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Analysis of Breathing Patterns in a Prospective Population of Term Infants Does Not Predict Susceptibility to Sudden Infant Death Syndrome

THOMAS B. WAGGENER, DAVID P. SOUTHALL, AND LOUIS A. SCOTT

The Floating Hospital for Infants and Children, New England Medical Center, Boston, Massachusetts 02111; Department of Pediatrics, Cardiothoracic Institute, Brompton Hospital, London

ABSTRACT. Oscillatory patterns in ventilation have been seen in term and premature infants and are indicative of the stability of the respiratory blood gas feedback control system. Apneas are related to these patterns and apnea duration is correlated with pattern characteristics. In our study breathing patterns were analyzed in recordings from 10 term infants who subsequently died of sudden infant death syndrome (SIDS) and 10 control infants matched for birth wt, gestational age, and postnatal age. Subjects were drawn from a prospectively studied population of 9856 infants. Breath-by-breath minute ventilation was estimated in each of these 24-h recordings and oscillatory patterns were detected using a comb of digital bandpass filters. Confidence limits on the filter output and a bad data flag for rejection of data during gross body movements or crying insured that only significant patterns in ventilation were evaluated. Pattern prevalence and amplitude were compared in three frequency regimes: 6- to 87-s cycle times, 6- to 28-s cycle times, and 28- to 87-s cycle times. There was no significant difference between the SIDS and the control infants in any of these pattern comparisons (paired t and Wilcoxon paired rank sum tests, $p < 0.05$). In light of the normal breathing patterns found in the SIDS infants, it is unlikely that susceptibility to SIDS is distinguished, at the time of these recordings, by instability of the respiratory blood gas feedback control system. (*Pediatr Res* 27: 113–117, 1990)

Abbreviation

SIDS, sudden infant death syndrome

A close relationship between apnea and SIDS has been postulated since the early 1970s when Steinschneider (1) reported that two of five infants with documented prolonged sleep apnea died of SIDS. Not only prolonged sleep apnea but also excessive amounts of periodic breathing, as seen in some populations of so called "near-miss" SIDS infants (2, 3), have been postulated as indications of increased susceptibility to SIDS. In a prospective study of 9856 infants, Southall *et al.* (4, 5) found that neither prolonged apneic pauses nor quantities of periodic breathing could identify susceptibility to SIDS.

Waggener *et al.* (6, 7) reported that most apneas seen in term and premature infants were not isolated or random events, but rather were related to underlying oscillatory breathing patterns as might be characterized by a periodic waxing and waning of ventilation. For example, periodic breathing as clinically observed is a particularly strong oscillatory breathing pattern. Duration of apnea was found to be correlated with the cycle time and amplitude of the accompanying pattern, and negatively correlated with the mean minute ventilation (7). They suggested that the oscillatory breathing patterns were characteristic of the stability of the respiratory control system and that the longer cycle time patterns (30 to 90 s cycle time) were of particular importance because longer apneas were associated with such patterns (6, 7).

We have applied the breathing pattern analysis methods of Waggener *et al.* (6, 7) to respiratory data from term infants who died of SIDS and matched controls provided by Southall *et al.* (4, 5). Data were provided without identification as to which were SIDS infants and the code was broken after the analysis was complete.The data were analyzed to determine the prevalence and amplitude of patterns.

This analysis differs from the earlier tests of prolonged apneic pauses and periodic breathing in important ways. First, apnea in the newborn often has an obstructive component. In the study of Southall *et al.* (4, 5), breathing movements were recorded using a pressure capsule taped to the abdomen. Obstructive apnea cannot be identified using this method, so the earlier analyses of prolonged apnea were based only on prolonged apneic pauses, *i.e.* they did not include any obstructive component. Waggener *et al.* (8) found that mixed and obstructive apneas, as well as central apneas, *i.e.* apneic pauses, are related to underlying oscillatory breathing patterns in premature infants. Furthermore, in preliminary tests we found that breathing movements of the abdomen, as monitored with magnetometers or inductance plethysmography, can be used to identify oscillatory breathing patterns with which obstructive apneas are related, despite the fact that we cannot identify the apneas themselves. Thus, being unable to directly identify obstructive apnea in the Southall data does not prevent us from identifying the associated oscillatory breathing patterns.

