human subjects. These differences concerned both the CCF between HP and SBP and the prevalence of baroreflex and nonbaroreflex HP-SBP sequences.

**Baroreflex coupling.** A positive CCF peak occurred for HP following SBP during the light and deep stages of NREMS, and SY.

### Table 2. Time shifts corresponding to the maximum and minimum values of the cross-correlation functions between heart period and systolic blood pressure

<table>
<thead>
<tr>
<th>State</th>
<th>%MAX</th>
<th>%MIN</th>
<th>LF-%MAX</th>
<th>LF-%MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>QW</td>
<td>-16.3 (35.5)</td>
<td>2.5 (1.8) ¤</td>
<td>-16.3 (35.0)</td>
<td>3.3 (0.8) ¤</td>
</tr>
<tr>
<td>NREMS 1 and 2</td>
<td>-4.0 (4.5) ¤</td>
<td>4.5 (3.5) ¤</td>
<td>-4.0 (3.0) ¤</td>
<td>4.0 (2.0) ¤</td>
</tr>
<tr>
<td>NREMS 3 and 4</td>
<td>-4.0 (1.3) ¤</td>
<td>5.3 (3.3) ¤</td>
<td>-3.5 (2.3) ¤</td>
<td>4.3 (1.8) ¤</td>
</tr>
<tr>
<td>REMS</td>
<td>-3.5 (18.5) *</td>
<td>3.3 (3.3) ¤</td>
<td>-2.8 (17.5) *</td>
<td>3.8 (2.0) ¤</td>
</tr>
</tbody>
</table>

Data are expressed as median values (interquartile range). %MAX and %MIN: time shifts corresponding to the maximum and minimum values of the cross-correlation function (CCF) between heart period (HP) and systolic blood pressure (SBP). LF-%MAX and LF-%MIN: time shifts corresponding to the maximum and minimum values of the CCF between the low-pass filtered (<0.15 Hz) time series of HP and SBP. Significance of the binomial test: *P < 0.05, † P < 0.01, ¤ P < 0.001.

### Table 3. Maximum and minimum values of the cross-correlation function between heart period and systolic blood pressure

<table>
<thead>
<tr>
<th>State</th>
<th>%MAX</th>
<th>%MIN</th>
<th>LF-%MAX</th>
<th>LF-%MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>QW</td>
<td>0.02 ± 0.01 ‡</td>
<td>0.41 ± 0.03</td>
<td>0.02 ± 0.01 ‡</td>
<td>0.43 ± 0.03 ‡</td>
</tr>
<tr>
<td>NREMS 1 and 2</td>
<td>0.26 ± 0.03 ‡</td>
<td>-37.03</td>
<td>0.27 ± 0.03 ‡</td>
<td>-39.04 ‡</td>
</tr>
<tr>
<td>NREMS 3 and 4</td>
<td>0.39 ± 0.03</td>
<td>-31.04</td>
<td>0.39 ± 0.03</td>
<td>-29.02</td>
</tr>
<tr>
<td>REMS</td>
<td>0.13 ± 0.02 ‡</td>
<td>-31.03</td>
<td>0.13 ± 0.02 ‡</td>
<td>-33.03</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. %MAX and %MIN: maximum and minimum values of the cross-correlation function (CCF) between heart period (HP) and systolic blood pressure (SBP). LF-%MAX and LF-%MIN: maximum and minimum values of the CCF between the low-pass filtered (<0.15 Hz) time series of HP and SBP. Friedman test: P < 0.001 for %MAX and LF-%MAX; P = 0.065 (not significant) for %MIN; P < 0.05 for LF-%MIN. Differences vs. NREMS 3 and 4: ‡P < 0.01, †P < 0.001.
while it was barely observable in REMS and absent in QW (Fig. 2). Accordingly, in REMS and particularly in QW, the time shifts at the CCF maxima showed a wide scatter (Table 2). As a result, the values of the CCF maxima in these states overestimated the correlation coefficients at the time shifts, which corresponded to the positive CCF peak in NREMS. Nonetheless, the values of the CCF maxima were significantly higher in deep NREMS than in any other state (Table 3).

Similar results were obtained in the CCF analysis performed on low-pass-filtered data (Fig. 2B and Tables 2 and 3). Thus, the CCF pattern of positive correlation between HP and the previous SBP values was the strongest in deep NREMS and mainly reflected the coupling between HP and SBP at low frequencies, according to previous results (33).

