Do β -Adrenergic Blockade and Sleep State Affect Cardiorespiratory Control in Neonatal Lambs? Multivariate Autoregressive Modeling Approach

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ABSTRACT. β -Blockers are used in pregnancy-associated hypertension and in postnatal cardiac arrhythmias, and the neonate may get them in breast milk. We therefore studied the effects of β -adrenergic medication on interrelations between heart rate (HR), respiration, and arterial blood pressure (aBP) in newborn lambs. The influence of sleep state on these cardiorespiratory interrelations was also examined. HR, aBP, and respiration (based on transthoracic electrical impedance) were recorded and the sleep state was visually documented in five healthy chronically instrumented newborn lambs before the age of 30 d. Propranolol was given (1 mg/kg). Two-min stationary segments of the three signals were analyzed using a multivariate autoregressive model, which yields oscillations of the signals and intersignal relationships as source contributions. The variabilities of aBP and HR were greatest at the low frequencies (<0.25 Hz) and so were their intersignal relationships (including baroreflex). The respiratory variability was greatest at the frequencies corresponding to the respiratory rate. During quiet sleep, the variabilities in HR, aBP, and respiration were lowest. The impact of respiratory oscillations on other signals increased but the impact of aBP variability decreased during quiet sleep. β -Blockade and sleep state affected separately the cardiovascular and respiratory variables and their interrelations. β -Blockade reduced HR and increased pulse pressure. The overall heart rate variability and the respiratory low-frequency contribution to heart rate variability decreased due to the β -blockade. We postulate that the β -adrenergic system is an important regulator of HR and HR variability in neonatal lambs and also of the low-frequency components of the respiratory sinus arrhythmia. However, inasmuch as the interrelations between HR and aBP were not altered by the β -blockade, even high doses of propranolol do not seem hazardous for the cardiovascular system in neonatal lambs. (*Pediatr Res* 29: 272–277, 1991)

Abbreviations

aBP, arterial blood pressure
aBPV, arterial blood pressure variability
AR, autoregressive
HR, heart rate
HRV, heart rate variability
MAR, multivariate autoregressive model
RSA, respiratory sinus arrhythmia

TEZ, transthoracic electrical impedance respirogram

The central and autonomic nervous control of the heart and respiration are under vigorous development at birth and yet many cardiovascular reflex mechanisms are operational in the neonate. Many adaptive changes are necessary in the cardiovascular system during the neonatal period. In neonatal animals (1–3) and newborn infants (4), some maturation of this control takes place during the first weeks of life. Also, the baroreceptor sensitivity has been found to be lower in newborn lambs than in adult sheep (5). Disturbances in this adaption may be hazardous for the infant's well-being.

The control system of arterial blood pressure comprises a negative feedback loop and a time delay. As a consequence, spontaneous oscillations occur in HR and aBP. In addition, respiratory activity is a physiologic "disturbance factor" of the system, and in part respiratory control is linked to the nervous control of the heart.

β -Blockers are used in the treatment of hypertension during pregnancy, e.g. in acute preeclampsia. β -Blockers can cross the placenta (6), and the neonate may receive considerable amounts of these compounds also in breast milk (7). Hypotension, bradycardia, and respiratory problems have been reported in newborns whose mothers have been receiving antihypertensive β -blocker treatment (8, 9). Also, propranolol has been found to be a strong inhibitor of vasoconstrictive thromboxane A_2 production in newborns (10). This drug can therefore affect both the work of the heart and the peripheral vascular bed in newborns and potentially influence the cardiovascular control.

Although changes of circulatory variables and respiratory activity have been studied separately during the neonatal period, quantitative information about the fairly complicated relationships between HR, respiration, and blood pressure is still very limited and somewhat controversial. We examined the role of β -adrenergic medication on the interrelations between HR, aBP, and respiration in a chronic newborn lamb model using a new multivariate AR signal analysis technique. We have previously shown that this technique provides quantitative frequency-selective information on complex interactions between the cardiac and respiratory control systems (11). We also examined whether changes in the sleep state alter relationships between cardiovascular variables and respiration and whether sleep state changes the effect of the β -blockade or vice versa.

