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Relation of Beat-to-Beat Variability to Heart Rate in Normal Sleeping Infants

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Summary

The relationship of beat-to-beat heart rate variability (delta RR) and instantaneous heart rate was studied in eight normal infants while asleep during the first four months of life. The sleep state (REM or quiet) was determined using neurophysiologic and behavioral criteria. The results of regression analyses indicated that the delta RR values were positively correlated with the instantaneous heart rate (RR intervals). The correlation coefficient range was 0.49 to 0.92 in quiet sleep and 0.50 to 0.93 in REM sleep. Regression analyses supported a linear approximation of the delta RR to RR relation over the RR range investigated (400 to 520 msec). The median slope was 0.124 in REM and 0.117 in quiet sleep. The slopes of these linear functions were similar in both sleep states and at all ages. If beat-to-beat variability is to be used as an index of the integrity of the autonomic nervous system, these results suggest that delta RR be corrected for RR. A model is presented which relates the demonstrated positive correlation of delta RR to RR with the physiology of cardiac output control.

Speculation

The positive correlation of delta RR with RR is consistent with the view that beat-to-beat heart rate variability is a homeostatic mechanism required for control of cardiac output.

Beat-to-beat or short-term heart rate variability (delta RR) is used for identification of fetal distress and is believed to reflect the integrity of the autonomic nervous system in the fetus and newborn (6, 11, 18). Autonomic dysfunction may be manifested by decreased short-term variability as seen in hypoxic newborn infants at delivery (15) and in infants of mothers given parasympatholytic drugs (7, 8, 13, 14).

Short-term variability may also prove to be a useful parameter for monitoring autonomic function during early infancy. However, as in the fetus (7, 8), short-term variability of the heart rate might be a function of the instantaneous heart rate (instantaneous heart rate defined as the inverse of the RR interval of the electrocardiogram, *i.e.*, 1/RR) during the first several postnatal months. If this were the case, the delta RR should be normalized to the instantaneous heart rate. Therefore, we investigated the relation between delta RR and RR. Because heart rate and delta RR change with age and sleep state (12), the effects of age and sleep state on the delta RR to RR relation were also studied.

MATERIALS AND METHODS

Studies were performed on eight normal infants during the first four months of life while asleep as part of a larger study on maturational changes in cardiorespiratory control mechanisms of early life. All the infants were the products of normal pregnancies (gestational age range, 38 to 42 wk; birth weight range, 2.7 to 4.5 kg) and had normal growth and development. Twelve lead elec-

trocardiograms done after each study were normal. The procedures and objectives of the study were explained to the parents, and informed consent was obtained. A total of four or five studies, lasting one to two hr, were performed on each infant while it was asleep. Serial studies were performed during the first two wk of life and subsequently at monthly intervals through four months of age. Each study was done in a quiet laboratory environment after a usual midmorning feeding.

MEASUREMENT OF THE RR INTERVALS

Electrocardiogram surface electrodes were positioned on the chest to obtain a unidirectional polygraph recording with a single prominent R wave which had a sharp peak. Each RR interval of this wide-band electrocardiogram signal (0.5 to 2000 Hz) was measured with an accuracy of 200 μsec using a digital preprocessor designed in this laboratory (17). The data was carefully reviewed, and less than 0.1% of the 10,000 to 15,000 of each study RR intervals were rejected as artifact.

SLEEP STAGING

Surface electrodes were placed to record the neurophysiologic signals necessary to determine sleep state. These were: A C4-A1 electroencephalogram, a single bipolar electrooculogram, and a submental electromyogram. All of these signals were recorded on the polygraph using low noise (<2 μV peak to peak) amplifiers. Sleep staging was performed visually for 30-sec epochs by two independent observers using the electroencephalogram, electrooculogram, electromyogram, and behavioral criteria (1). All RR intervals during a given sleep state were included in the analysis.

