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Development of Heart Rate Dynamics during Sleep-Waking States in Normal Infants

V. L. SCHECHTMAN, R. K. HARPER, AND R. M. HARPER

Brain Research Institute [V.L.S., R.K.H., R.M.H.] and Department of Anatomy and Cell Biology [R.M.H.], UCLA School of Medicine, Los Angeles, California 90024-1761

ABSTRACT. Previous studies show alterations in the dynamic patterns of cardiac rate in several "at-risk" populations, including apparently healthy infants who subsequently die of the sudden infant death syndrome. In the present study, we examined the maturation of cardiac rate dynamics in normal infants during sleep-waking states over the first 6 mo of life. Instantaneous changes in cardiac R-R intervals were examined in 12-h recordings of 24 normal full-term infants; each infant was recorded at 1 wk and at 1, 2, 3, 4, and 6 mo of age. Scatter plots, consisting of each cardiac R-R interval plotted as a function of the previous interval (Poincaré plots), were constructed for each sleep-waking state in each recording. Analyses of variance were performed on the dispersion of intervals after long and short R-R intervals. In neonates, Poincaré plots showed significantly more next-interval dispersion after a long R-R interval than after a short interval, a pattern similar to those observed in older infants and in healthy adults. However, between 1 wk and 1 mo of age, this pattern disappeared and returned gradually beginning at 2 mo of age. The scatter of points in Poincaré plots of infants 1 mo of age approached the patterns of at-risk populations, including infants who subsequently died of the sudden infant death syndrome. These patterns at 1 mo may be indicative of increased vulnerability in normal infants after the neonatal period. (*Pediatr Res* 34: 618–623, 1993)

Abbreviations

A-V, atrioventricular
REM, rapid eye movement
SIDS, sudden infant death syndrome

The largest proportion of heart rate variation studies in developing neonates has been based on spectral analytic techniques or summary time-domain procedures; these techniques assess variation "averaged" over relatively long (in most cases, 1-min) periods. Although these summary techniques are valuable for demonstrating particular trends over time, characteristics of moment-to-moment changes in heart rate can yield additional information on the nature of cardiac rhythm. Assessment of beat-to-beat changes requires the use of specialized measurement techniques that assess dynamic properties. In this paper, we explore developmental patterns of dynamic features in infant heart rate.

A simple method for the assessment of the beat-to-beat dynamics of heart rate involves plotting each R-R interval (the time between two successive R waves of the ECG) against the previous R-R interval. The resulting Poincaré plots (1) provide an indication of *1*) mean heart rate, *2*) overall extent of heart rate variation, *3*) extent of beat-to-beat heart rate variation at any given heart rate, and *4*) the pattern of change in beat-to-beat heart rate variation as basal heart rate increases or decreases (Fig. 1). Poincaré plots have been used to identify abnormalities of cardiac rate dynamics in numerous pathologic conditions, including congestive heart failure (2) and congenital central hypoventilation syndrome (3), and to assess dynamics of heart rate (4) and respiratory rate (5) after cocaine administration. Moreover, apparently healthy infants who subsequently succumb to SIDS demonstrate Poincaré plots markedly different from those of age-matched infants who survive (6).

The characteristics that distinguished Poincaré plots of infants who succumbed to SIDS from those of infants who survived principally related to the extent of R-R interval changes at slower heart rates. Although age was controlled in that study, only a few ages were represented, making it difficult to recognize the age trends in either the SIDS victims or the controls and thus difficult to determine whether SIDS victims showed patterns unlike those of the control infants or whether the patterns in the SIDS victims were simply similar to those present in controls at another age. The objective of this study was to determine the distribution of Poincaré plots in normal infants over the first 6 mo of life.

MATERIALS AND METHODS

Recordings. Polygraphic recordings of EEG, ECG, electrooculogram, digastric electromyogram, and expired CO_2 were obtained from 25 normal infants. Each infant was recorded on six occasions: at 1 wk of age and at 1, 2, 3, 4, and 6 mo of age. Each recording was begun at 1900 h and terminated at 0700 h the following morning. The ECG signal was fed into a Schmitt trigger generator that produced a pulse for each R wave. The resulting trigger event times were digitized along with the other signals.

