PERIODIC VARIATIONS OF BLOOD PRESSURE AND HEART RATE IN PREMATURE NEONATES

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The existence in adults of circadian rhythms (period 20-28 h) of arterial blood pressure (BP) and heart rate (HR) is one manifestation of adaptation to the alternation of light and darkness and the character of activity during the 24-h period. Depending on the person's age and state of health, these variations differ in amplitude (A), and deviations of the measured parameter from the mean 24-hourly value (mesor) reach their maximum (acrophase) at different times of day and night.

The question of the age at which the circadian rhythms of BP and HR are formed in man has not been adequately studied. All that can be found in the literature is that in some newborn infants no circadian rhythm of activity of the cardiovascular system can be detected, and that certain characteristics of circadian variations of BP and HR differ in newborn infants in families which contain patients with hypertension, and in infants whose parents and closest relatives are not hypertensive [2, 3, 4].

The study of the formation of the circadian rhythm of BP and HR in human ontogeny is interesting not only from the general biological point of view (as a characteristic of adaptation to the conditions of extrauterine life), but it is also of applied importance, for example, from the standpoint of developing diagnostic and prognostic tests.

The aim of this investigation was to study changes in BP and HR during the 24-h period in premature infants in the first month of life.

EXPERIMENTAL METHOD

BP (systolic, diastolic, mean) and HR of infants with gestation age of 25-37 weeks and with a birth weight of 650-2850 g were measured every 30 min by an oscillometric method and with the aid of BP-3200 (EME, Great Britain) and "Pulsemate BX-5" (Colin, Japan) monitors. The duration of monitoring was 24-72 h. Tests were carried out during the first week of life and thereafter at intervals of 7-10 days until the infant was discharged (age 30-40 days). Altogether there were 96 investigations of 50 infants. Monitoring was carried out on infants subjected to the usual program of care and treatment, determined by the severity of the child's state and the diagnosis.

Subsequent analysis of the results of measurement of BP and HR, by IBM PC XT personal computer, consisted of the detection of all regular (sinusoidal) fluctuations of these parameters with whole periods of between 1 and 48 h. The method envisaged calculation of different characteristics of these fluctuations. The place of each period among the others in a given investigation was determined by the sum of the squares of deviations of the experimental time series from the sinusoid approximating it; periods were arranged in order of an increase of this sum.

To estimate the number of significant periods in the sequence thus constructed (Ti) the criterion $di = \sigma - \sigma Ti$ was used for each investigation, where σ denotes the standard deviation of the experimental time series, σTi the mean square error of approximation of the experimental series by a sinusoid with period Ti. Thus, the criterion d characterizes the abundance of sinusoidal waves compared with random (nonperiodic) deviations from the mean value.

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Internal correlations between various characteristics of periodic processes in the infant were also studied.

EXPERIMENTAL RESULTS

Fluctuations of BP and HR during monitoring were observed in all infants. Their periods showed considerable variation, and first place according to the ranking procedure described above would be occupied by oscillations with any period from 1 to 48 h. The character of the rhythm of systolic and diastolic pressures was similar.

Before analyzing structure (hierarchy) of the periods for each infant, the significance of these periods was estimated, starting with the most abundant. For systolic BP dependence of A (in mm Hg) of this period on the value of the criterion d (mm Hg) was expressed by the equation $A = 4.5 \cdot d + 3.9$ ($r = +0.89$). Since the accuracy of measurement of BP did not exceed 1 mm Hg, all values of A corresponding to $d < 1$ must be interpreted as not significant. In these cases, approximation of the temporal series of BP by a sinusoid was not better than its approximation by a straight line, and the rhythm thus revealed is artificial. The value of A separating random deviations of BP (noise) from regular periodic oscillations is 8 mm Hg.

Special examination of circadian fluctuations of systolic BP showed that they can be regarded as significant likewise only when their amplitude exceeds 8 mm Hg.

Correspondingly, fluctuations of HR can be regarded as true rhythms if their A exceeds 12 beats/min ($d \geq 1$ beat/min). It will be noted that the use of these boundary values of A to discover true rhythmic fluctuations is rather less accurate than the use of the d criterion, for coefficients of correlation between A and d, although high, are not equal to 1. If, therefore, true periodic oscillations are distinguished on the basis of amplitude, both false-positive (distinguishing a regular rhythm where it does not exist) and also false-negative results may be obtained.

The use of the $d \geq 1$ criterion showed that in 30% of infants tested in the first month of life sinusoidal fluctuations of systolic BP could not be detected with any period comprising a whole number of hours, including circadian. Periodic fluctuations of HR were not found in 20% of infants. In the rest, fluctuations of BP and HR with different periods were observed.