DATA ANALYSIS

The absolute difference between the RR intervals of successive heart beats was used as a measure of short-term variability. It was calculated as

$$|\Delta RR_{(n)}| = |RR_{(n+1)} - RR_{(n)}| \tag{1}$$

where RR is the time in milliseconds from the peak of one R wave to the next, and "n" the interval number.

For each study, the RR interval range was divided into ten-msec cells or bins, and the average value of the delta RR for each RR bin was calculated. Only those RR bins which contained at least 10 delta RR values were considered. This approach provided an estimate of the expected delta RR value for each RR bin and allowed us to study the nature of the relation. Regression analysis was performed on this average delta RR as a function of RR for each individual study for REM and quiet sleep.

The effects of age and sleep state on the delta RR to RR relationship were then investigated. For this purpose, the average delta RR's representing each bin in all studies at each age and sleep state were pooled, and regression analyses were done. This

pooled data was analyzed for RR values between 400 and 520 msec (corresponding to heart rates of 150 and 115, respectively). This range covered the average heart rate ± 1 S.D. during the first four months of life (12). To characterize the slope of the regression relationship for any age and sleep state, we calculated the median of such slopes. The median was used rather than the mean to diminish the effects of outliers.

RESULTS

The results of regression analysis on the data for each sleep state in each study indicated that the delta RR values were positively correlated with the RR intervals. A typical plot of delta RR versus RR for one infant is shown in Figure 1. To determine whether the relation could be approximated by a linear function, we calculated the correlation coefficients of the delta RR to RR relationship. We considered the relation to be approximately linear if the correlation coefficient exceeded that threshold value (r) necessary to satisfy $t = r \sqrt{n - 2}/\sqrt{1 - r^2}$ for $P < 0.05$ (9). In 25 of 36 studies during quiet and 32 of 36 studies during REM sleep, the correlation coefficients were greater than these threshold values. The coefficients which were greater than the threshold values had a range of 0.49 to 0.92 in quiet sleep and a range of 0.50 to 0.93 in REM sleep.

To confirm the linearity of the relation of delta RR to RR, polynomial regression analysis was performed on these studies in both REM and quiet sleep. The results of this analysis also supported a linear model because, when second-and third-order regressions were considered, the improvement in the sum of squares of the deviation from regression was less than 5% in all studies where the correlation coefficient exceeded the threshold value.

In all 25 studies during REM and 32 studies during quiet sleep where the relationship could be considered linear, the slopes of the least-square linear regression functions were positive. The median slopes in these studies were 0.124 (interquartile range, 0.090 to 0.170) for REM and 0.117 (interquartile range, 0.081 to 0.214) for quiet sleep. In one-half of the cases, the slopes were greater in REM, and in the other one-half, the slopes were greater in quiet sleep and hence could not be considered different (sign test, $P > 0.25$). Therfore, there was not consistent trend with sleep state.

The data for each age were pooled to characterize the relation between delta RR and RR at each age. Figure 2 shows the linear regression lines of delta RR versus RR for the pooled data at each age in quiet and REM sleep, respectively. The slopes of these linear functions are similar, and these lines lie within the same narrow band (shaded areas) in both sleep states and at all ages.

To characterize the effect of sleep state on the delta RR-RR relation, the correlation coefficients of the pooled data for each age and sleep state were compared to their respective threshold values (calculated as defined previously). These correlation coefficients had a range of 0.42 to 0.61 in quiet sleep and 0.39 to 0.66 in REM sleep and are lower than those of individual states because they reflect intersubject differences. However, all exceeded their threshold values, further supporting approximation of the delta RR-RR relation by a linear function. Combining the pooled data for REM and quiet sleep at each age yielded correlation coeffi-
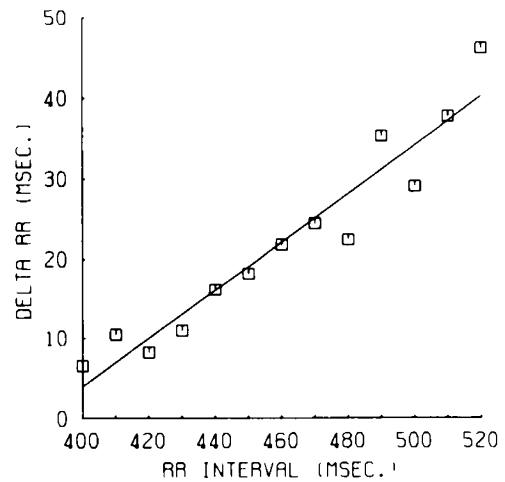