Second, we identify all oscillatory patterns with cycle times ranging from 6 to 87 s. This includes the cycle times of classic periodic breathing, 12–25 s, as well as longer cycle times. Because longer apneas are associated with longer cycle time patterns (7), we hypothesize an increased incidence and amplitude of these longer cycle time patterns in SIDS infants.

We have also shown that classic periodic breathing, which by definition incorporates short apneas, is simply an exaggerated form of a breathing pattern commonly seen even in healthy term infants (6, 7). Our analysis can identify those more subtle patterns, *i.e.* those showing a modulation of ventilation that is not so strong as to include apnea. Therefore we can determine if, for example, there is a periodic breathing precursor that is exaggerated in the susceptible infants.

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Correspondence Thomas B. Waggener, Ph.D., Department of Pediatrics, Box 45, New England Medical Center, 750 Washington Street, Boston, MA 02111.
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Gordon *et al.* (10) have reported that infants who have been referred to the hospital for apparent life-threatening events and subsequently die of SIDS differ from controls in that they have a wider respiratory frequency peak in the power spectrum of their breathing signal. One possible explanation for this would be that SIDS infants have greater variability of breathing than do the controls. However, their analysis did not distinguish between random variations in breathing and coherent autocorrelated variations in breathing, *e.g.* oscillatory patterns. They also did not distinguish between variations in respiratory rate, tidal volume, and ventilation, and their results could be influenced by variations in background noise in the signal. Their technique did not detect a difference between SIDS infants and controls when it was applied to the prospective data of Southall and coworkers (11).

The patterns we have previously identified in term and premature infants would produce the type of widening of the respiratory frequency peak as seen in the analysis of Gordon *et al.* (11). Thus, a wider peak would correspond to greater prevalence and/or amplitude of the corresponding patterns. However, our analysis goes further than that of Gordon *et al.* (11) in identifying the source of the breathing variability. Our analysis could detect a difference that the analyses of Gordon *et al.* missed but should not miss a difference that their analysis could detect.

MATERIALS AND METHODS

The data were supplied by Southall *et al.* (4, 5) and consisted of tape recordings of breathing movement and heart rate for 24 h in 20 term infants. The data were provided in pairs that matched each of 10 SIDS infants with a non-SIDS infant of similar birth wt, gestational age, and postnatal age (Table 1). Breathing movements were detected by a small plastic capsule taped to the abdomen. Abdominal girth increases with inspiration and causes an increase in capsule pressure. Capsule pressure changes were the recorded signal. When used for detecting apneic pauses, quantities of periodic breathing and respiratory rate, the pressure capsule method compares favorably with transthoracic impedance pneumography, jacket plethysmography, and inductance plethysmography (12).

There are several problems with analyzing breathing patterns from 24-h recordings of abdominal movement. One is that abdominal movement, as recorded by the pressure capsule technique, gives only a very rough estimate of tidal volume and minute ventilation. The recorded signal is clearly not linear with changes in lung volume, yet we require a measure of minute ventilation, and thus of tidal volume, for our analysis. The pressure capsule signal was adequate for this analysis because we were analyzing variations in ventilation rather than mean minute ventilation. Inaccuracies in our estimate of tidal volume from this signal can be considered as noise superimposed upon a true tidal volume signal. When the patterns were large compared to this noise, then we could still detect them, otherwise we could not. The net result of using this rough signal is that we could detect only strong patterns.

Table 1. *Population characteristics*

Subject	SIDS/ control	Sex	Birth wt (g)	Gestational age (wk)	Age at recording (d)	Recording/death interval (d)	% of data usable
01	S	M	2120	38	16	287	54.9
02	C	M	2320	39	17		56.4
03	S	F	3770	40	63	11	80.5
04	C	F	3460	39	65		60.6
05	S	M	3960	41	40	47	96.0
06	C	M	3975	40	40		90.7
07	S	M	2780	39	16	11	53.3
08	C	M	2750	40	17		77.7
09	C	M	2980	38	56		99.6
10	S	M	3030	40	40	119	98.2
11	S	F	2810	39	52	96	62.9
12	C	F	2840	40	48		96.5
13	C	F	2980	39	48		96.1
14	S	M	2920	40	47	61	99.8
15	S	M	4790	40	41	71	53.5
16	C	M	3950	40	42		87.0
17	C	F	3000	40	53		87.1
18	S	F	2980	40	61	34	84.1
19	S	M	2350	40	30	35	79.8
20	C	M	2380	40	41		81.8