This CCF pattern was independent of the tight coupling between oscillations of SBP and HP at the breathing rate, which partly results from central autonomic commands associated with the respiratory drive (9, 11, 25) and may vary among wake-sleep states due to sleep-dependent differences in ventilation (29). On the other hand, since correlation does not imply causality, this CCF pattern might be explained by postulating a central and parallel autonomic modulation of HP and vascular resistance at low frequencies. However, a more conservative explanation is that this CCF pattern resulted from the arterial baroreflex, which operates as a delayed negative-feedback control (37) and is effective in coupling heart rate to slow blood pressure fluctuations (16). In this respect, it must be noted that the time shifts corresponding to the CCF maxima (Table 2) were higher than the latency of the earliest cardiac baroreflex response, which is lower than 1 s (2). Data in dogs (23) and rats (16) indicate that the time shift of the cardiac baroreflex response to slow SBP fluctuations may exceed the pure baroreflex time delay, likely due to the time constants of the vagal and particularly the sympathetic cardiac control (5, 37). Moreover, the coexistence of the baroreflex and feed-forward regulations in real-life conditions may alter the apparent dynamics of both regulatory mechanisms. Accordingly, biphasic changes of HP have been described in association with pressure surges during sleep, with the expected baroreflex increase of HP being delayed several seconds after the pressure peak and preceded by a tachycardic response (30, 33).

The baroreflex sequences were a substantial fraction of the SBP ramps in each state (Table 4), with BEI values higher than those originally reported (12) but consistent with more recent results (18). Interestingly, BEI was significantly higher in deep NREMS than either in QW or REMS, suggesting that NREMS entails the strongest baroreflex contribution to the coupling between HP and SBP also at a much shorter timescale than that investigated by the CCF analysis. The sequence technique also yielded estimates of BRS that were lower in deep than in light sleep (%) fluctuations.

**Table 4. Results of the analysis of baroreflex and nonbaroreflex sequences**

<table>
<thead>
<tr>
<th></th>
<th>QW</th>
<th>NREMS 1 and 2</th>
<th>NREMS 3 and 4</th>
<th>REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEI</td>
<td>0.51 ± 0.03†</td>
<td>0.61 ± 0.03</td>
<td>0.60 ± 0.03</td>
<td>0.51 ± 0.03†</td>
</tr>
<tr>
<td>BRS, ms mmHg⁻¹</td>
<td>10.7 ± 1.5</td>
<td>12.6 ± 2.0*</td>
<td>11.1 ± 1.6</td>
<td>11.8 ± 2.0</td>
</tr>
<tr>
<td>NBEI</td>
<td>0.11 ± 0.01†</td>
<td>0.08 ± 0.01†</td>
<td>0.06 ± 0.01</td>
<td>0.10 ± 0.01†</td>
</tr>
<tr>
<td>NB slope, ms mmHg⁻¹</td>
<td>−9.4 ± 1.2</td>
<td>−9.8 ± 1.3</td>
<td>−8.7 ± 1.2</td>
<td>−9.2 ± 1.2</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. BEI, baroreflex effectiveness index; BRS, baroreflex sensitivity; NBEI, ratio between the number of nonbaroreflex sequences and the total number of pressure ramps; NB slope, slope of the regression line between heart period and systolic blood pressure in the nonbaroreflex sequences. Friedman test: *P < 0.05 for BEI and NBEI; †P < 0.05 for BRS; ‡P = 0.155 (not significant) for NB slope. Differences vs. NREMS 3 and 4: *P < 0.05, †P < 0.01, ‡P < 0.001.

Fig. 3. Combined application of the cross-correlation function (CCF) and the sequence technique to the same time series. Data were obtained during quiet wakefulness. Beat-to-beat values of SBP (red; A) and HP (blue; B) are shown. A: missing data were due to P-tapres calibration. Baroreflex and nonbaroreflex sequences are indicated by black and green segments, respectively. The yellow segments (A) indicate SBP ramps not associated with either baroreflex or nonbaroreflex sequences. C: the CCF computed on unfiltered (black) and low-pass filtered (<0.15 Hz, red) time series of HP and SBP. D: low-pass filtered (<0.15 Hz) fluctuations of SBP (red line) and HP (thin blue line) in standardized units. The thick blue line (D) illustrates the result of the application to the HP data of a 3-s time shift, which corresponds to the minimum value of the CCF (C). In this example, a baroreflex coupling prevailed between the short SBP and HP sequences. However, a feed-forward type of coupling clearly prevailed between the whole time series of HP and SBP and was driven by their low-frequency fluctuations.
NREMS (Table 4), suggesting differences in sleep microstructure such as the cyclic alternating pattern (17). In contrast, BRS is reported to decrease in anesthesia with respect to wakefulness (36). This difference emphasizes that although deep NREMS and anesthesia share some remarkably similar physiological traits (22), they may not be comparable in terms of cardiovascular control.