Fig. 1. Typical delta RR versus RR for one normal infant at age four months in REM sleep. The average delta RR values for each 10 msec RR cell or bin are plotted. The linear regression line through these points is shown.
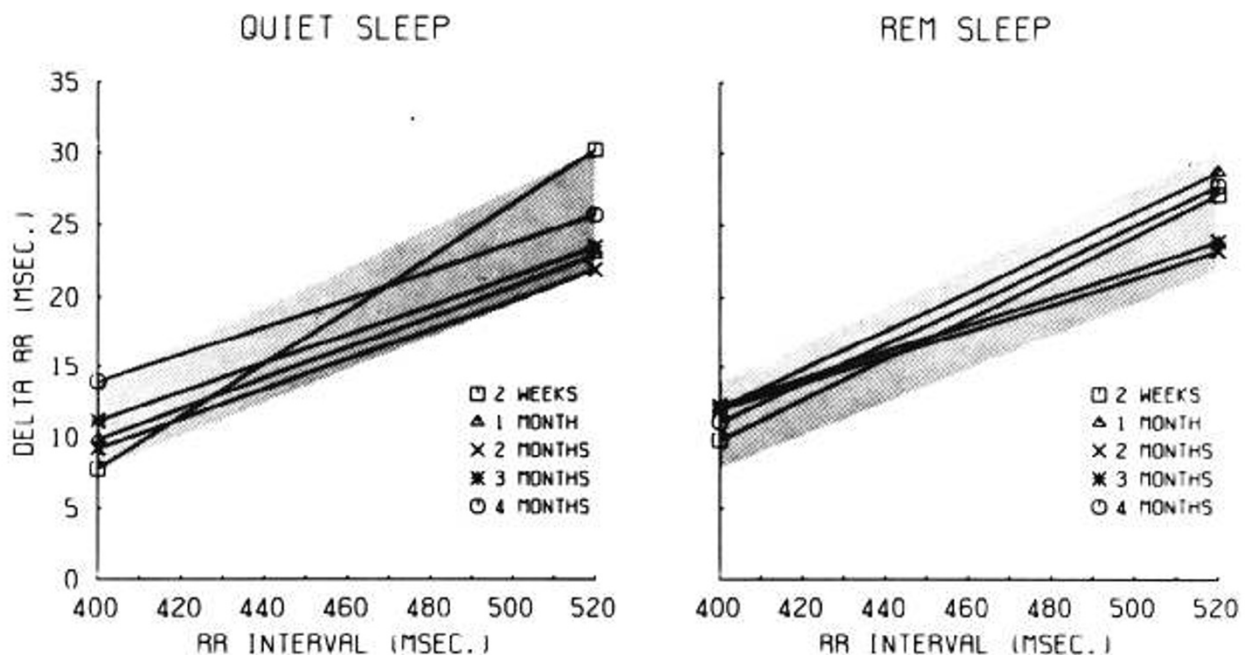

Fig. 2. The linear regression lines for delta RR versus RR at each age are shown for quiet (left) and REM (right) sleep. All of these regression lines for REM and quiet sleep fit into the same narrow range indicated by the shaded area in both plots.

cients, slopes, and intercepts which were similar to those found for each sleep state alone. Indeed, the range of correlation coefficients for the combined data was 0.40 to 0.62. Thus, to a first approximation, the delta RR-RR relation may be considered independent of sleep state.