The second problem with these 24-h tape recordings is that we did not know when the infant was asleep, awake, moving, feeding, etc. Some of these activities distort the respiratory signal to the extent that it is unusable. As an objective means of determining which parts of the data should be analyzed, we developed a "respiratory data rejection flag" (13). This flag was based on the percentage of the signal that was respiratory. The respiratory portion of the signal was defined as that portion that occurred between the first subharmonic and the fourth harmonic of the mean respiratory rate. When the flag value was less than 50%, the data were rejected. The flag was developed and tested with fully documented laboratory studies. The cutoff value had to be low enough to avoid rejecting rapid eye movement sleep yet high enough to reject episodes when the infant was moving and crying. The cutoff value of 50% was chosen to give the best agreement with our laboratory studies and was the value used when processing the data in this study.

The data were played back at four times the speed at which they were recorded. They were digitized at a sampling rate of 400 Hz and respiratory variables for each breath were identified using a DEC Micro 11/73 computer. For each breath, inspired volume, duration of inspiration, expired volume, duration of expiration, total breath duration, and minute ventilation (inspired volume divided by total breath duration) were calculated. Heart rate and values for identifying the respiratory data rejection flag were also acquired for each breath. The breath-by-breath data were converted to time based data to give an equivalent real time sampling rate of 1 Hz.

Patterns in minute ventilation were detected using a comb of digital bandpass filters with center frequencies ranging from a cycle time of 6 s to a cycle time of 87 s (14, 15). Each filter had a half width of one-half octave and the center frequencies were spaced one-third octave apart. The filters were zero phase shift "Hanning," raised cosine, filters.

Confidence limits were calculated to determine the probability that any filter output was due to white noise at the input (14, 15). This probability is a function of how high above the confidence limits the signal goes and how long it stays above the confidence limits. Filter output was considered a significant oscillatory pattern if it had a probability of less than 4% of being due to noise. Because the theoretical basis for the confidence limit calculations requires that consecutive samples are independent, the autocorrelation function used in determining the confidence limits was based on the breath-by-breath, rather than the time-based, data.

Any excursion of minute ventilation of more than 2 SD was truncated at the 2 SD level. This helped eliminate ringing of the filters in response to spikes or impulses in the input.

The data were analyzed for susceptibility to SIDS by comparing prevalence and amplitudes of patterns in three frequency ranges. We compared patterns with cycle times of 6 to 28 s, the range of classic periodic breathing, patterns with cycle times of 28 to 87 s, the longer cycle time patterns with which longer apneas are associated, and patterns with cycle times of 6 to 87 s. The data were analyzed with paired t tests and Wilcoxon paired sample rank sum tests.

RESULTS

The subject population is characterized in Table 1. The percentage of the data that was usable, according to our respiratory data rejection flag, ranged from 53 to 99% with an average of 80%.

There was no significant difference between the SIDS and non-SIDS populations in terms of prevalence or amplitude of patterns in any of the three frequency regimes tested (paired t and Wilcoxon paired sample rank sum tests, $p < 0.05$ for significance). As can be seen in Figures 1 and 2, the SIDS and non-SIDS infants were quite intermingled. One SIDS infant (subject 1) had a great deal of periodic breathing, and is seen as an outlier in both amplitude and prevalence of short cycle time patterns (Fig. 1, *graph A*; Fig. 2, *graph A*). This infant has been identified in previous analyses as having an inordinate amount of periodic breathing (16). Note that the other nine SIDS infants have on average slightly, and not significantly, lower amplitude and less prevalent short cycle time patterns than the non-SIDS infants.