On the basis of the existence and abundance of the different periods of BP and HR the infants could be divided into three groups: 1) circadian oscillations occupy the dominant position (i.e., have the maximal value), 2) circadian oscillations are present in significant numbers ($d \geq 1$) but are not dominant, and 3) only oscillations with periods differing from circadian are abundant.

The results of the study of systolic BP showed that 10% of infants belong to group 1, 15% to group 2, and 45% to group 3. With respect to HR, the distribution of the infants among the groups was 5, 25, and 50%, respectively.

The relative number of premature infants with the significant presence of a circadian rhythm of HR is the same as that obtained for infants born at term [2]. However, this is not true of the circadian rhythm of BP, which has been considered to be present in all neonates for whom the value of A of the oscillations differs from zero [4]. The results of the present investigation show that significant fluctuations of BP with a circadian period can be detected in only 25% of premature infants. Their A value, as already stated, should exceed 8 mm Hg. It can be tentatively suggested that the boundary value of A in premature infants will be close to this value, for it is mainly determined by the technical characteristics of the apparatus used for monitoring.

To investigate how inaccuracy of detection of the circadian rhythm of BP influences the classification of newborn infants from the standpoint of their risk of developing hypertension in later life, further investigations are needed. An examination confined to cases of a distinctly regular rhythm can lead both to improvement of the classification of appraisal and to modification of the combination of informative parameters.

It is also interesting to examine the age dynamics of formation of the circadian rhythm of BP and HR. If the results of the present investigation on a relatively small group of infants are analyzed, a tendency will be seen for this rhythm to appear by the 5th week.

Since about half of infants with only rhythms that differ from circadian, in the search for diagnostic and prognostic criteria the analysis of the hierarchy of these rhythms with a view to evaluating the state of the child's adaptation assumes special significance.

The following conclusions can thus be drawn from these results. When periodic fluctuations of physiological parameters are examined, attention must be paid to the abundance of these oscillations. The use of the suggested criterion showed that in the case of traditional assessment of the significance of oscillations on the basis of their amplitude, the examination must be limited only to oscillations with am amplitude of over 8 mm Hg for systolic BP and over 12 beats/min for HR.

Oscillations of BP and HR only with rhythms which differ from circadian are found in 45-50% of infants, no rhythm can be found in 20-30%, and only 25-30% of infants have a circadian rhythm.

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APPEARANCE AND SPREAD OF EXCITATION IN THE FROG MOTOR NERVE ENDING

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During the conduction of excitation in nerve fibers changes of potential along the membrane are heterogeneous, and local currents arise between neighboring areas, which on the one hand lead to conduction of the impulse into resting parts of the nerve fiber and, on the other hand, exert a significant effect on the development of the action potential (AP) in the part already excited [5, 9].

Processes of generation and spread of excitation in motor nerve endings, which are terminal ramifications of the motor axon and are responsible for the transmission of excitation from nerve to skeletal muscle, have not yet been elucidated. Until quite recently it was considered [6-10] that the AP spreads along the nerve ending of both warm- and cold-blooded animals actively and without decrement, but that depolarization of the presynaptic membrane induces a flow of Ca^{2+} ions into the axoplasm of the ending and secretion of the mediator [4, 5, 11].

However, recently it was found, when ionic currents of a mouse nerve ending were recorded [7, 10], that the endings do not contain sodium channels, and they are depolarized passively due to local currents from the Ranvier node and the preterminal segment. It was later shown [1, 2, 12] that frog motor nerve endings can generate excitation and cause its active spread, although the value of the sodium current falls along the course of the nerve ending.

In the investigation described below local application of tetrodotoxin (TTX), a specific sodium channel blocker, to different parts of the nerve ending and Ranvier nodes, the generation and spread of excitation in the frog motor nerve ending and the role of these processes in mediator secretion were studied.

EXPERIMENTAL METHOD

Experiments were carried out on nerve-muscle preparations of the cutaneosternal muscle of *Rana ridibunda* in the winter period, during continuous perfusion of the preparation with solution of the following composition (in mM): NaCl – 115.0, KCl – 2.0, $CaCl_2$ – 0.4-0.6, $MgCl_2$ – 2.0, $NaHCO_3$ – 2.4, pH 7.2-7.4, temperature 18-20°C.

Evoked electrical responses of the nerve ending and subsequent end-plate currents (EPC) were recorded extracellularly by means of glass microelectrodes with a tip having an internal diameter of 1-2 μ, and filled with the perfusion solution. Microelectrodes with a tip under 1 μ in diameter, filled with TTX in a concentration of 100 μM (resistance 100-200 MΩ), were used for iontophoretic application [3].

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