DISCUSSION

Our results show that short-term variability (delta RR) is positively related to instantaneous heart rate and may be approximated by a linear function for the RR range investigated (400 to 520 msec). This relation implies that delta RR measurements should be corrected for heart rate because delta RR depends not only on the activity and integrity of the autonomic nervous system (21, 23-26) but also on the heart rate itself. This is analogous to the interpretation of the QT interval (4). The delta RR *versus* RR relationship we have demonstrated does not appear to be influenced by sleep state or age. This implies that this striking relationship is resistant to maturational changes in heart rate and beat-to-beat variability (12), to postnatal developmental changes in the autonomic innervation of the heart (10), and to fluctuations in autonomic activity associated with various sleep states (2, 3, 5). The linear relations we have used appear to adequately describe the delta RR *versus* RR relation for the heart rate range normally seen. The relation is, of course, not truly linear over a broader range because the regression lines intersect the RR interval axis at approximately 300 msec, implying that there would be no variability beyond that point. If there were no variability, the heart rate would be fixed, which is clearly not the case under normal circumstances.

If beat-to-beat variability is to be used as an index of the integrity of the autonomic nervous system (6, 11, 18), the results of this study suggest that correction of this index for heart rate may be desirable. This correction may be most important in those clinical situations where there is a wide range of heart rate.

The positive correlation of delta RR to RR may depend on the way cardiac output is regulated. Cardiac output (CO) under normal circumstances is adjusted primarily by heart rate (HR) rather than stroke volume (SV) changes (16, 19, 20, 22, 27). Under conditions where SV is constant, the heart rate may be considered a measure of cardiac output since

$$CO = SV \times HR \qquad (1)$$

The relationship of instantaneous heart rate or cardiac output to the RR interval is hyperbolic (Fig. 3). From this model, one can predict that for a fixed increment in CO change, a larger delta RR is necessary at a higher RR. By substituting 1/RR for HR in equation 1 above, and considering SV to be constant, one can show that

$$dRR = -RR^2/SV \times dCO \qquad (2)$$

or

$$|\Delta RR| = RR^2/SV \times |\Delta CO| \qquad (3)$$

If ΔCO is independent of RR, this model predicts that delta RR should be positively correlated with RR. Figure 3 demonstrates this relationship. Our empirical finding tht delta RR is positively correlated with RR suggests that short-term heart rate variability may indeed represent attempts to control cardiac output in an incremental fashion.

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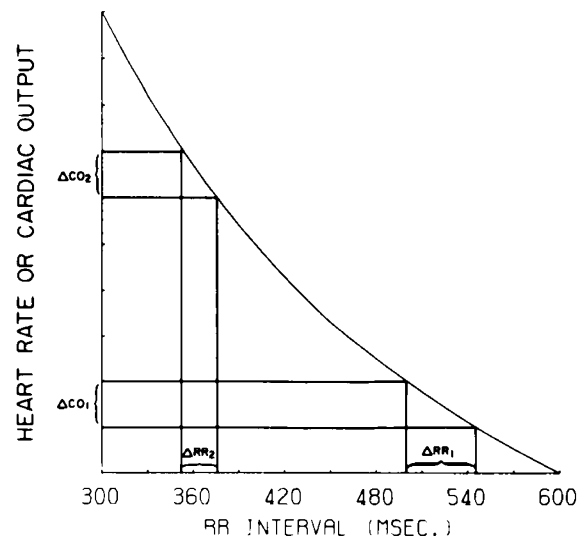4. Bazett, H. C.: An analysis of the time relations of electrocardiograms. Heart, *7:* 353 (1920).

Fig. 3. Heart rate or cardiac output *versus* RR interval. Case 1 shows the relation of delta CO and delta RR at a low heart rate; case 2, at a high heart rate. For equal cardiac output changes (ΔCO), a larger delta RR is required at a lower heart rate (higher RR).

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