Nonbaroreflex coupling. A negative CCF trough occurred for HP preceding SBP in all wake-sleep states (Fig. 2 and Table 2), with the minimum negative correlation being weaker in deep NREMS than either in light NREMS or QW (Table 3). These differences were statistically significant in the CCF computed on low-pass-filtered data, in which this pattern of coupling was overall more evident (Fig. 2B). Thus, this CCF pattern mainly reflected the coupling between HP and SBP at frequencies below the breathing rate.

A negative correlation between HP and SBP may result from the feed-forward action of HP on cardiac output, and hence on SBP. Accordingly, HP fluctuations around 0.05 Hz may cause those of SBP under alpha-adrenergic blockade (10), while a feed-forward interaction between HP and SBP has been evidenced at frequencies between 0.04 and 0.15 Hz in physiological conditions (27). However, fixed-rate atrial pacing does not alter SBP variability at these frequencies (35), casting doubts on the effectiveness of the mechanical feed-forward action of HP on SBP. On the other hand, central autonomic commands (15) may cause opposite changes in HP and vascular resistance (13), thereby apparently enhancing the feed-forward interaction between HP and SBP. To a variable extent (13, 32), central commands act by altering the baroreflex operating point, a mechanism demonstrated in rabbits even during mild activities such as changes in posture (21). Thus, the role played by central commands in cardiovascular regulation is not limited to the conditions of physical exercise (13, 15) or defense reaction (32). Accordingly, phasic increases of vascular resistance, blood pressure, and heart rate, which are consistent with central commands, have been shown in animal models during REMS (7, 14, 33) and in human subjects upon arousal from NREMS (26). During these events, heart rate and blood pressure start to increase almost simultaneously, but the maximal tachycardia precedes the pressure peak (7, 26, 30, 33). This temporal arrangement, which agrees with the positive values of the time shifts at the CCF minima (Table 2), may result from the buffering exerted by the cardiac baroreflex in real-life conditions once the pressure surges are fully blotted.

Nonbaroreflex sequences were only a minor fraction of the total SBP ramps in each wake-sleep state, in agreement with published results (19, 20). While the NB-slope did not vary significantly among states, NBEI was the lowest in deep NREMS (Table 4). Thus, both the sequence technique and the CCF analysis indicated a low effectiveness of nonbaroreflex mechanisms of HP control during deep NREMS. Notably, the two techniques yielded different and complementary information. Nonbaroreflex sequences were characterized by a 1-beat delay of HP with respect to SBP (see METHODS), thus being consistent with the operation of positive-feedback cardiovascular reflexes (20, 24). Moreover, the sequence technique yielded information on nonbaroreflex coupling between HP and SBP at a much shorter timescale than the CCF analysis. The relevance of this observation is emphasized by Fig. 3, which shows that a clear-cut pattern of negative correlation between slow fluctuations of HP and SBP may not be captured by the analysis with the sequence technique.

Limitations of the study. Although multiple nonlinearities characterize cardiovascular control (37), the CCF analysis and the sequence technique only detect the linear component of the coupling between HP and SBP. Another limitation of our study is the relatively small size of the subject sample investigated, which was sufficient to demonstrate sleep-dependent changes in the HP vs. SBP coupling but inadequate to provide normative values.

Conclusions. We demonstrated that the pattern of coupling between the spontaneous fluctuations of HP and SBP substantially differs among wake-sleep states in human subjects. The results suggest that in human subjects, deep NREMS entails the greatest baroreflex contribution to HP control and a low effectiveness of central autonomic commands and positive-feedback reflexes.

Perspectives and Significance

In spontaneously hypertensive rats, derangements in the central and baroreflex contributions to cardiovascular control become evident during specific wake-sleep states (6, 7). The assessment of the regulatory derangements associated with cardiovascular disease may thus be improved by taking into account the wake-sleep state in clinical research settings. On the other hand, in human patients, sleep apneas (1) and the restless legs syndrome (30) entail repetitive episodes characterized by a feed-forward type of coupling between HP and SBP. The CCF analysis may be useful to assess the impact of these disorders on cardiovascular control by quantifying the disruption of the physiological pattern of coupling between HP and SBP.

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