Polysomnographic Parameters in Anaemic Infants Before and After Transfusion

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Apnoea and periodic breathing are common problems in premature babies, the mechanisms are still unclear. But it is well-known that anaemia plays a significant role in the pathogenesis of these disorders. The borders between tolerable hemoglobin-hematocrit reduction in infants and pathological anaemia, which may endanger undisturbed growth in infants, are blurred. Therefore the attempt to observe breathing and circulation in cases of anaemia through the use of a polysomnography is recommended. Irregularities should be remedied after balancing the anaemia. Examinations of 12 infants with anaemia in a sleep research laboratory were compared both before and after transfusion of erythrocytes. While sleep patterns showed no significant changes, certain breathing and circulatory parameters such as the incidence of central apnoea, mean heart rate or mean breathing showed significant drops. A complete polysomnography may be helpful in determining whether a blood transfusion should be undertaken or not. (Sleep and Hypnosis 2001;3(4):144-151)

Key words: *polysomnography, anemic infants, effect of transfusion*

INTRODUCTION

Anaemia plays a considerable role in pathogenesis of apnoeas in premature babies. This study aimed to answer the question whether polysomnographic investigations are helpful in causal clarification of breathing disorders. Despite the risk of a reduction in the arterial partial oxygen pressure and therefore the saturation of tissue with oxygen as a result of a lack of haemoglobin, causing hypovolemia, it is often difficult to persuade parents of the necessity for blood transfusion. This is based not only on the risk that blood compounds may become infected, but also on the difficulty of predicting the long-term significance of a latent lack of oxygen, as no objective means of diagnosis is available. Complete polysomnography before and after administration of concentrated erythrocytes should be used to ascertain whether clinically relevant symptoms correlate to polysomnographic findings.

METHODS

Infants with breathing disorders underwent a complete polysomnography in a pediatric sleep laboratory. Conventional pulsoximetric monitoring showed clinically significant recurrent prolonged apnoea with desaturation and bradycardia. Diagnosis in the sleep laboratory was undertaken before and after the administration of identical blood group, radiated erythrocytes concentrate. The radiation of the used blood groups was supposed to reduce the risk of a graft-versus-host reaction in infants with special risk. The parents gave their con-

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sent to the examinations. The children under examination were eight formerly very premature infants (gestation period between 27 and 32 weeks), four of whom had to be supplied with oxygen during the early neonatal period on account of idiopathic respiratory distress syndrome (IRDS). One child was born prematurely with an uncomplicated prenatal progress (35 weeks pregnancy). Three infants were newborn after an uneventful pregnancy and normal postnatal period.

Relevant anaemia was registered in all twelve infants (median weight 2594 g; minimum 1580 g, maximum 3630 g; median age before transfusion, 38 days; minimum 20 days, maximum 77 days): hemoglobin (median)=6.1 mmol/l (Hb min.=3.4 mmol/l, max.=6.7 mmol/l). At the time of the examination none of the children were not under respiratory therapy. Using different forms of diagnosis in order to clarify cases of apnoea, the following predisposed factors for the occurrence could be excluded:

Infection - insignificant clinical and laboratory tests
Metabolic disorders - normal laboratory values of metabolic parameters, including amino-acid metabolism
Vitium cordis - echocardiographic findings according to age, insignificant ECG and blood pressure levels
Hypoxia, acidosis - normal blood gas levels, recurrent brief desaturation periods in stationary monitoring

In six premature infants, apnoea persisted during ongoing serum level checks despite methylxantine treatment. This treatment could therefore only be completed after transfusion. Two of the premature newborn infants did not receive drugs to stimulate breathing due to intercurrent tachycardias (1). All parameters were recorded over at least 4 hours (latent starts at an average of 12 hours) under identical laboratory conditions between 8 p.m. and 8 a.m., and was only terminated after the infants woke up on their own. The polysomnography (PSG), which were validated manually by the same analyst, comprised the following parameters before and after transfusion respectively:

- EEG (CA3/A1 and C4/A2)
- left and right EOG
- submental EMG
- SaO_2 with showing of pulse wave
- ECG
- transcutaneous pO_2 and pCO_2
- registration of breathing by impedance of the thorax
- registration of breath flow through capnography
- an actimeter, i.e. a movement mat–the most reliable method of testing movement in very young infants