Each 1-min epoch of data was classified as quiet sleep, REM sleep, waking, or indeterminate state by two trained observers using criteria (7) similar to those suggested by Anders *et al.* (8) for state classification of newborns. One of the recordings was later eliminated due to missing signals, leaving 24 subjects with recordings at all six ages.

R-R intervals. The intervals between successive R waves of the ECG (R-R intervals) were calculated from the R wave trigger times with an accuracy of ±2 ms. Cardiac R-R intervals were subjected to an automated artifact detection and correction procedure (9), which identified those epochs containing considerable artifact as unsuitable for analysis. All 12 h of data, with the exception of 1-min epochs classified either as artifact-contaminated or of indeterminate sleep state, were used for analyses.

Cardiac R-R intervals from each recording were separated into three files depending on the sleep-waking state of the infant during each 1-min epoch. One file contained all the R-R intervals from those epochs classified as quiet sleep, another contained all

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Correspondence and reprint requests: Vicki L. Schechtman, Ph.D., Brain Research Institute, UCLA School of Medicine, Los Angeles, CA 90024-1761.
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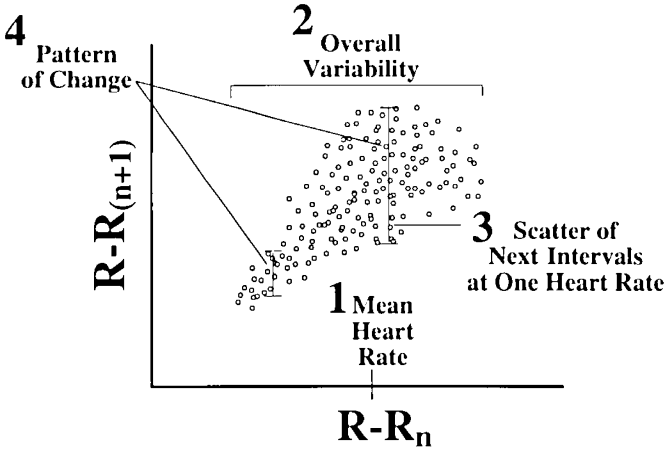

Fig. 1. Sample Poincaré plot. Each cardiac R-R interval (the interval between two successive R waves of the ECG) is plotted against the previous R-R interval. Information that can be obtained by examination of Poincaré plots includes: *1*, mean heart rate; *2*, overall extent of heart rate variation; *3*, extent of beat-to-beat heart rate variation at a given heart rate; and *4*, the pattern of change in beat-to-beat heart rate variation as basal heart rate increases or decreases.

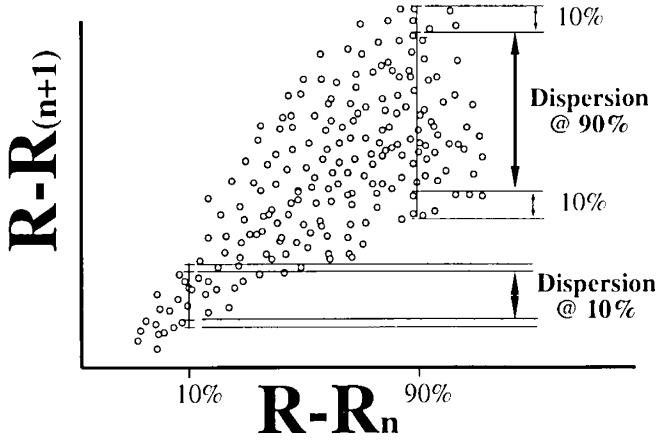

Fig. 2. Quantification of ranges of R-R intervals after a relatively long (slow heart rate) and a relatively short (rapid heart rate) R-R interval. The two base heart rates used for analyses were the 10th percentile and the 90th percentile of all R-R intervals in each state in the recording. Scatter was quantified as the range of values excluding the extremes (the top and the bottom 10%).