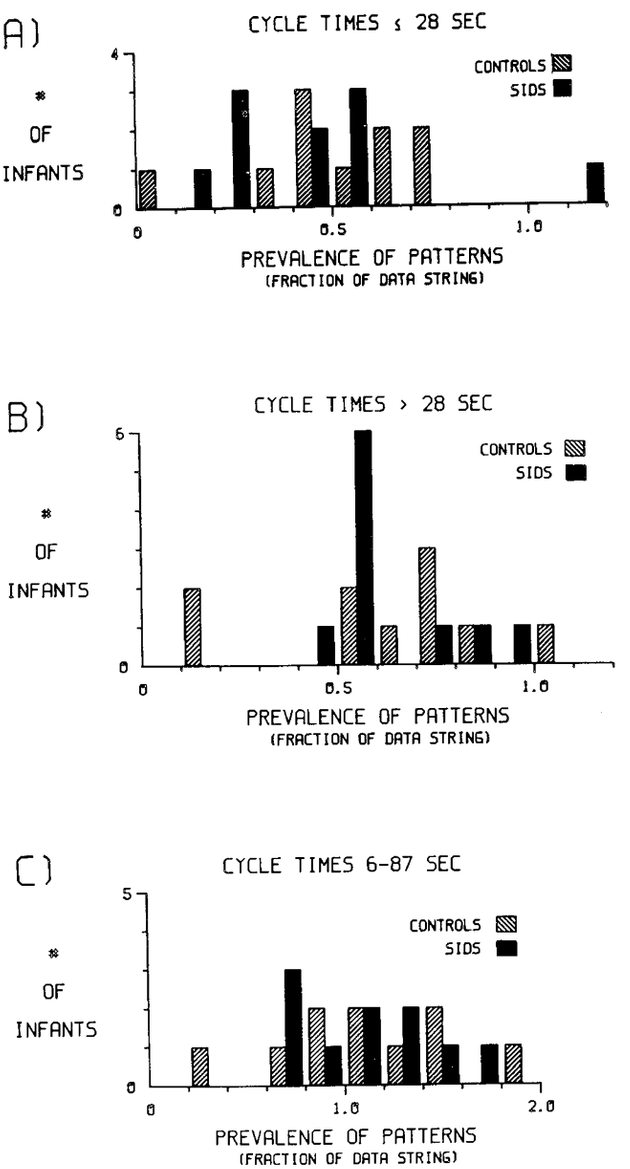

Fig. 1. Prevalence of significant oscillatory patterns in ventilation in 10 term infants who subsequently died of SIDS and 10 matched controls. *A*, Sum of the prevalence of patterns with cycle times ranging from 6 through 28 s. *B*, Sum of the prevalence of patterns with cycle times ranging from 28 through 87 s. *C*, Sum of the prevalence of patterns with cycle times ranging from 6 through 87 s.

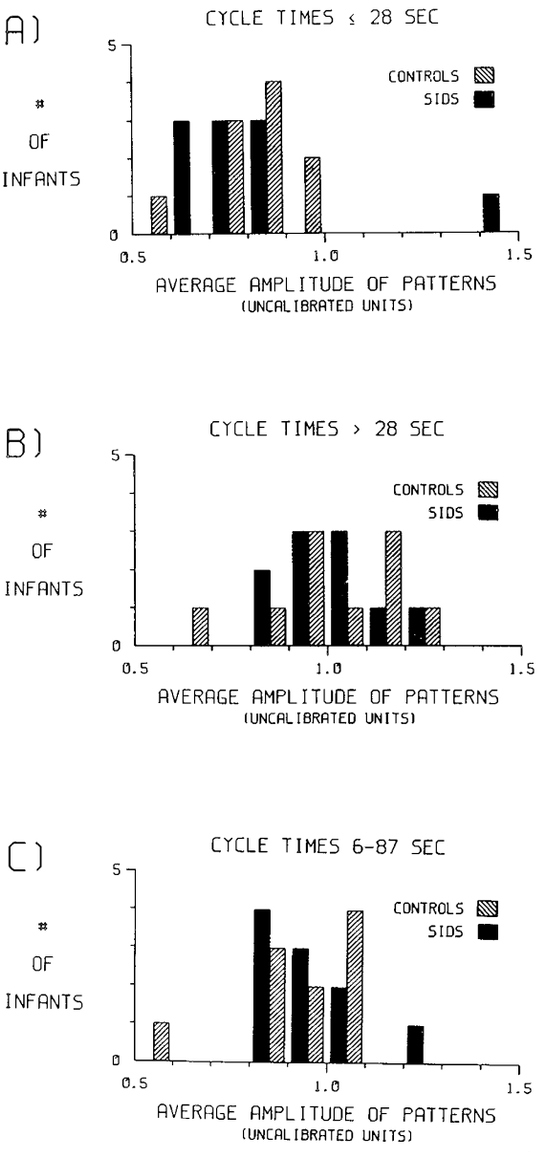

Fig. 2. Average amplitude of significant oscillatory patterns in ventilation in 10 term infants who subsequently died of SIDS and matched controls. *A*, Average amplitude of patterns with cycle times ranging from 6 through 28 s. *B*, Average amplitude of patterns with cycle times ranging from 28 through 87 s. *C*, Average amplitude of patterns with cycle times ranging from 6 through 87 s.