For evaluating the examination, the following PSG results before and after transfusion were contrasted and compared:
- total sleep time (TST)
- duration of active sleep
- duration of quiet sleep
- number of apnoeas per hour of sleep coinciding with desaturation levels of ≥3%
- number of central apnoeas per one hour of sleep (≥3 sec)
- number of obstructive apnoeas per one hour of sleep (≥5 sec)
- number of mixed apnoeas per one hour of sleep (≥5 sec, defined as at least a 50% reduction in capnographic signals during simultaneous desaturation of at least 5% of the baseline value)
- respiratory disturbance index (RDI)
- mean respiratory frequency
- mean heart frequency
- mean oxygen saturation (SaO_2)
- mean duration of apnoeas (=sum of the duration of all apnoeas
>3 sec per minute of sleep)
- mean transcutaneous pCO_2

Comparisons of the stages of sleep were based on the definitions of Anders, Emde and Parmelee (2). If not all assessment criteria of quiet or active sleep were fulfilled (indeterminated sleep), the stages were arranged so as to cover most of the parameters.

Sleep polygraphies were recorded by the Alice 3™ system, version 1.20 (Healthdyne Inc. U.S.A.). Data management and statistical evaluation were carried out using the statistical programmes SPSS® Base 8.0 (SPSS Inc. U.S.A.). Median (MD) and interquartile range (IQR) were given.

The ethical review board agreed to the study, parental consent was obtained, and the participants were randomly chosen.

RESULTS

Table 1 shows selected parameters of all 12 children, including polysomnographic findings before and after administering erythrocytes. Table 2 lists median levels and interquartile ranges (IQR) of the most important findings before and after transfusion, as well as the results of a test to determine the significance of the above parameters (Wilcoxon-Test). The median hemoglobin level of 6.1 mmol/l (IQR 5.45–6.5 mmol/l) was increased to 8.2 mmol/l (IQR 7.62–8.87 mmol/l), and the average level of hematocrit increased from 29% (IQR 24%-30%) to 39% (IQR 37%-41%) after transfusion. Whereas certain breathing parameters (mean duration of apnoeas during active sleep, incidence of central apnoeas lasting 3-5 sec and 6-10 sec, incidence of apnoeas with desaturations, apnoea index, respiratory disturbance index during active sleep) clearly showed significant decreases after the administration of erythrocytes, other parameters associated with breathing (such as the incidence of obstructive apnoea, mean breathing frequency or transcutaneous partial CO_2 pressure) remained unaffected. The duration of sleep of the registered sleep time was shorter after combating anaemia, although the proportion of quiet sleep increased very significantly. During both active sleep (from MD 159.9 to MD 151.4) and quiet sleep (from MD 152.4 to MD 143.2) the mean heart frequency decreased (statistical significantly so during quiet sleep), while the median values of mean oxygen saturation (SaO_2) and of the median transcutaneous partial CO_2 pressure (tc pCO_2) remained almost unaffected (Figures 1 and 2). In all cases of the children examined under hospital conditions during a minimum observation period of 15 days, no more clinically significant breathing disturbances were registered.

DISCUSSION

De Maio and colleagues postulated in 1986 in their paper, "Effect of Blood Transfusion on Apnoea Frequency in growing premature Infants":

"Pathogenesis of apnoea and periodic breathing in premature babies is unclear. However, apnoea and periodic breathing apparently reflect that the mechanism to control breathing is not fully developed. Factors associated with apnoea are e.g. respiratory tract obstructions, hypoxia, hypothermia, seizures, sepsis. Anaemia also plays a significant role in the pathogenesis of apnoea in premature infants." (3). But the borders between tolerable hematocrit reduction and pathological aneamia are blurred.

One the one hand the literature on the subject offers numerous references postulating the relationship between breathing disturbances and anaemia: De Maio et al. (3), Joshi et al. (4), Bifano et al. (5), Sasidharan et al. (6,7), Poets et al. (8,9), Colina et al. (10). On the other hand it appears difficult to prove significant differences between cardio-respiratory parameters before and after blood transfusion. Various reasons for this lack of significance may be discussed as follows:

1. The children under examination may not have had a clinically relevant case of anaemia. However, the diversity of the gestation age in premature infants with often very differentiated anamnesis can only indicate blurred borderline values for the case for transfusion. Far more clinically relevant symptoms such as apnoeas with desaturations are often at the heart of a decision for therapeutic consequences. Hemoglobin borderline values for premature babies with a birth weight of between 1000 and 1500 g are for example at 8.8 mmol/l in the 5th week, which does not necessarily call for a