MATERIALS AND METHODS

Surgical procedures. Five healthy newborn lambs were operated on at the age of 3 d. Two silver ECG electrodes were

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implanted bilaterally in the chest wall and polyvinyl catheters were inserted into the carotid artery and jugular vein, tunneled s.c., and guided into a nylon pocket attached to the skin. The catheters were filled with heparin solution and flushed daily with saline. The lambs were allowed to recover for at least 3 d. Cephalosporin and gentamicin were given for 4 d. The body weight was regularly assessed to confirm normal growth. The blood gases were examined several times a week, as well as before and 10 min after each blockade, and found to be normal. A detailed description of the surgical procedures has been published previously (2). β -Adrenergic blockade was induced with an i.v. bolus of propranolol (1 mg/kg). This dose was considered to cause a total blockade on the basis of previous experiments (12). Measurements were made on five animals before the age of 30 d. One lamb was studied twice and one three times.

Signal acquisition. The ECG and TEZ were recorded on tape (Philips Analog 7, Eindhoven, Netherlands) using a Corometrics (Wallingford, CT) 512 Neonatal Monitor. The arterial blood pressure was also recorded on tape by means of a Statham pressure transducer connected to the monitor after calibration.

The recording sessions lasted for 60 min before and 10 min after the administration of the drug. Two-min stationary and noise-free periods of ECG, aBP, and TEZ signals were selected for the analysis, 66 segments before and 41 segments after the administration of the drug. The samples were visually selected because the final analysis with the MAR method requires stationary signals. The length of each sample was 2 min to guarantee a sample as stationary as possible.

During the recording session, the lambs were lying or standing undisturbed in a sling. A change in the sleep state has been found to affect cardiorespiratory oscillations: variability in HR, respiration, and aBP is lowest during quiet sleep (13). The sleep state was determined by means of a visual classification method modified from that of Prechtl (14). The following categories were used: moving, awake, sleepy, active sleep, and quiet sleep (2). The segments became distributed between the sleep state categories as follows: 3 during moving, 15 when awake, 14 during sleepy periods, 22 during quiet sleep, and 45 during active sleep. Eight segments could not be classified typically to any of these categories and they formed a group: nondefinite. The environmental temperature was kept stable between 20 and 24°C.

The R waves of the ECG signal were detected with an analogue hardware processor. The R-R intervals were measured with an interval counter (frequency 1 kHz) and transformed into instantaneous HR values. The aBP and TEZ signals were low-pass filtered at 3 Hz (3 decibel point) using an analogue filter (roll-off rate 24 decibel/octave) and then digitized at a sampling frequency of 16.7 Hz using a minicomputer (Nova 3; Data General, Southboro, MA). The systolic and diastolic aBP were computed from the raw signal of each 2-min segment as the mean value over the time period. Pulse pressure was computed as systolic pressure – diastolic pressure and mean pressure was computed as diastolic pressure + (1/3 $\times$ pulse pressure). The respiratory rate was determined by detecting the highest peak from the power spectrum of respiration.

The final analysis of the source signals, HR, aBP, and TEZ, was done in a super minicomputer (VAX 11/750, Digital Equipment Corp., Marlboro, MA). The HR time series was synchronized with the aBP and TEZ signals and their sampling rate was lowered to 3 Hz with the interpolator/decimator method by Crochiere and Rabiner (15). Before resampling, the signals were low-pass filtered with FIR low-pass (antialiasing) filter at 1.5 Hz.

Signal analysis. The analysis of the variability and the dynamics of the cardiovascular control system was performed using a closed-loop model between HR, aBP, and TEZ signals. The interactions between the signals are described with three transfer functions that describe 1) the system branch between HR and aBP, 2) the branch between aBP and respiration, and 3) the branch between respiration and HR.

Besides the measured signals (HR, aBP, TEZ), the model also

includes inherent signal sources related to the measured signals. Energy, *i.e.* external disturbances, are fed to the closed-loop system through these signal sources. A novel method to analyze such a closed-loop system is an AR model technique (11).