The distribution of prevalence of significant patterns as a function of cycle time is bimodal for both the SIDS and non-SIDS populations, as seen in Figure 3. The cycle times of the peaks in these distributions is not significantly different between the SIDS and non-SIDS infants (Wilcoxon paired sample rank sum test, $p > 0.05$).

Considering the wide range of the intervals between the day of the recording and the day of the death due to SIDS (11 to 287 d, Table 1), we calculated the correlation between paired differences in patterns and interval before death. This correlation was not significantly different from zero (Spearman's ρ, $p > 0.05$).

Comparison of mean minute ventilation between these two groups was not possible in that there was no calibration for tidal

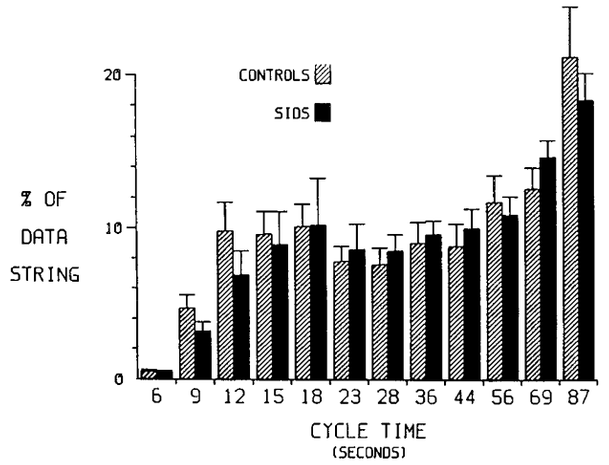

Fig. 3. Prevalence of significant oscillatory patterns in ventilation expressed as a percent of the usable data from 24-h recordings. Prevalence at each cycle time is averaged across the population of 10 term infants who subsequently died of SIDS and across the population of 10 matched control infants. Error bars indicate the SEM.

volume. During playback, amplitude of the respiratory signal was adjusted to give an average tidal volume of approximately 1 V. There was no significant difference between mean respiratory rates during usable data sections between SIDS and non-SIDS (paired t, $p > 0.05$).

In that unusable portions of a recording may reflect sleep disturbance or stress, we tested whether SIDS was related to the percentage of the data that was usable, expecting less usable data in SIDS. There was no significant difference between the two populations based on the percentage of data that was usable (paired t, $p > 0.05$).

DISCUSSION

Analysis of breathing patterns with cycle times ranging from 6 to 87 s did not distinguish SIDS from matched non-SIDS infants in this double-blind prospective study. Before addressing the implications of this finding in regard to SIDS, we shall critique the analysis.

In using such a crude estimate of minute ventilation for identifying patterns we have to be concerned as to whether the patterns have been accurately identified. We believe they have been for two reasons. First, the confidence limits on the filter output prevent noise in the data from being identified as signals. Although introduction of noise may obscure existing patterns, it should not create patterns where there were none (more than 4% of the time, considering our 96% confidence level). If virtually no patterns had been detected in either group then it would be possible that noise related to the poor estimate of ventilation was obscuring the signal. However, significant patterns were observed, and in some infants they persisted for up to 80% of the usable data. We feel confident that those patterns that have been identified have been accurately identified. The noise introduced by the very rough estimate of tidal volume may well have obscured small amplitude patterns. However, it seems highly unlikely that small amplitude patterns would distinguish susceptibility to SIDS when the larger amplitude patterns do not.

Second, the distribution of pattern prevalence is bimodal with cycle time just as it was in our earlier work (6, 7), although the incidence of patterns at all frequencies is less in these new data. This lowered incidence may be due to the poor estimate of minute ventilation as discussed above, *i.e.* some of the lower amplitude patterns have been obscured by noise, or may be due to the fact that these infants were monitored without a face mask and pneumotachograph as used in our earlier studies, or may be due to the older postnatal age of these infants compared to earlier studies.