REM epochs, and a third contained the R-R intervals from all periods of waking. These three files of R-R intervals from each recording—a total of 18 files per subject (three sleep-waking states × six ages)—were used for all analyses. Each file contained an uninterrupted list of R-R interval durations (on average, 25 260, 31 246, and 12 947 intervals over the entire night in quiet sleep, REM sleep, and waking, respectively). Changes in sleep-waking state and epochs eliminated due to artifacts produced occasional false pairs of adjacent intervals; however, the number of these aberrant pairs was so small relative to the total number of points (always under 1%, and usually far less than 1%) that their contributions to the overall plots were minimal.

Poincaré plots. Each R-R interval was plotted against the previous R-R interval to produce a Poincaré plot for every infant in each sleep-waking state and at each age (a total of 18 plots per subject). Because the large number of points caused extensive overplotting, different gray levels were used to represent point density in each part of the plots. The scattergrams were plotted and examined visually for patterns of change across sleep-waking states and across ages.

The shape of Poincaré plots can be quantified in a number of ways. The power of Poincaré plots to identify pathologic conditions depends on the extent of scatter of points at various positions along the line of identity (2, 3, 6). For some conditions, the scatter in the upper right-hand quadrants of the plots (those areas depicting slow heart rates) are particularly effective; in other conditions, deviations at faster rates supply the most useful discriminators. We examined scatter of next intervals (range of y values) at two widely separated heart rates (two particular values of x), one fast and one slow.

The quantification of dispersion at fast and slow heart rates is illustrated in Figure 2. The two base heart rates used for analysis were selected by sorting all the intervals within a given file in order of their lengths and eliminating the longest and shortest 10% to obtain the R-R intervals at the 10th percentile (relatively rapid heart rate) and the 90th percentile (relatively slow heart rate). To determine the spread of next-interval values at each of these rates, we sorted all y values for the given value of x (all R-R intervals preceded by intervals of the selected value) and eliminated the longest and shortest 10%; the scatter was quantified as the range of values excluding the extremes (*i.e.* the R-R interval at 90% minus the R-R interval at 10%).

Analysis. Three-way analysis of variance (age × sleep state × heart rate) was used to identify state-related differences at both high and low heart rates and the patterns of change in these measures as the infants matured. Because the distributions of ranges were nonnormally distributed, the common log of each of these values was used for analysis. Analysis of simple effects was used to identify the bases of significant interactions.

Because several types of heart rate variation are profoundly affected by basal heart rate (10), this three-way analysis of variance was also repeated using the mean heart rate during each sleep-waking state from each recording as a covariate. This analysis was used to determine whether changes in next-interval dispersion parallel the changes in heart rate that occur with state changes and maturation.

Tests of sphericity (11) were applied to all interactions to assess the degree of dependence of the factors. When these tests revealed significant dependence, the Huynh-Feldt adjustment (12) was used, and the adjusted probability values are reported.

RESULTS

Typical Poincaré plots from one normal infant at each of the six ages are shown in Figure 3. A gray scale is used to indicate the density of points at each location in the plots; this was necessary because the large number of points (typically 20 to 40 thousand) plotted in a finite space resulted in considerable overplotting, thereby obscuring the morphology of each plot.

The placement of points with respect to the origin is an indication of heart rate, with points closest to the origin reflecting short R-R intervals (high rate). Note that overall R-R interval length decreased (points moved closer to the origin) between 1 wk and 1 mo and increased (points moved further from the origin) between 1 mo and 6 mo of age.

Neonates typically showed Poincaré plots similar to those observed in adults, characterized by increased next-interval dispersion after long R-R intervals (slow heart rate) relative to after short intervals (fast heart rate). Although this pattern was also observed in older infants, it was significantly less pronounced in infants 1 mo of age.

The mean values of the $\log_{10}$ ranges of next intervals at slow (90th percentile of R-R intervals) and fast (10th percentile) heart rates are shown in Figure 4 (*actual*). Analysis of variance demonstrated a significant interaction of state and heart rate ($p < .005$), indicating a significant sleep state effect only when heart rate is high; note that when heart rate is low the three sleep-waking states show very similar values.