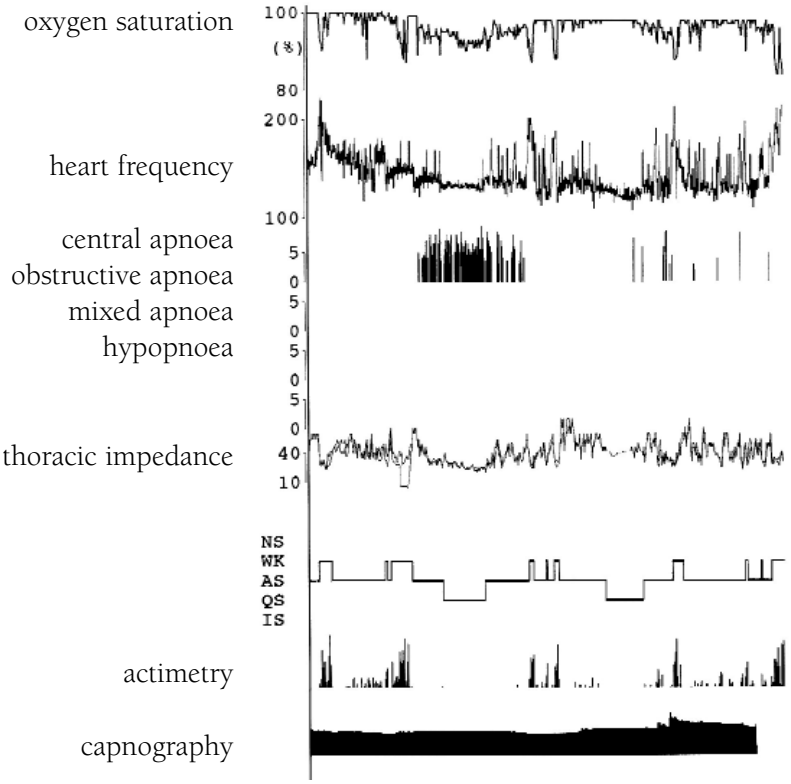

Figure 1. Comparison of polysomnographic recordings during the total night of an anaemic infant before and after transfusion of erythrocytes. In the pre-transfusion polygraphy, a protracting sleeping phase with periodic breathing can be seen, associated with severe desaturations.

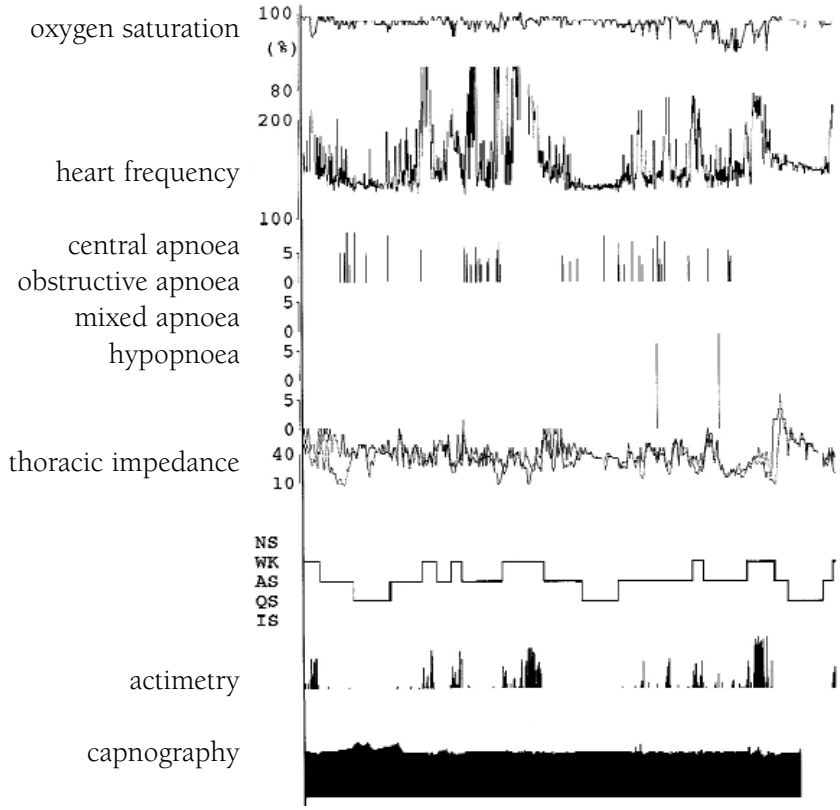

Figure 2. The control hypnogram of the same infant shows a normal record after transfusion.

