Cardiovascular control during sleep: “Sleep-dependent changes in the coupling between heart period and blood pressure in human subjects,” by Silvani et al.

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IT HAS BECOME increasingly apparent that there is a bidirectional relationship between sleep and cardiovascular health (5). For example, hypertension in humans is often associated with a diminution or loss of the normal sleep-related fall in BP, a phenomenon referred to as a nondipping profile (2). Furthermore, cardiovascular morbidity has been shown to be higher in women with a nondipping profile (8), and BP level during sleep is a sensitive predictor of cardiovascular mortality (3). On the other hand, disorders of sleep, in particular obstructive sleep apnea, are associated with a range of cardiovascular disorders (5). In general, an understanding of the mechanisms leading to these associations has lagged behind the identification of the statistical relationships. However, the identification of pathophysiological processes requires an understanding of the influence of sleep on cardiovascular control mechanisms in healthy individuals with normal sleep. Silvani et al. (6) have made a significant contribution to this knowledge in identifying sleep-dependent changes in the coupling between HP and BP in healthy human subjects.

Fluctuations in HP and BP reflect two cardiovascular control mechanisms, the arterial baroreflex and the feed-forward effect of HP on BP. The baroreflex regulates arterial pressure around a preset value. It is reflected in a positive relationship between HP and systolic BP (SBP) and acts as a delayed negative feedback of BP on HP. The feed-forward effect of HP on BP is reflected in a negative correlation between HP and SBP. Two independent mechanisms have been proposed as the cause of the feed-forward effect: 1) reflex mechanical influences, such as reflexes from cardiac and aortic walls that modify HP and feed forward to BP via cardiac output (1); and 2) central autonomic commands, such as occur in dynamic exercise or the transient periods of tachycardia that occur during phasic rapid eye movement (REM) sleep and at an arousal from sleep (7). In some of these events, changes in BP are due to changes in peripheral resistance rather than an HP-mediated effect on cardiac output. It is likely that the feed-forward effect produced by central command is the more important, and it is likely that it operates by bringing about changes in baroreflex operating set point.

In the Silvani et al. study (6), the relationship between HP and SBP was assessed using a cross-correlation function in which the maximum positive correlation with a negative time shift (SBP preceded HP) identified the baroreflex influence, while the maximum negative correlation with a positive time shift (HP preceded SBP) identified the feed-forward influence. In addition, the sequencing technique was used to estimate baroreflex sensitivity, and the baroreflex effectiveness index (BEI) and nonbaroreflex effectiveness index (NBEI) were used to assess the relative effectiveness of baroreflex and feed-forward events.

The results indicated that the strength of the baroreflex component was systematically related to the sleep-wake state, being greater in non-REM (NREM) stages 3–4, than NREM stages 1–2 and REM, while the component was essentially absent in quiet wakefulness. Appropriately, while the strength of the feed-forward effect showed the inverse relationship over the sleep-wake state, with NREM sleep having the weakest effects and quiet wakefulness the strongest, the overall relationship was weaker than for the baroreflex effect. The sequencing technique provided confirmatory evidence with the added information that baroreflex events were considerably more effective than feed-forward events.

As indicated above, this study makes an important observation that is in general accord with the concept that regulatory control of the cardiovascular system is sleep-wake state dependent. The challenge for the future is to develop the technique to identify abnormal regulation. Without detracting from the importance of the Silvani et al. study (6), some difficulties can be foreseen when applying the technique to the sleep-cardiovascular health interface. One of these, as recognized by the authors, is that the technique identifies the linear component of the relationship between HP and BP. However, under certain circumstances, interactive or nonlinear components are likely to be substantial. For example, an arousal from sleep presumably reflects a central-command-driven feed-forward event, such that HP falls and then increases approximately two beats in advance of the rise and fall of BP (7), the latter being driven primarily by increases in peripheral resistance. While it is likely that baroreflex influences will be present, they will be masked over much of the event. Under conditions where arousals from sleep are frequent, as in sleep disorders, such as obstructive sleep apnea, it is possible that the baroreflex component will be underestimated, although it may be operating perfectly well.

Silvani et al. study (6) infers, but does not explicitly state, that the observed sleep-wake-state-dependent differences reflect state-dependent differences in regulatory control, that is, differences in the response to a similar perturbation. However, there may be an alternative interpretation. Sleep-wake states may differ in the extent to which the control system is challenged, i.e., differences in the frequency of perturbations. In a cross-correlation analysis of a time series, both the tightness of the relationship under investigation and the frequency of events that show the relationship will influence the strength of the
correlation coefficient. The alternative interpretation may be particularly pertinent to feed-forward events driven by central autonomic commands, events that Nollo et al. (4) referred to as “perturbative” to indicate that feed-forward events are not strictly regulatory. Thus, the weaker strength of the feed-forward component observed by Silvani et al. (6) in NREM stages 3–4 may reflect fewer HP perturbations.

The same problem may arise when using the cross-correlation technique to identify pathophysiology in the control system. Inadequate control system activity is presumably reflected in a weaker-than-normal correlation for a particular state. However, if the strength of a correlation can be influenced by both the strength of the particular relationship and the frequency with which it is present in the time series, inadequacies in the control system may be masked by changes in the frequency of perturbations. Nevertheless, it is noted that, consistent with the utility of the technique, the same authors have shown that spontaneously hypertensive rats have a weaker feed-forward component than Wistar-Kyoto rats during REM sleep, an effect that is probably not due to fewer events in the spontaneously hypertensive rats (1).

Silvani et al. (6) report measures of the effectiveness of feedback and feed-forward mechanisms and argue that the feed-forward mechanism was less effective than the feedback, particularly in NREM stages 3–4. The BEI is the proportion of SBP sequences (SBP ramps) that result in appropriate HP changes. If BP has a ramp and HP does not change, the effectiveness of the baroreflex is considered poor. The NBEI gives the proportion of SBP ramps not preceded by an appropriate change in HP. The NBEI was substantially less than the BEI and thus the conclusion that the feed-forward mechanism was less effective in NREM stages 3–4. However, it appears that the two indexes are not equivalent. The absence of a response in the presence of the appropriate stimulus is quite a different event to the absence of a stimulus to a putative response. The directionality of causation is stimulus to response, and nothing can be inferred from the absence of a particular stimulus.

I have raised a number of quibbles concerning the interpretation of the data generated by the cross-correlation technique and its potential application to the assessment of cardiovascular regulation in disturbed sleep. In general, these are expansions of points recognized by the authors. To reiterate, the importance of Silvani et al. (6) is in their continued development of a technique to independently assess feedback and feed-forward coupling of HP and BP and in the demonstration that these control systems are sleep-wake state dependent.

REFERENCES