The decrease in dispersion over the first month of life was especially pronounced at slow heart rates. Across all three sleep-waking states, infants showed a significant decrease in next-

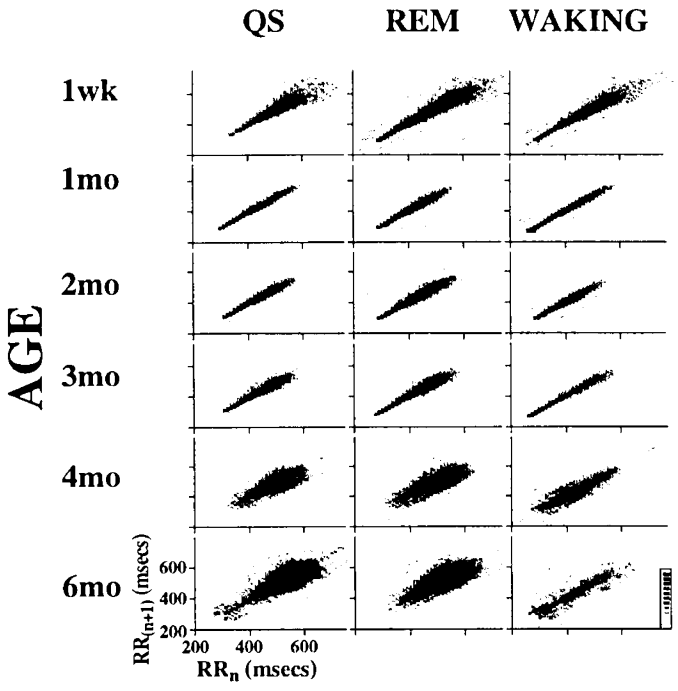

Fig. 3. Typical Poincaré plots from one normal infant at 1 wk and 1, 2, 3, 4, and 6 mo of age. A gray scale is used to indicate point density at each location in the plot.

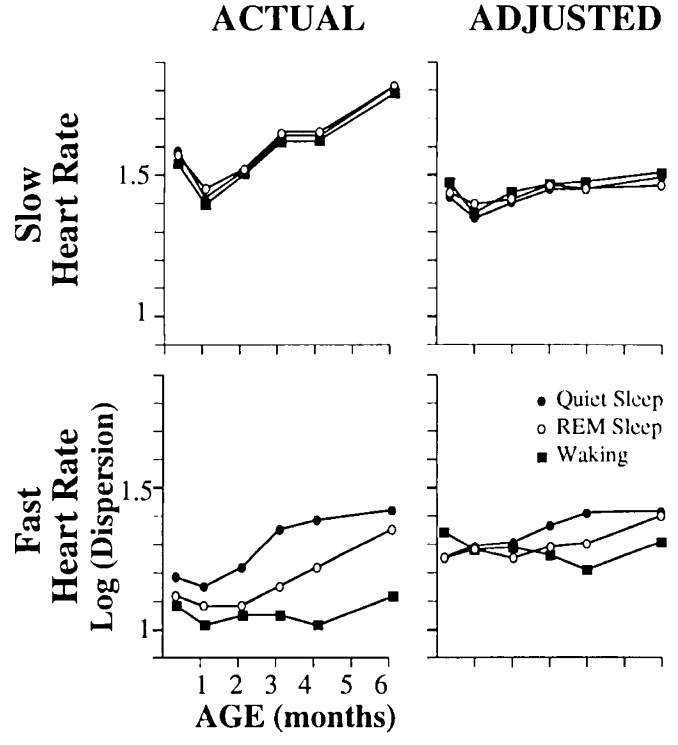

Fig. 4. The mean values of the $\log_{10}$ dispersion (ranges) of next intervals at low and high heart rates before (*actual*) and after (*adjusted*) compensating for changes in mean heart rate. At slow heart rates, dispersion shows a consistent decline over the first month of life, which is eliminated by covariation of heart rate.

interval dispersion from 1 wk to 1 mo of age ($p < .05$), and this decrease was significantly more pronounced after long than after short R-R intervals ($p < .05$). Thus, at 1 mo the pattern of scatter was more equally distributed at the high and low heart rates, with less "fanning" of the distribution at low rates.