A MAR was computed for the analysis of 2-min periods of HR, aBP, and TEZ signals (11). The MAR model describes a system where all signals are related to each other. Within the MAR model, each signal is modeled as a linear combination of its own past values and the past values of the other signals plus a predictive modeling term. The multivariate AR stochastic process $x(k) = [x_1(k), x_2(k), \dots, x_m(k)]^T$ of m variables is described by the equation

$$x(k) = \sum_{i=1}^M a(i)x(k-i) + e(k)$$

where

$$a(i) = \begin{pmatrix} a_{11}(i) & a_{12}(i) & \cdots & a_{1m}(i) \\ a_{21}(i) & a_{22}(i) & \cdots & a_{2m}(i) \\ \vdots & \vdots & \ddots & \vdots \\ a_{m1}(i) & a_{m2}(i) & \cdots & a_{mm}(i) \end{pmatrix}$$

for $i = 1, 2, \dots, M$ are the AR coefficients' matrices and $e(k)$ is a white noise vector process $e = [e_1(k), e_2(k), \dots, e_m(k)]^T$. The model order M denotes the number of the past values that are used to generate a new value for the process. In the present study, M was 20.

The whole closed-loop system is then characterized with the MAR. The characterization is done in frequency domain, first by determining power spectral density estimates to the measured data and also to the internal signal sources. The density values characterize the variability of the measured variables and their internal signal sources. The contributions between signals are characterized by transfer functions. The effect of inherent source to the signal is called autocontribution and the effects of other signals are called cross-contributions.

The analysis was performed at five spectral regions, 0.00–0.02 Hz (F1), 0.02–0.08 Hz (F2), 0.08–0.25 Hz (F3), 0.25–0.40 Hz (F4), and 0.40–0.75 Hz (F5). The individual power spectral density estimates and source contributions were band integrated over frequency bands for intergroup, interstate, and interregional comparisons.

Each animal acted as its own control. The statistical analysis between the blockades and controls as well as between the different sleep states was done by applying the unbalanced three-way mixed model analysis of variance. This model allows one to examine the effects of the factors medication and sleep state separately. It also takes into account the random effect of each individual lamb ($n = 5$). Furthermore, the interaction between the effect of medication and change in sleep state was computed. This interaction effect reveals whether these two factors influence each other or whether they operate separately. The programs used were BMDP 7D and BMDP 3V (16). The analysis of variance was also utilized in comparing the five spectral regions with each other. The multiple comparisons were performed with the Bonferroni and Tukey methods. The program used was BMDP 7D (17).

RESULTS

The average HR was lower after the β -blockade (170/min; range 126–206/min), than before (209/min; range 134–251/min) ($p < 0.001$). The mean systolic blood pressure was unaltered before (72 mm Hg; range 53–89 mm Hg) and after (70 mm Hg; range 54–89 mm Hg) β -blockade, and there was no significant change in diastolic blood pressure before (58 mm Hg; range 34–76 mm Hg) and after (45 mm Hg; range 27–75 mm Hg) the blockade. However, the pulse pressure was significantly ($p = 0.021$) higher after the β -blockade (25 mm Hg; range 9–36 mm Hg) than before it (14 mm Hg; range 16–25 mm Hg). The mean

arterial pressure was not significantly affected by the β -blockade before (63 mm Hg; range 40–79 mm Hg) and after (53 mm Hg; range 35–78 mm Hg) the blockade. The respiratory rate was 40/min (range 27–49/min) before and 36/min (range 19–48 min) after propranolol (NS). Sleep state did not significantly influence HR or arterial blood pressure. However, respiratory rate was significantly higher ($p = 0.007$) during sleepy periods (45/min) than during quiet sleep (36/min), active sleep (35/min), or when awake (38/min). The interaction between medication and sleep state was not significant for HR, aBP, or respiratory rate, *i.e.* the β -blockade and sleep state had independent impacts on the cardiorespiratory variables measured.

Power spectral estimate. The frequency areas of interest were the low-frequency area (0.02–0.08 Hz, F2) corresponding to vasomotor thermoregulation (18, 19) and the renin-angiotensin system (20), the area around the natural oscillation of baroreflex

(0.08–0.25 Hz, F3) (21), and that of the respiratory rate (0.40–0.75 Hz, F5).