Table 1. Selected individual values of 12 patients before and after transfusion

patient	Hb mmol/l	Hk	mean apnoea in active sleep s/min as	mean apnoea in quiet sleep s/min qs	central apnoea 3 – 5 s / h TST	apnoea with desaturation / h TST	apnoea index	RDI (active sleep)	RDI (quiet sleep)	mean heart frequency in active sleep	mean heart frequency in
Single values before transfusion											
1	6,1	0,29	2,67	1,22	8,35	9,5	11,5	12,4	13,2	208,6	200,9
2	5,6	0,26	1,92	2,14	6,12	14	16,8	17,7	25,1	161,8	169,5
3	3,4	0,15	2,28	4,27	1,42	3,2	12,9	10,2	24	155,3	155
4	4,8	0,23	3,5	0	3,39	1,6	2,6	5,4	0	172,3	169,5
5	6,2	0,3	2,54	9,45	18,39	18	37,7	29,8	104,5	141,5	129,4
6	6,2	0,3	0,24	0	0,88	2	1,5	2,7	0	129,1	124
7	6,7	0,29	1,15	0,29	2,77	1,8	8,5	12	2,2	124,6	115,8
8	6,6	0,31	2,77	0,08	5,44	9,3	14,3	23	1,5	161,2	151,9
9	6,1	0,3	8,96	2,9	36,46	60	72,9	95	31,6	160,3	156,9
10	6,6	0,31	2,08	0,26	5,89	12,4	12	23,5	4	159,6	151,5
11	6,1	0,3	5,4	1,15	18,31	28,4	47,4	54,5	11,5	152,6	144,3
12	5,4	0,24	5,3	0,48	24,05	36	47,3	61,3	6,5	160,9	157,8
Single values after transfusion											
1	9	0,42	0,98	0,38	2,08	2,85	6,1	6,5	6,4	166,5	165,2
2	9,6	0,46	0,84	0,4	1,83	6,2	7,8	8,4	4	153,1	150,8
3	6,9	0,32	0,65	1,38	1,0	2,8	6,5	6,1	8,1	145,1	139,8
4	6,7	0,33	0,67	0,39	0,85	1,86	3,5	4,4	4	161,3	156,7
5	9,5	0,45	1,86	0,36	11,06	2,85	13,8	23,1	2,4	150,9	140,3
6	8,1	0,39	0,22	0,07	1,0	1	1,8	2,6	0,8	114,5	108,8
7	8,2	0,38	0,56	0,05	2,24	1,11	4	6,5	0,5	118,4	114
8	8,3	0,39	1,32	0,69	5,22	6,5	6,2	12,4	6,9	145,7	136,1
9	8,5	0,4	1,59	0,68	9,69	8,75	12,3	19,8	6,9	154,7	146,2
10	8	0,39	0,39	0,76	4,24	6,12	5,7	11,2	8,6	146,6	136,3
11	8,2	0,39	1,7	0,92	12,24	8,57	16	20,1	13,8	170,6	164,5
12	7,5	0,37	1,97	0,48	10,42	10,42	16,3	26,5	6,1	151,9	146,8

Table 2. Median values,uinterquartile range before and after transfusion as well as result from Wilcoxon-test for selected parameters.

parameter	median values before transfusion	median values after transfusion	IQR before transfusion		IQR after transfusion		Wilcoxon (p<0,05) bold type = significant
Hb (mmol/l)	6,1	8,2	5,45	6,5	7,62	8,87	0,002
Hk	0,29	0,39	0,24	0,3	0,37	0,41	0,002
total sleep time (TST in min)	200,7	186,2	168,75	236,75	149,12	226,12	0,48
quiet sleep in min (QS)	45,5	52,2	38,37	74	47,5	62,37	0,754
active sleep in min (AS)	147,7	144,2	123,62	162,87	112	163,25	0,875
mean duration of apnoeas (MA) in active sleep s/min	2,6	0,9	1,96	4,85	0,65	1,67	0,002
mean duration of apnoeas (MA) in quiet sleep s/min	0,8	0,44	0,12	2,71	0,36	0,74	0,131
central apnoea 3 – 5 s / h TST	5,9	3,2	2,92	18,37	1,20	10,22	0,003
central apnoea 6 – 10 s / h TST	4,5	3,3	2,14	22,40	1,77	5,27	0,028
apnoea with desaturation / h TST	10,9	4,4	2,3	25,8	2,09	8,05	0,003
longest obstructive apnoea	9	8,7	1,75	15,87	0	10,25	0,406
longest hypopnoea	16,5	20,2	0	23,62	3,25	26,37	0,959
longest mixed apnoea	9	6	6,25	12,50	0	9,87	0,075
apnoea index	13,6	6,3	9,25	44,90	4,42	13,42	0,005
RDI (active sleep)	20,3	9,8	10,65	48,32	6,2	20,02	0,002
RDI (quiet sleep)	9	6,2	1,67	24,82	2,8	7,8	0,239
mean heart frequency in active sleep	159,9	151,4	144,27	161,65	145,25	159,65	0,071
mean heart frequency in quiet sleep	153,4	143,2	133,1	166,57	136,15	155,22	0,05
mean respiratory frequency/min	44,5	53	40,37	57,25	41,62	59,5	0,501
mean oxygen saturation in % (active sleep)	97	97	96	98	96	97	0,317
mean oxygen saturation in % (quiet sleep)	97,5	97	97	99	96,25	98	0,314
mean CO_2 mmHg (active sleep)	33	34,5	26,50	40,5	25,5	40,5	0,373
mean CO_2 mmHg (quiet sleep)	36	33	27	40,25	24	41	0,959

transfusion (11-14).