Figure 4 (*adjusted*) reflects the mean ranges ($\log_{10}$) of next intervals at low and high heart rates [the same values shown in Fig. 4 (*actual*)] after the effects of differences in mean heart rate were partitioned from the data. Controlling for differences in heart rates eliminated the reduction in dispersion from 1 wk to 1 mo of age at slow heart rates ($p > .05$) and the significant difference between the three sleep states at fast heart rates ($p > .05$).

Figure 5 indicates the dispersion of y values at seven values of x representing a wide range of heart rates. At the lowest heart rates, differences among the three sleep-waking states were minimal, and all states show a marked developmental pattern characterized by a reduction over the first month of life (*arrows*), an increase from 1 to 3 mo of age, a consistent plateau from 3 to 4 mo, and a continuation of the increase thereafter. During REM sleep and waking, this pattern became gradually less pronounced as heart rate increased (*i.e.* R-R interval decreased). The effect of sleep-waking state was also more prominent at higher heart rates.

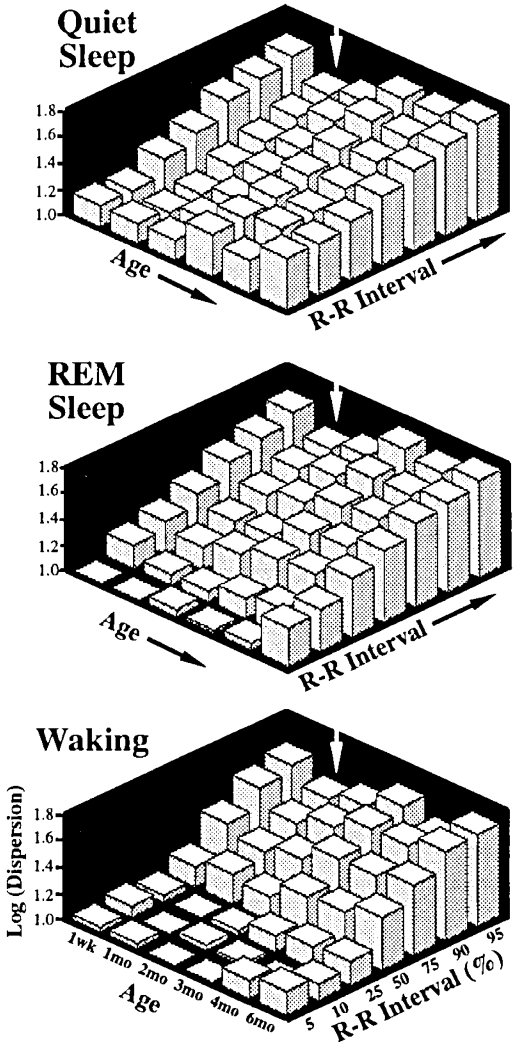

Fig. 5. Log_{10} dispersion of y values at seven values of x, representing a wide range of heart rates, during each sleep-waking state. Age and previous interval length are plotted on the two horizontal axes. Each bar represents the mean $\log_{10}$ dispersion of all 24 infants at each age and at seven different previous interval values. Previous R-R interval values are represented as percentile of R-R intervals in each recording (*i.e.* 50% indicates the median interval in each recording, despite differences in the actual interval duration) to control for differences in basal heart rate between individual infants and across ages and sleep-waking states. Note that at 1 mo of age (*arrows*) dispersion drops after all interval lengths, but the change is most pronounced after long intervals.

At high heart rates (particularly, in REM sleep and waking) $\log_{10}$ next-interval dispersion approached 1.0, reflecting a range of 10 ms; thus, at high heart rates, it was highly unlikely for the next interval to differ by more than ±5 ms from its predecessor, indicating an extremely fixed heart rate. At the slowest heart rates, $\log_{10}$ dispersion ranged from approximately 1.5 (next-interval range of 30 ms) at 1 mo to approximately 1.8 (next-interval range of 65 ms) at 6 mo across all states, indicating a wide range of next intervals after an interval of a given length. These values indicate the potential for large changes between one R-R interval and the next.