In the HR spectra, the power density (HRV) was significantly higher ($p < 0.01$) at the low frequencies, F1, F2, and F3, than at the higher frequencies, F4 and F5 (Fig. 1). The same difference was observed after the β -blockade. Also, in the aBP the low-frequency variability (F1 and F2) dominated those of the higher frequencies before and after β -blockade ($p < 0.01$). The spectral power density of respiration was highest at the band of the respiratory rate (F5) before and after the β -blockade ($p < 0.01$) (Fig. 1).

The spectral power density of HR decreased significantly in all frequency bands after the β -adrenergic blockade (F1, $p < 0.001$; F2, $p < 0.001$; F3, $p < 0.001$; F4, $p < 0.001$; F5, $p < 0.001$) (Fig. 1). The blockade did not alter the blood pressure spectral density significantly (Fig. 1). In the power spectrum of the respirogram, the oscillation at F1–F4 remained almost unchanged after the β -blockade. Although the oscillation at the frequency of respiration rate seemed to increase due to β -blockade, this was not significant (Fig. 1).

In general, the variabilities of HR, aBP, and respiration were lowest when the animal was in quiet sleep. In the HR signal, the variability was lower during quiet sleep than during active sleep or when awake at F2 ($p = 0.045$). The variability of aBP at F3 was lower during quiet sleep than during active sleep, sleepy periods, or when awake ($p = 0.006$). The aBPV at F1 ($p = 0.008$) and at F2 ($p = 0.032$) was higher during active sleep than during quiet sleep or sleepy periods. In respiration, the decrease of power during quiet sleep was significant when compared to active sleep and to the awake state at F1 ($p = 0.029$), F2 ($p = 0.026$), and F4 ($p = 0.007$). The interaction between medication and sleep state was not significant. Therefore, β -blockade and sleep state had separate mechanisms to affect HR, aBP, and respiratory variabilities.

Signal source contribution. In the analysis of the HR signal source contribution, there was an overall preponderance of HRV autocontribution. The autocontribution of HRV was greatest at F4 when compared with the other frequency ranges ($p < 0.01$) both before and after the β -blockade. The autocontribution of HRV was also greater at the high-frequency area F5 than at F1 and F2 ($p < 0.01$) before and F1 ($p < 0.01$) after the β -blockade (Fig. 2). The cross-contribution of aBPV to HRV was greater at the low-frequency areas F1–F3 when compared with F4 and F5 ($p < 0.01$) before and after the β -blockade (Fig. 2). The respiratory cross-contribution to HRV (respiratory HRV, RSA) was greatest at F5 ($p < 0.01$) before and after the β -blockade (Fig. 2).

In the aBP signal, the autocontribution of aBPV was dominant at each frequency area studied (Fig. 2). The contribution of HRV to aBPV was slightly smaller than that of aBPV. The contribution of HRV to aBPV was significantly greater at frequency areas F1–F3 when compared with F4 and F5 ($p < 0.05$) before and after the β -blockade (Fig. 2). The respiratory cross-contribution (respiratory aBP variability) was greatest at the frequencies corresponding to the mean respiratory rate ($p < 0.01$) before and after the β -blockade (Fig. 2).

The autocontribution of respiratory variability was dominant at all frequency areas when compared with the cross-contributions of the circulatory signals. The autocontribution of respiratory variability was higher and the cross-contributions of aBPV and HRV lower at F4 and F5 than at F1 and F2 both before and after the β -blockade ($p < 0.01$) (Fig. 2).

β -Blockade decreased the respiratory cross-contribution to HR significantly at F2 ($p = 0.040$) and at F3 ($p = 0.019$) (Fig. 2).

The respiratory cross-contribution to aBPV was higher during quiet sleep than during active sleep, sleepy periods, and when awake at F5 ($p = 0.011$), and the autocontribution of aBPV was respectively lower ($p < 0.001$). The cross-contribution of aBPV to HRV was higher during active sleep than during quiet sleep at F5 ($p = 0.045$).