2. The polysomnographies before and after transfusion did not follow a standardised schedule (e.g. same time of day, same recording duration and conditions etc.).

3. Since the change in volume after transfusion may affect the blood circulation and therefore indirectly also the breathing, the period between completing the substitution of erythrocytes and starting polysomnography may well be significant and influential.

4. Drug treatment for cardio-respiratory disturbances might have already occurred before transfusion (as was the case here in 6 of the 9 premature babies). After transfusion this therapy can be terminated. Differentiated polysomnographic results cannot be obtained in these cases, however.

Different studies reported changes in individual breathing parameters due to transfusion. Thus De Maio (3) reported a significant decrease in apnoea frequency and the portion of periodic breathing after transfusion, Joshi (4) showed a significant decrease in longer breathing intervals and in periodic breathing; whereas Stute (15) mentioned a reduction in bradycardias and a significant drop of apnoea of more than 10 seconds. Similar significant points (periodic breathing, mean heart rate) are also reported by Sasidharan (7). Other authors have not succeeded in showing a relationship between anaemia and apnoea. Various theories are aired to explain a relationship between a lack of oxygen transport agents and the apparent resulting breathing disorders which can frequently be found in neonatal practice (13,16,17). It is conceivable that an increase in the breathing frequency compensates for the relative lack of oxygen associated with anaemia. In the long term this might lead to tiring effects on the breathing muscles or even to a decrease in the pCO_2 level due to hyperventilation. This could well result in necessary recuperation phases, i.e. apnoea. While central apnoea in the chain of events is to be expected, obstructive apnoea in premature newborns as a possible consequence of centrally disregulated pharynx muscles cannot be excluded in advance (18).

In the infants we examined, there appears to exist a direct relationship between changes after a transfusion (hemoglobin, hematocrit) and the significant changes of polysomnographic parameters (i.e. incidence of short [3–5 sec] central apnoea [p=0.003], longer [6–10 sec] central apnoea [p=0.028], incidence of apnoea with desaturation >3% of the baseline level [p=0.003], respiratory disturbance index in active sleep [RDIa; p=0.002], mean duration of apnoeas in active sleep [MA; p=0,002] and the mean heart frequency in quiet sleep [p=0.05]). A correlation between the extent of the anaemia and the severity of the breath disorders could not be established owing to the small number of patients under examination. It seems to be important that decreasing tendencies of cardio-respiratory parameters during sleep could be found in infants after a normal pregnancy as well as in premature babies. This study was triggered by a patient with severe changes in parameters (Table 1, no. 5), a barely 5-week-old infant with a "physiologic nadir", who had hitherto developed normally after a regular birth. While it has to be taken into account that significant anaemia is more likely to occur more frequently in the case of premature infants than in fully developed newborn babies, no clear relationship between the corrected gestation period and its effect on breathing patterns after transfusion could be established in such a small group.

The slightly longer duration of sleep before the administration of erythrocytes (Table 2) could indicate that the point of arousal in the infants concerned is reduced under anaemia. On the other hand the recuperative effect brought on by quiet sleep seems to be more pronounced together with balanced hemoglobin values. It is doubtful whether these changes in sleep duration have affected the total sleeping patterns of the babies. Moreover, a direct relationship with the anaemia treatment is difficult to prove. Having evaluated the existing statistical results, the limitations of such a small number of investigated cases should be pointed out.

It might be assumed that severe deviations

even in individual breathing parameters-e.g. the rate of periodic breathing compared with the total sleeping time, median apnoea, mean oxygen saturation or the duration of the longest desaturation period–might have a long-term negative effect on the cognitive abilities or even the total development of the infants in question (19-21). If significant disorders in vital parameters could be shown objectively even in individual cases, the indications for a possibly necessary blood transfusion might be better justified.

In conclusion we recommend that standardised polysomnography should be included in differential diagnostics when it comes to difficult decisions concerning the treatment of anaemic children. The question whether polysomnography before and after transfusion might also reveal significant differences in children with symptomatic anaemia beyond infancy remains open (4,22,23).

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