Complex patterns. A number of Poincaré plots showed patterns more complex than the typical "fan-shaped" morphology. One case with a distinctive morphology proved to reflect frequent A-V junctional premature beats in one infant at 1 mo of age. Junctional premature beats result in two aberrant intervals, an uncharacteristically short interval (reflecting the premature contraction of the ventricle) followed by an uncharacteristically long interval (reflecting the subsequent compensatory pause). These two aberrant intervals translate into three abnormal pairs (normal/short, short/long, and long/normal) and thus three abnormal clusters on a Poincaré plot.

Another type of complex pattern indicated alternating short and long R-R intervals, with few points between the two extremes (Fig. 6*A*). This pattern was visually obvious in one or more recordings of three of the 24 infants; most occurrences were observed at 1 to 3 mo of age, but at least one infant showed the pattern at 6 mo. Examination of the raw ECG signals responsible for these patterns confirmed the presence of alternating short and long intervals between successive R waves (Fig. 6*B*). In these sequences, all "long" R-R intervals were of approximately equal size and all "short" R-R intervals were similarly restricted to a relatively narrow range; however, very few intervals had values between those of the two extreme groups. These alternating short and long intervals resulted in two distinct clusters on the Poincaré plots, one representing a long interval followed by a short one (point A) and the other reflecting a short interval followed by a long one (point B). Because the aberrations were most pronounced at the lowest heart rates (the lower the basal heart rate, the larger the difference between the adjacent short and long intervals), these two clusters formed lines radiating away from the line of identity.

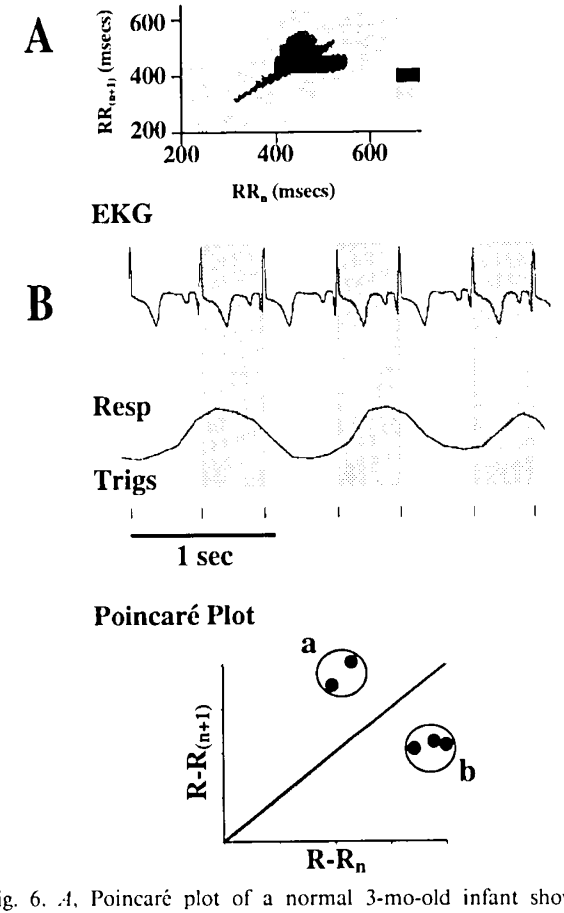

Fig. 6. *A*, Poincaré plot of a normal 3-mo-old infant showing a frequently observed complex pattern. *B*, ECG, airflow respiration, and R wave triggers from a portion of a recording that showed this complex Poincaré morphology, together with a simulation portraying contributions from such intervals to Poincaré plots. Note that the alternating intervals produce two distinct clusters on the Poincaré plot, one reflecting a short interval followed by a long one (*point a*) and the other a long interval followed by a short one (*point b*).

DISCUSSION

The pattern of next-interval dispersion observed in neonates is similar to that observed in healthy adults, showing increased next-interval dispersion after long compared with short R-R intervals (2). This "fanning" pattern was greatly attenuated at 1 mo of age and then increased over the ensuing months. The loss of dispersion at long R-R intervals observed in 1-mo-old infants is similar to, although not as profound as, the next-interval restriction seen in several "at-risk" groups (2, 3), including healthy infants who subsequently died of SIDS (6).