The autocontribution of respiratory variability was higher

Fig. 1. Power spectral densities of HR, aBP, and respiration. Each signal is divided into five frequency regions: F1 (0.00–0.02 Hz), F2 (0.02–0.08 Hz), F3 (0.08–0.25 Hz), F4 (0.25–0.40 Hz), and F5 (0.40–0.75 Hz). The most interesting were F2 (thermoregulation), F3 (baroreflex area), and F5 (respiratory rate area).

Fig. 2. Signal source contributions of HR, aBP, and respiration. *Upper boxes* are before and *lower boxes* during β -blockade. The contribution of aBP is on the bottom, respiration in the middle, and HR on the top of each pillar. * represents $p < 0.05$.

during quiet sleep than during active sleep and when awake at F2 ($p = 0.04$), higher during quiet sleep than during active sleep, sleepy periods, and when awake at F3 ($p = 0.042$), and higher during quiet sleep than when awake at F4 ($p = 0.002$). There was no interaction effect between β -blockade and sleep state to autocontributions and cross-contributions. β -Blockade and sleep state thus affect relationships between signals separately.

DISCUSSION

Spectral analysis has been found helpful in the study of periodic variability of different cardiovascular signals (22–25). The use of AR modeling to determine the spectrum of a signal has several benefits over the old Fourier analysis (26).

The classical method to characterize the joint variability between two signals is to compute cross-spectral values between them. This provides a measure of common variability but does not give any identification of the origin and describes interrelations only between two signals at a time. However, in the MAR model we can utilize internal noise sources to provide measures of the signal source contribution and thus display directly the magnitude of the interaction between the variables, as well as the direction of the influence. This can be done simultaneously between numerous signals. The method does not display the physiologic origin of the control mechanisms and therefore a certain physical and physiologic understanding is a prerequisite for the interpretation of the results. The length of the sample is a limiting factor to the relevance of the low-frequency variability. It is commonly believed that three cycles of the lowest oscillation must be included in the sample. Thus, frequencies above 0.025 Hz are reliable when 2-min samples are used. The 2-min sample was chosen because the behavioral state of the lamb is prone to change over longer time periods.

Bolus dose (1 mg/kg) of propranolol exceeds the amounts used in clinical practice (0.01–0.1 mg/kg). It was given to induce a strong sympathetic blockade. It has previously been shown that a β -blockade decreases neonatal HR (27) and HRV (3, 12). The present study confirms this. The variability in the HR signal decreased in each frequency band. This indicates that in neonatal lambs the β -adrenergic system has an important general regulatory effect on HR. Thus, the cardiovascular control system may be affected and the spontaneous variability of HR may decrease in infants whose mothers have received propranolol treatment during pregnancy.

The arterial blood pressure in newborns has been found to be lower when mothers have been treated with β -blockers (28). In our study, the systolic blood pressure remained unchanged and changes in the diastolic blood pressure were rather small after the β -blockade. However, an elevated pulse pressure was caused by the β -blockade but the variability of aBP was not altered.

The variabilities of HR and aBP were greatest at the low-frequency areas (0.00–0.25 Hz). It was also interesting to notice that the magnitudes of the cross-contributions were frequency selective. The cross-contribution of aBPV to HRV was dominant at low frequencies and the cross-contribution of HRV to aBPV was also highest there (0.02–0.25 Hz). These relationships were not changed by the β -blockade. On the bases of these signal source contributions, the low-frequency HRV and aBPV can mainly be regarded as of nonrespiratory origin. This indicates a prominent role of the baroreflex and possibly of vasomotor thermoregulation in the cardiorespiratory control of the newborn lamb. This is in agreement with the findings that at the frequencies 0.03–0.20 Hz there is a strong coherence between HR and aBP fluctuations in adult man (29).