Our selection of data by using the bad data flag did not prevent identification of susceptibility to SIDS. When the data are analyzed as in "Materials and Methods," but on the basis of all data rather than just the "good" data segments, there is still no difference between the SIDS and non-SIDS populations (paired t and Wilcoxon paired sample rank sum, $p > 0.05$).

Although this analysis does not eliminate the possibility that there are differences in obstructive apnea between the two groups, in that obstructive apnea was not directly measured, it does eliminate the possibility that such apneas are related to abnormal oscillatory breathing patterns.

We have hypothesized that oscillatory patterns as observed in this and earlier studies are indicative of the stability of the respiratory blood gas feedback control system, with decreased stability leading to more and larger amplitude patterns (6, 7). Interpreted in this light, our study indicates that the SIDS infants were not abnormal in the stability of this control system at the time these data were collected. Although an increased prevalence of short cycle time patterns, periodic breathing, was seen in one infant, and previously has been demonstrated in three of 16 term infants who died of SIDS (16), this is clearly not representative of most of the SIDS population. Note that this infant died of SIDS 9½ mo after the data were recorded, whereas infants who died within 2 wk of the recording showed no abnormality in short cycle time patterns.

One important hypothesis suggests that infants die of SIDS because they stop breathing. Considerable effort has been expended to determine why they initially stop breathing and why normal protective mechanisms, such as a last gasp, do not reinitiate breathing. On the basis of our breathing patterns and apnea work, we hypothesized that SIDS infants may have abnormal breathing patterns leading to abnormally prolonged, or an abnormally high incidence of, central and/or obstructive apneas. Our results indicate that such abnormal patterns, if they occur at all, were not present at the time of these recordings. Having found the patterns to be normal, we are left with the alternatives that these infants either have an abnormal tendency to prolong apnea by obstruction, as might be seen in abnormal configuration or control of the upper airways, or they have abnormal susceptibility to essentially normal apneas; or a combination of both. The hypothesis that a proportion of SIDS deaths are related to "prolonged expiratory apnea" (17–19), *i.e.* apnea accompanied by a major defect in ventilation/perfusion relationships, is not addressed by our analysis. The apparent normality of breathing patterns in the SIDS infants we studied makes it unlikely that SIDS is distinguished at the time of these recordings by instability of the respiratory blood gas feedback control system.

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Errata

NOTICE OF DUPLICATION OF PUBLICATION

GALACTOSE METABOLISM IN HUMAN OVARIAN TISSUE
Y-K. Xu, W. G. Ng, F. R. Kaufman, R. A. Lobo, and G. N. Donnell
(Pediatr Res 25:151–155, 1989)

The following announcement is reproduced from the December 1989 issue of Acta Endocrinologica:

We would like to inform the readers of this journal that duplication of data appeared in our article entitled "Gonadal function and ovarian galactose metabolism in classic galactosemia," Acta Endocrinol 120:129–131, 1989 with data published in "Galactose metabolism in human ovarian tissue," Pediatr Res 25:151–155, 1989. We sincerely regret this occurrence. Figure 2 in Acta Endocrinologica was duplicated from Figure 1 of Pediatric Research. In addition, the data from Table 1 in Acta Endocrinologica and from Table 2 in Pediatric Research, derived from the same patient and experiments, showed discrepancies that are at erratum. For Table 1 in Acta Endocrinologica, for the TCA insoluble fraction with labeled galactose, the range should be 92–290 cpm/mg and for CO_2 production with labeled galactose, the range is 144–196 cpm/mg.

In the article by J. P. Mullon, C. M. Tosone, and R. Langer "Simulation of Bilirubin Detoxification in the Newborn Using an Extracorporeal Bilirubin Oxidase Reactor" 26:452–457, November 1989, there are several errors.

In equation 5, the last term should be −WEC(4) instead of −wE/V4. In Results and Discussion the following rate constants should have been, $k = 0.075\ h^{-1}$ instead of $0.005\ h^{-1}$, $k_2 = 0.045\ h^{-1}$ instead of $-0.045\ h^{-1}$, En = 5/kg/d instead of 5 mg/kg/d, $k_{41} = 0.01\ h^{-1}$ instead of $0.4\ h^{-1}$, and $B_4 = 100$ mg instead of 250 mg.