The pattern of next-interval dispersion at slower heart rates follows the pattern of change in heart rate over the early postnatal period, decreasing over the first month of life when heart rate increases and increasing thereafter as heart rate decreases (13). This similarity of patterns breaks down as the rate of the previous heart beat increases, suggesting that factors influencing short term (beat-to-beat) changes in heart rate play a greater role at higher heart rate, while factors responsible for very gradual changes in heart rate (such as those observed at monthly intervals) play a more pronounced role in the pattern of variation at lower heart rates.

Results of this study also show that complex patterns in Poincaré plots can indicate particular information about factors influencing cardiac rate. One type of complex pattern was shown to be indicative of frequent A-V junctional premature beats in one infant, whereas another complex pattern indicated alternating short and long R-R intervals.

Next-Interval Dispersion Decreases Over First Month of Life. The pattern of next-interval dispersion observed in 1-mo-old infants is most similar to that observed in infants who died of SIDS (6). Thus, this pattern, which is also typical of several other at-risk groups (2, 3), may be indicative of increased vulnerability of infants after the immediate postnatal period. The concept of vulnerability increasing after the early postnatal period is not a new one. During the neonatal period, vital functions are controlled reflexively via brainstem mechanisms. As forebrain influences mature, the reflexes, which protect the neonate, may be modulated, allowing for a wider and more complex range of reactions.

Dispersion Increases from 1 to 6 Mo of Age. From 1 to 6 mo postnatal age, extent of next-interval dispersion at slower heart rates gradually increases, such that infants 6 mo of age show the greatest degree of next-interval dispersion. This increase in next-interval dispersion from 1 to 6 mo of age is interrupted by a plateau (or even a slight decrease) between 3 and 4 mo. This plateau between 3 and 4 mo is not observed in the curve of heart rate (13) or that of respiratory sinus arrhythmia assessed by a time-domain method (14); however, a similar plateau is observed at this age in plots of spectral power of respiratory sinus arrhythmia (15), as well as plots of lower frequency heart rate variation assessed by time-domain methods (14).

The pattern of a plateau or even a slight decline between 3 and 4 mo is seen consistently at all of the lowest heart rate ranges

in Poincaré plots reflecting all sleep-waking states (Fig. 5). The finding of similar plateaus in all sleep-waking states is a further indication that this nonlinear pattern of maturation is not an artifact of particular epochs in some or all recordings, inasmuch as different epochs were used for analysis of the different states. This study and previous studies of heart rate variation therefore suggest that decreases in many types of heart rate variation occur between 3 and 4 mo of age. However, the diminution in variability is not associated with a change in basal heart rate; thus, the reduction in variability is unlikely to be mediated by a tonic change in autonomic drive.

In the waking state, the next-interval dispersion shows a fairly linear pattern of change after R-R intervals from 95% to 50%, but the next-beat dispersion is markedly reduced as heart rate increases above the median (50%). Thus, in the waking state, heart rate dynamics are profoundly different at high and low heart rates. This division may separate "relaxed" waking (heart rate at or below the median) from "aroused" waking (heart rate above the median); different factors may be involved in heart rate control in these two "substates" of waking.

Complex Patterns. Two different complex patterns were identified in the Poincaré plots of these normal infants. In one recording, multiple A-V junctional premature beats resulted in three outlying clusters of points on the Poincaré plots; this complex pattern has also been documented in adults with premature ventricular contractions (16). The junctional premature beats and the associated complex Poincaré plots were apparent during all sleep-waking states in one infant only at 1 mo of age; neither was detected in the same infant at either 3 wk earlier (at 1 wk of age) or 1 mo later (at 2 mo of age).