The influence of respiratory activity on HRV, RSA, or more appropriately respiratory HRV, is a fairly well-described entity

(30, 31). Its magnitude appears to be smaller in the neonatal period than in adults (4, 32). However, the origin of the RSA is still in dispute. Giddens and Kitney (4) suggested an interaction of two nonlinear systems, respiration and baroreflex, whereas Eckberg *et al.* (33) and Langhorst *et al.* (34) proposed a common neural input from the medullary centers to the heart and respiratory muscles. According to Melcher (35), RSA is caused by the Bainbridge reflex tachycardia due to increased atrial filling in inspiration. Linden (36) has suggested that tachycardia induced by inspiration is mediated by increased sympathetic activity to the sinus node.

The variability of respiration was greatest at 0.40–0.75 Hz (respiratory rate area). In the respirogram, the autocontribution (inherent respiratory variability) was very prominent. This means that the variability of the respirogram was affected very little by cardiac rate and aBP. The oscillations in the respiratory signal and their cross-contributions to HRV and aBPV were greatest at the area corresponding to the respiratory rate. The respiratory cross-contribution to HRV was decreased by the β -blockade at low frequencies (0.02–0.25 Hz). These low-frequency components of respiratory variability (0.04–0.20 Hz) probably originate from periodic changes in breath amplitude (4). The low-frequency oscillatory components in the HRV can thus be in part of respiratory origin and be caused by this breath amplitude modulation. Another explanation of the low-frequency respiratory HRV may be "cardiac aliasing" (37). Witte *et al.* (37) suggested that when respiratory rate is greater than HR divided by two, RSA can be observed in a frequency range that is lower than the frequency of breathing. The former explanation, HRV induced by periodic respiration, is more likely because the respiratory rate in our study seldom exceeded HR/2. Nevertheless, the low-frequency respiratory HRV described here seems to be under β -adrenergic control, as is the overall HRV.

In this study, we found that the aBPV and HRV had only minor effects on the variability of the respirogram. However, they were greatest at the low frequencies (0.00–0.25 Hz) at which area the variability caused by baroreflex and thermoregulation occurs (18, 20, 22). This could mean that the low-frequency variability of respiration in part originates from the cardiovascular signals. This is in accordance with previous findings that the stimulation of the baroreceptors in pulmonary arteries has an influence on respiration (38). The effect of oscillation in aBP and HR on respiratory variability was not altered by β -blockade. This suggests that the effect is not under sympathetic control even though it occurs at low frequencies. Therefore, it could originate from the vagal stretch receptors or there may be a common neural input. However, the contributions of HRV and aBPV to respiration may in part result from the computational principle of the MAR model. In this study, TEZ signal was used as respirogram. Thus, this signal itself contains information from the cardiac cycle. This could also explain the contributions of HRV and aBPV to respiratory variability.

The variabilities of HR, aBP, and respiration were lowest during quiet sleep. A prominent interaction between HR and respiration during quiet sleep has been noticed in neonates (13). We found a prominent respiratory cross-contribution to aBPV during quiet sleep at the area of the respiratory rate (0.40–0.75 Hz). The respiratory autocontribution was highest during quiet sleep at 0.02–0.40 Hz despite the fact that respiratory variability decreased at the low frequencies during this sleep state. This leads to the hypothesis that, even though the nervous control of respiration is mostly automatic, the respiratory modulatory effects on the circulatory signals are most profound during stable steady state conditions such as quiet sleep. We also found that the cross-contribution of aBPV to HRV decreased during quiet sleep, but the contribution of respiration variability to HRV increased. It seems that the effects of respiration on cardiorespiratory control override those of aBP during quiet sleep. No significant interaction between the influences of the β -blockade and sleep state was detected. This leads to the assumption that

the sleep state does not alter the effects of the β -blockade or vice versa. Therefore, the β -adrenergic system and sleep state have separate effects on the cardiovascular and respiratory control in neonatal lambs.

We conclude that the β -adrenergic sympathetic control system is an important regulator of HR and HRV in newborn lambs because both HR and HRV were greatly reduced after the β -blockade. Also, the low-frequency RSA seems to be in part under sympathetic control. However, the low-frequency components of HRV are mainly of nonrespiratory origin and relationships between HRV and aBPV do not seem to be under β -adrenergic control. These results indicate that even high doses of propranolol do not abolish or critically impair the essential cardiovascular control mechanisms in neonatal lambs.

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