Another pattern of complex Poincaré plot appeared in several infants. Careful examination of the ECG during periods when these patterns were generated showed alternating short and long R-R intervals. These alternations were apparently vagally mediated, because they occurred only when heart rate was very slow and disappeared concurrent with an increase in heart rate; the extent of the oscillation was also greatest at slowest heart rates. Although in many cases the ECG appeared to be loosely phase locked with the respiratory signal, the short and long R-R intervals showed no consistent relationship to respiratory phase. Further studies are currently under way to examine this phenomenon and to study its relationship to respiratory sinus arrhythmia, which is usually quite pronounced in conjunction with high vagal tone.

Heart Rate Dynamics Versus Summary Measures of Heart Rate Variation. Maturation. Many previous studies have used summary measures to assess patterns of heart rate variation in infants. These studies have shown that extents of various types of heart rate variation decline over the first month of life during all sleep-waking states (14, 17) and then increase (14). This pattern of decline at 1 mo postnatal age and increase thereafter parallels the pattern of development of range of next intervals after a long R-R interval; however, clear developmental patterns do not occur in next-interval dispersion after short R-R intervals.

Sleep-waking states. Previous studies have shown that heart rate variation at the respiratory frequency (respiratory sinus arrhythmia) predominates during epochs of quiet sleep (14, 15), particularly after 2 mo of age (14), whereas during REM periods lower frequency variation is enhanced (14). Heart rate variability at both frequencies is greatly diminished in waking relative to the two sleep states. The findings of the present study show that one interval–next interval dispersions after a slow heart rate are similar in the three states. The interval dispersion after a rapid heart rate does differ, however, in the three states at all ages. Across all ages, next-beat dispersion after a rapid heart rate is greatest during quiet sleep and least in the waking state. During quiet sleep, next-interval dispersion decreased linearly with increasing heart rate. In REM sleep, this linear decrease is also apparent at low heart rates, but dispersion falls more rapidly for R-R intervals in the lowest 10% (Fig. 5). In waking, next-interval dispersion is reduced after R-R intervals in the lowest 25%. Thus, heart rate dynamics show state-dependent patterns only when heart rate is high.

It is intriguing that interval dispersion shows little or no state dependency at low heart rates, when quiet sleep shows greatly increased respiratory sinus arrhythmia relative to the other sleep-waking states; when heart rate is high, however, and all states show very little heart rate variation of any kind, dynamic patterns of heart rate variation differ markedly in the three states. Because the changes at these high rates tend to be rapid, vagal mechanisms most likely are the mediators, inasmuch as only vagal mechanisms can operate sufficiently quickly to effect significant changes in heart rate from one beat to the next (18, 19).

Implications for SIDS. Infants 2 to 65 d of age who subsequently die of SIDS show reduced dispersion of next intervals, especially at low heart rates, relative to infants who survive (6). The present findings indicate that dispersion of next intervals in normal infants decreases over the first month of life, and then increases. Thus, at 1 mo of age, the dynamic cardiac rate patterns of normal infants most closely approximate those of SIDS victims, perhaps indicating increased vulnerability to SIDS at that age.

Findings of the present study indicate that particular components of the normal maturational changes in point dispersion of Poincaré plots are related to the concomitant age-related changes in heart rate (*i.e.* age-related differences in point dispersion are eliminated by controlling for maturational changes in heart rate). In contrast, differences between the Poincaré plots of SIDS victims and control infants remained significant after contributions of heart rate differences were partitioned from the data (6). Thus, although SIDS victims and infants at risk for SIDS demonstrate several signs indicative of delayed nervous system maturation (20–23), the dynamic patterns of their cardiac rates are not analogous to those of normal infants at an earlier stage of development.

Conclusions. Poincaré plots of normal neonates are similar to plots of older (2–6 mo of age) infants; however, normal infants at 1 mo of age show decreased dispersion of next intervals, particularly after a long R-R interval, similar to patterns shown in at-risk populations and infants who subsequently died of SIDS. After the first month of life, the dispersion, especially at slower heart rates, begins to increase, and by 6 mo of age the plots begin to approximate the fan-shaped formation typical of healthy adults. The similarity of Poincaré plots of normal infants during a particular phase of development to Poincaré plots from at-risk groups may indicate that the period after the immediate neonatal period is a time of increased vulnerability in normal infants.

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